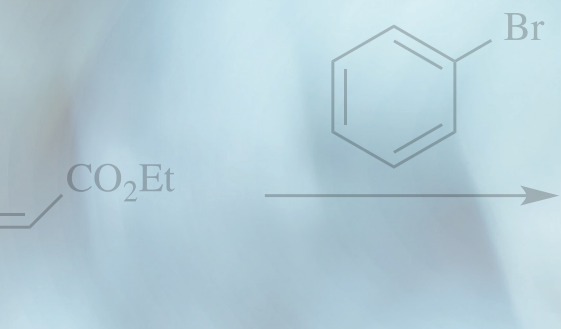
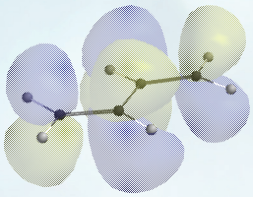
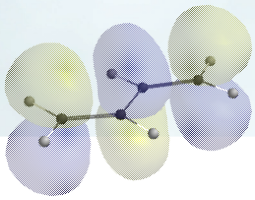
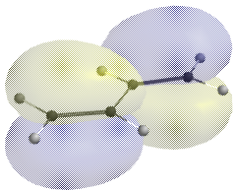
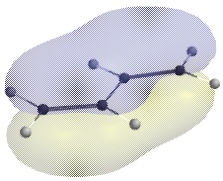




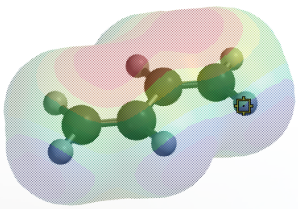




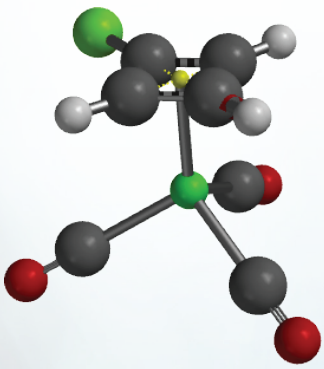


MARCH'S ADVANCED ORGANIC CHEMISTRY

REACTIONS, MECHANISMS, AND STRUCTURE



EIGHTH EDITION



MICHAEL B. SMITH

WILEY

MARCH'S ADVANCED ORGANIC CHEMISTRY

MARCH'S ADVANCED ORGANIC CHEMISTRY

REACTIONS, MECHANISMS, AND STRUCTURE

EIGHTH EDITION

Michael B. Smith
Professor Emeritus
University of Connecticut
Department of Chemistry
69 Eldredge Road
Willington, CT
USA

WILEY

This edition first published 2020

Published by John wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada.

Registered Office
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA

Editorial Office
111 River Street, Hoboken, NJ 07030, USA

For details of our global editorial offices, customer services, and more information about Wiley products visit us at www.wiley.com.

Wiley also publishes its books in a variety of electronic formats and by print-on-demand. Some content that appears in standard print versions of this book may not be available in other formats.

Library of Congress Cataloging-in-Publication Data

Names: Smith, Michael, 1946 October 17- author. | March, Jerry, 1929–1997.
Title: March's advanced organic chemistry : reactions, mechanisms, and structure.
Other titles: Advanced organic chemistry
Description: Eighth edition / Michael B Smith (University of Connecticut, Department of Chemistry). | Hoboken, NJ : John Wiley & Sons, Inc., 2020. | Includes index.
Identifiers: LCCN 2019023265 (print) | LCCN 2019023266 (ebook) | ISBN 9781119371809 (cloth) | ISBN 9781119371786 (adobe pdf) | ISBN 9781119371793 (epub)
Subjects: LCSH: Chemistry, Organic.
Classification: LCC QD251.2 .M37 2020 (print) | LCC QD251.2 (ebook) | DDC 547—dc23
LC record available at https://lccn.loc.gov/2019023265
LC ebook record available at https://lccn.loc.gov/2019023266

Cover image: Background © atakan/iStock.com, All other images courtesy of Michael B. Smith
Cover design by Wiley

Set in 10/12pt TimesLTStd by Aptara Inc., New Delhi, India

10 9 8 7 6 5 4 3 2 1

CONTENTS

NEW REACTION SECTIONS CORRELATION: 7TH EDITION → 8TH EDITION

7TH → 8TH

10-1 → 10-1
10-2 → 10-2
10-3 → 10-3
10-4 → 10-4
10-5 → 10-5
10-6 → 10-6
10-7 → 10-7
10-8 → 10-8
10-9 → 10-9
10-10 → 10-10
10-11 → 10-11
10-12 → 10-12
10-13 → 10-13
10-14 → 10-14
10-15 → 10-15
10-16 → 10-16
10-17 → 10-17
10-18 → 10-18
10-19 → 10-19
10-20 → 10-20
10-21 → 10-21
10-22 → 10-22
10-23 → 10-23
10-24 → 10-24
10-25 → 10-25
10-26 → 10-26
10-27 → 10-27
10-28 → deleted, now with 10-27
10-29 → 10-28
10-30 → 10-29
10-31 → 10-30
10-32 → 10-31
10-33 → 10-32
10-34 → 10-33
10-35 → 10-34
10-36 → 10-35
10-37 → 10-36
10-38 → 10-37
10-39 → 10-38
10-40 → 10-39
10-41 → 10-40
10-42 → 10-41
10-43 → 10-42
10-44 → 10-43
10-45 → 10-44
10-46 → 10-45
10-47 → 10-46
10-48 → 10-47
10-49 → 10-48
10-50 → 10-49
10-51 → 10-50
10-52 → 10-51
10-53 → 10-52
10-54 → 10-53
10-55 → 10-54
New 10-55
10-56 → 10-56
10-57 → 10-57
10-58 → 10-58
10-59 → 10-59
10-60 → 10-60
10-61 → 10-61
10-62 → 10-62
10-63 → 10-63
10-64 → 10-64
10-65 → 10-65
10-66 → 10-66
10-67 → 10-67
10-68 → 10-68
10-69 → 10-69
10-70 → 10-70
10-71 → 10-71
10-72 → 10-72
10-73 → 10-73
10-74 → 10-74
New 10-75
10-75 → 10-76
10-76 → 10-77
10-77 → 10-78
New 10-79

11-1 → 11-1
11-2 → 11-2
11-3 → 11-3
11-4 → 11-6
11-5 → 11-5
11-6 → 11-4
11-7 → 11-7
11-8 → 11-8
11-9 → 11-9
11-10 → 11-10
11-11 → 11-11
11-12 → 11-12
11-13 → 11-13
11-14 → 11-14
11-15 → 11-15
11-16 → 11-16
11-17 → 11-17
11-18 → 11-18
11-19 → 11-19
11-20 → deleted, now with 11-19
11-21 → 11-20
New 11-21
11-22 → 11-22
11-23 → 11-23
11-24 → 11-24

11-25 → 11-25
11-26 → 11-26
11-27 → 11-27
11-28 → 11-28
11-29 → 11-29
11-30 → 11-30
11-31 → 11-31
11-32 → 11-32
11-33 → 11-33
11-34 → 11-34
11-35 → 11-35
11-36 → 11-36
11-37 → deleted, now with 19-61
11-38 → deleted, now with 19-74
11-39 → deleted, now with 19-58
11-40 → 11-37
11-41 → 11-38

12-1 → 12-1
12-2 → 12-2
12-3 → 12-3
12-4 → 12-4
12-5 → 12-5
12-6 → 12-6
12-7 → 12-7
12-8 → 12-8
12-9 → 12-9
12-10 → 12-10
12-11 → 12-11
12-12 → 12-12
12-13 → 12-13
12-14 → 12-14
12-15 → 12-15
12-16 → 12-16
12-17 → 12-17
12-18 → 12-18
12-19 → 12-19
12-20 → 12-20
12-21 → 12-21
12-22 → 12-22
12-23 → 12-23
12-24 → 12-24
12-25 → 12-25
12-26 → 12-26
12-27 → 12-27
12-28 → deleted now with 12-27
12-29 → 12-28
12-30 → 12-29
12-31 → 12-30
12-32 → 12-31
12-33 → 12-32
12-34 → 12-33
12-35 → 12-34
12-36 → 12-35
12-37 → 12-36
12-38 → 12-37
12-39 → 12-38
12-40 → 12-39
12-41 → 12-40
12-42 → 12-41
12-43 → 12-42
12-44 → 12-43
12-45 → 12-44
12-46 → 12-45
12-47 → 12-46
12-48 → 12-47
12-49 → 12-48
12-50 → 12-49
12-51 → 12-50
12-52 → 12-51
12-53 → 12-52

13-1 → 13-1
13-2 → deleted, now with 13-1
13-3 → 13-2
13-4 → 13-3
13-5 → 13-4
13-6 → 13-5
13-7 → 13-6
New 13-7
13-8 → 13-8
13-9 → 13-9
13-10 → 13-13
13-11 → 13-10
13-12 → 13-11
13-13 → 13-14
13-14 → 13-15
13-15 → 13-16
13-16 → 13-17
13-17 → 13-12
13-18 → 13-18
13-19 → 13-19
13-20 → 13-20
13-21 → 13-21
13-22 → 13-22
13-23 → deleted, now with 13-22
New 13-23
13-24 → 13-24
13-25 → 13-25
New 13-26
13-26 → 13-27
13-27 → 13-28
13-28 → 13-29
13-29 → 13-30
13-30 → 13-31
13-31 → 13-32
13-32 → 13-33
13-34 → 13-34

14-1 → 14-1
14-2 → 14-2
14-3 → 14-3
14-4 → deleted, now with 14-1
14-5 → 14-4
14-6 → 14-5
14-7 → 14-6
14-8 → 14-7
14-9 → 14-8
14-10 → 14-9
14-11 → 14-10
14-12 → 14-11
14-13 → 14-12
14-14 → 14-13
14-15 → 14-14
14-16 → 14-15
14-17 → 14-16
14-18 → 14-17
14-19 → 14-18
14-20 → moved to 13-22
14-21 → moved to 13-7
14-22 → moved to 13-21
14-23 → moved to 13-26
14-24 → 14-19

14-25 → 14-20
14-26 → 14-21
14-27 → 14-22
14-28 → deleted, now with 14-22
14-29 → 14-23
14-30 → 14-24
14-31 → 14-25
14-32 → 14-26

15-1 → 15-1
15-2 → 15-2
15-3 → 15-3
15-4 → 15-4
15-5 → 15-5
15-6 → 15-6
15-7 → 15-7
15-8 → 15-8
15-9 → 15-9
15-10 → 15-10
15-11 → moved to 19-34
15-12 → moved to 19-35
15-13 → moved to 19-36
15-14 → moved to 19-37
15-15 → moved to 19-38
15-16 → 15-11
15-17 → 15-12
15-18 → 15-13
15-19 → 15-14
15-20 → 15-15
15-21 → 15-16
New 15-17
15-22 → 15-18
15-23 → 15-19
15-24 → 15-20
15-25 → 15-21
15-26 → 15-22
15-27 → 15-23
15-28 → 15-24
15-29 → 15-25
15-30 → 15-26
15-31 → 15-27
15-32 → 15-28
15-33 → 15-29
15-34 → 15-30
15-35 → 15-31
15-36 → 15-32
15-37 → 15-33
15-38 → 15-34
15-39 → 15-35
15-40 → 15-36
15-41 → 15-37
15-42 → 15-38
15-43 → 15-39
15-44 → 15-40
15-45 → 15-41
15-46 → 15-42
15-47 → 15-43
15-48 → 15-44
15-49 → 15-45
15-50 → 15-46
15-51 → 15-47
15-52 → 15-48
15-53 → 15-49
15-54 → 15-50
15-55 → 15-51
15-56 → 15-52
15-57 → 15-53
15-58 → 15-54
15-59 → 15-55
15-60 → 15-56
15-61 → 15-57
15-62 → 15-58
15-63 → 15-59
15-64 → 15-60
15-65 → 15-61
15-66 → 15-62

16-1 → 16-1
16-2 → 16-2
16-3 → 16-3
16-4 → 16-4
16-5 → 16-5
16-6 → deleted, now with 16-5
16-7 → 16-6
16-8 → 16-7
16-9 → 16-8
16-10 → 16-9
16-11 → 16-10
16-12 → 16-11
16-13 → 16-12
16-14 → 16-13
16-15 → deleted, now with 16-13
16-16 → 16-14
16-17 → 16-15
16-18 → 16-16
16-19 → 16-17
16-20 → 16-18
16-21 → 16-19
16-22 → 16-20
16-23 → 16-21
16-24 → 16-22
16-25 → 16-23
New 16-24
16-26 → 16-25
16-27 → 16-26
16-28 → 16-27
16-29 → 16-29
16-30 → 16-30
16-31 → 16-31
16-32 → 16-32
16-33 → 16-33
16-34 → 16-34
16-35 → 16-35
16-36 → 16-36
16-37 → 16-37
16-38 → 16-38
16-39 → 16-39
16-40 → 16-40
16-41 → 16-41
16-42 → 16-42
16-43 → 16-43
16-44 → 16-44
16-45 → 16-45
16-46 → 16-46
16-47 → 16-47
16-48 → 16-48
16-49 → deleted, now with 16-48
16-50 → 16-49
16-51 → 16-50
16-52 → 16-51
16-53 → 16-52
16-54 → 16-53
16-55 → 16-54
16-56 → 16-55
16-57 → 16-56

16-58 → 16-57
16-59 → 16-58
16-60 → 16-59
16-61 → 16-60
16-62 → 16-61
16-63 → 16-62
16-64 → 16-63
16-65 → 16-64
16-66 → 16-65
16-67 → 16-66
16-68 → 16-67
16-69 → 16-68
16-70 → 16-69
16-71 → 16-70
16-72 → 16-71
16-73 → 16-72
16-74 → 16-73
16-75 → 16-74
16-76 → 16-75
16-77 → 16-76
16-78 → 16-77
16-79 → 16-78
16-80 → deleted, now with 16-78
16-81 → 16-28
16-82 → moved, now with 18-29
16-83 → 16-79
16-84 → 16-80
16-85 → 16-81
16-86 → 16-82
16-87 → deleted, now with 16-82
16-88 → 16-83
16-89 → moved, now with 12-10
16-90 → 16-84
16-91 → 16-85
16-92 → 16-86
16-93 → 16-87
16-94 → 16-88
16-95 → 16-89
16-96 → 16-90
16-97 → 16-91
16-98 → 16-92
16-99 → 16-93
16-100 → 16-94
16-101 → 16-95
16-102 → 16-96
16-103 → 16-97
16-104 → moved, now with 19-75
16-105 → 16-98

17-1 → 17-1
17-2 → 17-2
17-3 → 17-3
17-4 → 17-4
17-5 → 17-5
17-6 → deleted, now with 17-5
17-7 → 17-6
17-8 → deleted, now with 17-2
17-9 → 17-7
17-10 → 17-8
17-11 → 17-9
17-12 → 17-10
17-13 → 17-11
17-14 → 17-12
17-15 → 17-13
17-16 → 17-14
17-17 → 17-15
17-18 → 17-16
17-19 → 17-17
17-20 → 17-18
17-21 → 17-19
17-22 → 17-20
17-23 → 17-21
17-24 → 17-22
17-25 → 17-23
17-26 → 17-24
17-27 → 17-25
17-28 → 17-26
17-29 → 17-27
17-30 → 17-28
17-31 → 17-29
17-32 → 17-30
17-33 → 17-31
17-34 → 17-32
17-35 → 17-33
17-36 → 17-34
17-37 → 17-35
17-38 → 17-36
18-1 → 18-1
18-2 → 18-2
18-3 → 18-3
18-4 → 18-4
18-5 → 18-5
18-6 → 18-6
18-7 → 18-7
18-8 → 18-8
18-9 → 18-9
18-10 → 18-10
18-11 → 18-11
18-12 → 18-12
18-13 → 18-13
18-14 → 18-14
18-15 → 18-15
18-16 → 18-16
18-17 → 18-17
18-18 → 18-18
18-19 → 18-19
18-20 → 18-20
18-21 → 18-21
18-22 → 18-22
18-23 → 18-23
18-24 → 18-24
18-25 → 18-25
18-26 → 18-26
18-27 → 18-27
18-28 → 18-28
18-29 → 18-29
18-30 → 18-30
18-31 → 18-31
18-32 → 18-32
18-33 → 18-33
18-34 → 18-34
18-35 → 18-35
18-36 → 18-36
18-37 → 18-37
18-38 → 18-38
18-39 → 18-39
18-40 → 18-40
18-41 → 18-41
18-42 → 18-42
18-43 → 18-43
18-44 → 18-44

19-1 → 19-1
19-2 → 19-2

19-3 → 19-3
19-4 → 19-4
19-5 → 19-5
19-6 → 19-6
19-7 → 19-7
19-8 → 19-8
19-9 → 19-9
19-10 → 19-10
19-11 → 19-11
19-12 → 19-12
19-13 → 19-13
19-14 → 19-14
19-15 → 19-16
19-16 → 19-17
19-17 → 19-18
19-18 → 19-15
19-19 → 19-19
19-20 → 19-20
19-21 → 19-21
19-22 → 19-22
19-23 → 19-23
19-24 → 19-24
19-25 → 19-25
19-26 → 19-26
19-27 → 19-27
19-28 → deleted, now with 19-27
19-29 → 19-28
19-30 → 19-29
19-31 → 19-30
19-32 → 19-31
19-33 → 19-32
19-34 → 19-33
19-35 → 19-39
19-36 → 19-40
19-37 → 19-41
19-38 → 19-42
19-39 → 19-43
19-40 → 19-44
19-41 → 19-45
19-42 → 19-46
19-43 → 19-47
19-44 → 19-48
19-45 → 19-49
19-46 → 19-50
19-47 → 19-51
19-48 → 19-52
19-49 → 19-53
19-50 → 19-54
19-51 → 19-55
19-52 → 19-56
19-53 → 19-57
19-54 → 19-59
19-55 → 19-60
19-56 → 19-61
19-57 → 19-63
19-58 → 19-64
19-59 → 19-62
19-60 → 19-65
19-61 → 19-66
19-62 → 19-67
19-63 → deleted, now with 19-67
19-64 → 19-68
19-65 → 19-69
19-66 → 19-70
19-67 → 19-71
19-68 → 19-72
19-69 → 19-73
19-70 → 19-74
19-71 → 19-75
19-72 → 19-76
19-73 → 19-77
19-74 → 19-78
19-75 → 19-79
19-76 → 19-80
19-77 → 19-81
19-78 → 19-82
19-79 → 19-83
19-80 → 19-84
19-81 → 19-85
19-82 → 19-86
19-83 → 19-87
19-84 → 19-88

PREFACE

This eighth edition of *March's Advanced Organic Chemistry* has been thoroughly updated to include new advances in areas of organic chemistry published between 2011 and 2017. Every topic retained from the seventh edition has been brought up to date if there was activity in that area during that six-year period. Changes also include a significant rewrite of most of the book. More than 5800 new references have been added for work published since 2011. As with the seventh edition, many older references were deleted to make room for new ones. In cases where a series of papers by the same principal author were cited, most but the most recent were deleted. Be aware that the older citations can usually be found by referring to the more recent publications. It is noted that more than 250 000 articles for the years 2011–2017, from 31 journals, were scanned for this edition. Of this huge number of articles, just over 8000 were examined in detail for inclusion in this work, with 5853 finally chosen. With such numbers, it is inevitable that some work was not included, and it was impossible to include representative research in many areas. For example, over 2000 of the 8000 articles examined were relevant to the transition metal-catalyzed reactions covered in reactions **13-3** to **13-13**. It was simply impossible to keep a representative number of articles for this subject area. There were other areas of research that were also too extensive for complete inclusion of all references.

Many of the reaction drawings considered to be redundant or not very useful were deleted when compiling the eighth edition. A few new sections of text were added to better reflect some areas of research. Several of the older sections were moved to new chapters, especially the ones that deal with hydrogenation of alkenes and alkynes; as these are clearly reductions they were moved to Chapter 19. Some sections were combined with others and the original section deleted. These actions required renumbering the sections for the eighth edition. A correlation table of the sections in the seventh edition and their placement in the eighth edition is provided below. However, the fundamental structure of the eighth edition is essentially the same as that of all previous editions.

The goal, as in previous editions, is to give equal weight to three fundamental aspects of the study of organic chemistry: reactions, mechanisms, and structure. References are provided, and every effort has been given to provide a snapshot of current research. Specific but specialized areas of organic chemistry—terpenes, carbohydrates, proteins, many organometallic reagents, combinatorial chemistry, polymerization and electrochemical reactions, steroids, etc.—have been incorporated into a great many pertinent sections rather than segregated into their own sections.

This book is largely directed at graduate students in their first year of study and to undergraduates advanced in their studies, but previous editions have, for many years, been used as an off-the-shelf reference book. This practice should continue with the eighth edition. It is hoped that this book will lead a student to consult the many excellent books and review articles cited for various topics in order to understand the subject in more detail. Indeed, most of these topics are so vast they cannot be explained completely in this book.

The structure of organic compounds is discussed in Chapters 1–5 (found in Part I); these chapters provide the background that is necessary for understanding mechanisms, but are important in their own right. The discussion begins with chemical bonding (Chapter 1) and ends with a chapter on stereochemistry (Chapter 4). Chapter 5 discusses the structure of intermediates. Chapters 6 and 7 then address reaction mechanisms in general, Chapter 6 for ordinary reactions and Chapter 7 for photochemical reactions. Other methods related to reactions are included in Chapter 7, including microwave chemistry, the use of ultrasound, mechanochemistry, and the relatively new area of reactions done under flow conditions. Part I concludes with Chapters 8 and 9, which give further background to the study of mechanisms and reaction conditions.

The Introduction to Part II briefly describes how the second part of the book is organized. The organization is based on reaction types, and a relatively few principles suffice to explain nearly all the types, despite the large number of organic reactions. Accordingly, the reactions and mechanisms section of this book (Part II) is divided into ten chapters, each being concerned with a different type of reaction. In the first part of each chapter the appropriate basic mechanisms are discussed, along with considerations of reactivity and orientation. The second part of each chapter is devoted to individual reaction types, where the scope and the mechanism of each reaction are discussed. Numbered sections are used for the reactions and theses are set in boldface when given as cross-references. Since the methods for the preparation of individual classes of compounds (e.g., ketones, nitriles, etc.) are not treated all in one place, an updated and revised index has been provided (Appendix B) by use of which the synthesis of a given type of compound may be found.

It is important to note that the reaction numbers (e.g., **10-25**) for many reactions in the eighth edition are *different* from those in the sixth and seventh editions. A table is included that precedes this Preface that directly correlates the reaction numbers found in the eighth edition with the reaction numbers that were used in the sixth and seventh editions. Note also that changes in the sixth edition made the reaction numbers from editions 1–5 different in many cases to those in the sixth edition. To see the differences between the fifth and sixth editions, the reader is referred to the sixth edition.

Although IUPAC has published a system for designating reaction mechanisms, the designations for reactions that were featured in editions 1–7 have been removed, in large part because they are not extensively used and in part because many reactions were deemed by this author as difficult to categorize using only one designation.

In treating subjects as broad as structure, reactions, and mechanisms of organic chemistry, it is impossible to cover each topic in great depth, though this would not be desirable even if possible. This book is intended to point the reader to the primary literature (the original journal publications). Secondary literatures sources, including reviews, books, and monographs, have also been included.

Appendix A provides a brief introduction to using modern computer-based search engines such as *Reaxys*® and *SciFinder*®.

Although basically designed as a reference text for a one-year course at graduate level, this book can also be used in advanced undergraduate courses but is most useful after completion of a one-year course in organic chemistry. It has been my experience that students who have completed the first-year courses often have a hazy recollection of the material and greatly profit from a re-presentation of the material if it is easily accessible. The material in the first nine chapters, particularly chapters 1, 2, 4, 6, and 8, may be helpful for reviewing such material when this book is used in connection with a course.

This book is probably most valuable as a reasonably up-to-date reference work. Both students preparing for qualifying examinations and practicing organic chemists will find that Part II contains a survey of the mechanism and scope of a large number of reactions, arranged in an orderly manner based on reaction type and on which bonds are broken and formed.

IUPAC mandates joules for units of energy, but many journals do not use this unit exclusively. Indeed, organic chemists who publish in United States' journals commonly use calories. Virtually all energy values are presented here in both calories and joules.

Although IUPAC does not recommend angstrom units (Å) for bond distances, preferring instead picometers (pm), a vast number of bond distances published in the literature are in angstrom units, and this book therefore uses angstrom units.

I would like to acknowledge the contributions of those chemists cited and thanked by Professor March in the first four editions, and those I thanked in the fifth, sixth, and seventh editions. This book would not be possible without their contributions. I thank the many people who have contributed comments or have pointed out errors in editions 5–7 that were invaluable to putting together this edition. I thank Warren Hehre and Sean Ohlinger of Wavefunction, Inc., Irvine, CA (www.wavefun.com) for providing Spartan 10 Macintosh (v. 1.0.1), allowing the incorporation of Spartan models for selected molecules and intermediates. All structures and line drawings in this book were done using ChemDraw® Professional 15.1.0.144 (2348350), graciously provided by PerkinElmer Corporation, Waltham, MA.

Special thanks are due to the Interscience division of John Wiley & Sons and to Stefanie Volk and to Jonathan Rose, and also to Katrina Maceda at Wiley for their fine work as editors in turning the manuscript into the finished book. I also thank Tim Jackson for an excellent job of copy editing the manuscript.

With gratitude, I acknowledge the work of the late Jerry March, upon whose work all the editions I have authored is built, although updates and changes have been made, beginning with the fifth edition, However, Jerry is responsible for the concept and fundamental organization of this book and he carried it through four very successful editions. I used Jerry's book as a student and it is an honor to continue this tradition.

I encourage those who read and use the eight edition to contact me directly with comments and errors and with publications that might be appropriate for future editions. I hope that this new edition will do justice to the tradition that Professor March began nearly 60 years ago.

My email address is: michael.smith@uconn.edu

Finally, I want to thank my wife Sarah for her patience and understanding during the preparation of this manuscript. I also thank my son Steven. Without them, this work would not have been possible.

MICHAEL B. SMITH
Professor Emeritus
October, 2018

COMMON ABBREVIATIONS

Note that other, less common, abbreviations are explained in the text when the term is used.

1°	primary	
2°	secondary	
3°	tertiary	
3D	three-dimensional	
Ac	acetyl	
acac ligand	acetylacetonate	
AIBN	*azo-bis*-isobutyronitrile	
Amberlyst	an ion-exchange resin	
aq.	aqueous	
ax	axial	
BDE	bond dissociation energy	
BER	borohydride exchange resin	
BINAP	(2*R*,3*S*)-2,2′-*bis*-(diphenylphosphino)-1,1′-binaphthyl	
BINOL	1,1′-bi(2-binaphthol)	
BMS	borane methyl sulfide	
9-BBN	9-borabicyclo[3.3.1]nonane	
Bn	benzyl	—CH_2Ph
Boc	*tert*-butoxycarbonyl	—CO_2-*t*-Bu
	9-borabicyclo[3.3.1]nonylboryl	
Bpy (Bipy)	2,2′-bipyridyl	
Bromamine-T	*N*-bromo-4-methylbenzenesulfonamide, sodium salt	
Bs	brosylate	*O*-(4-bromophenyl)sulfonate
BSA	bis(trimethylsilyl)acetamide	
Bu	*n*-butyl	—$CH_2CH_2CH_2CH_3$
Bz	benzoyl	
°C	temperature in degrees Celsius	
CAN	ceric ammonium nitrate	$(NH_4)_2Ce(NO_3)_6$
cat	catalytic	
Cbz	carbobenzyloxy	—CO_2CH_2Ph
CD	circular dichroism	
Chap	Chapter(s)	
Chirald	(2*S*,3*R*)-(+)-4-dimethylamino-1,2-diphenyl-3-methylbutan-2-ol	
Chloramine-T	*N*-chloro-4-methylbenzenesulfonamide, sodium salt	

CIDNP	chemical induced dynamic polarization	
CIP	Cahn-Ingold-Prelog	
CNDO	complete neglect of dynamic overlap	
cod ligand	1,5-cyclooctadienyl	
cot ligand	1,3,5-cyclooctatrienyl	
Cp	cyclopentadienyl	
Cy	cyclohexyl	
DABCO	1,4-diazabicyclo[2.2.2]octane	
DAST	diethylaminosulfur trifluoride	
dba ligand	dibenzylidene acetone	
DBN	1,5-diazabicyclo[4.3.0]non-5-ene	
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	
DCC	1,3-dicyclohexylcarbodiimide	*c*-C_6H_{11}—N=C=N—*c*-C_6H_{11}
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone	
DDT	dichlorodiphenyltrichloroethane	
% de	% diastereomeric excess	
DEA	diethylamine	$HN(CH_2CH_3)_2$
DEAD	diethylazodicarboxylate	EtO_2C—N=N—CO_2Et
DHQD	dihydroquinidine	
DHU	dicyclohexylurea	
DIAD	diisopropylazodicarboxylate	*i*-PrO_2C—N=NCO_2-*i*-Pr
Dibal-H	diisobutylaluminum hydride	$(Me_2CHCH_2)_2AlH$
DMA	dimethylacetamide	
DMAP	4-dimethylaminopyridine	
DME	dimethoxyethane	$MeOCH_2CH_2OMe$
DMF	*N*,*N*′-dimethylformamide	
DMS	dimethyl sulfide	
DMSO	dimethyl sulfoxide	
DNA	deoxyribonucleic acid	
DOSY	diffusion oriented NMR spectroscopy	
DPM	dipivaloyl-methane	
dpp	diphenylphosphino	
dppb	1,4-diphenylphosphinobutane	$Ph_2P(CH_2)_4PPh_2$
dppe	1,2-diphenylphosphinoethane	$Ph_2PCH_2CH_2PPh_2$
dppf	*bis*-(diphenylphosphino)ferrocene	
dppp	1,3-diphenylphosphinopropane	$Ph_2P(CH_2)_3PPh_2$
e^-	transfer of electrons	
EDA	electron donor acceptor	
EDTA	ethylenediaminetetraacetic acid	
% ee	% enantiomeric excess	
EPR	electron paramagnetic resonance	
Equiv	Equivalent(s)	
ESCA	electron spectroscopy for chemical analysis	
ESR	electron spin resonance (spectroscopy)	
Et	Ethyl	—CH_2CH_3
FMO	frontier molecular orbital	
FVP	flash vacuum pyrolysis	
GC	gas chromatography	
gl	glacial	
h	hour (hours)	

^{1}H NMR	proton nuclear magnetic resonance (spectroscopy)	
HFIP	hexafluoroisopropanol	
HMO	Hückel molecular orbital	
HMPA	Hexamethylphosphoramide	$(Me_2N)_3P{=}O$
HOMO	highest occupied molecular orbital	
HPLC	high-performance liquid chromatography	
HSAB	hard/soft acid/base	
$h\nu$	irradiation with light	
i-Pr	isopropyl	$-CH(Me)_2$
IBX	iodosobenzoic acid	
IP	ionization potential	
IR	infrared (spectroscopy)	
ISC	intersystem crossing	
IUPAC	International Union of Pure and Applied Chemistry	
LCAO	linear combination of atomic orbitals	
LDA	lithium diisopropylamide	$LiN(i\text{-}Pr)_2$
LHMDS	lithium hexamethyldisilazide	$LiN(SiMe_3)_2$
LICA (LIPCA)	lithium *N*-isopropyl-*N*-cyclohexylamide	
LTMP	lithium 2,2,6,6-tetramethylpiperidide	
LUMO	lowest unoccupied molecular orbital	
mcpba	*meta*-chloroperoxybenzoic acid	
Me	methyl	$-CH_3$
MEM	2-methoxyethoxymethyl	$MeOCH_2CH_2OCH_2-$
Mes	mesityl	2,4,6-tri-Me-C_6H_2
min	minutes	
MMPP	magnesium monoperoxyphthalate	
MO	molecular orbital	
MOM	methoxymethyl	$MeOCH_2-$
Ms	methanesulfonyl	$MeSO_2-$
MS	molecular sieves (3Å or 4Å)	
MTO	methyltrioxorhenium	
MTPA	Mosher's acid	
NBS	*N*-bromosuccinimide	
NCS	*N*-chlorosuccinimide	
NHC	*N*-heterocyclic carbene	
NHS	*N*-hydroxysuccinimide	
Ni(R)	Raney nickel	
NIS	*N*-iodosuccinimide	
NMO	*N*-methylmorpholine *N*-oxide	
NMP	*N*-methylpyrrolidinone	
NMR	nuclear magnetic resonance	
NOESY	nuclear Overhauser effect spectroscopy	
Ns	nosyl (4-nitrobenzene-1-sulfonyl chloride)	
Nu (Nuc)	nucleophile	
OBs	brosylate, *O*-(4-bromophenyl)sulfonate	
ORD	optical rotatory dispersion	
OS	*Organic Syntheses*	
OSCV	*Organic Syntheses Collective Volume*	

Oxone®	2 $KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$	
PCC	pyridinium chlorochromate	
PDC	pyridinium dichromate	
PEG	polyethylene glycol	
PES	photoelectron spectroscopy	
Ph	phenyl	$-C_6H_5$
Phen	phenanthroline	
PhH	benzene	
PhMe	toluene	
PIFA	bis(trifluoroacetoxy)iodobenzene	
Pin	pinacolato	
	polymeric backbone	
PPA	polyphosphoric acid	
PPHF	pyridinium poly(hydrogen fluoride)	
Pr	*n*-propyl	$-CH_2CH_2CH_3$
Py	pyridine	
quant	quantitative yield	
Red-Al	$[(MeOCH_2CH_2O)_2AlH_2]Na$	
ROESY	rotating frame NOE spectroscopy	
rt	room temperature	
s	seconds	
salen ligand	*N*,*N*′-ethylenebis(salicylimine)	
s-BuLi	*sec*-butyllithium	$CH_3CH_2CH(Li)CH_3$
$scCO_2$	supercritical carbon dioxide	
SCF	self-consistent field	
Sec.	section(s), referring to sections in this book.	
Selectfluor	1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]-	
SET	single electron transfer	
$(Sia)_2BH$	disiamylborane (siamyl is *sec*-isoamyl)	
SOMO	singly occupied molecular orbital	
t-Bu	*tert*-butyl	$-CMe_3$
TBAF	tetrabutylammonium fluoride	$n\text{-}Bu_4N^+ F^-$
TBDMS	*tert*-butyldimethylsilyl	$t\text{-}BuMe_2Si$
TBDPS	*tert*-butyldiphenylsilyl	$t\text{-}BuPh_2Si$
TBHP (*t*-BuOOH)	*tert*-butylhydroperoxide	Me_3COOH
TEAB	tetraethylammonium bromide	
TEBA	benzyltriethylammonium	$Bn(Et)_3N^+$
TED	tetraethylenediamine	
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl free radical	
Tf (OTf)	triflate	$-SO_2CF_3$ ($-OSO_2CF_3$)
TFA	trifluoroacetic acid	CF_3COOH
tfa ligand	trifluoroacetyl as a ligand	CF_3COO-
$ThexBH_2$	thexylborane (*tert*-hexylborane)	
THF	tetrahydrofuran	
THP	tetrahydropyran	
TMEDA	tetramethylethylenediamine	$Me_2NCH_2CH_2NMe_2$
TMS	trimethylsilyl	$-Si(CH_3)_3$

TMS (sometimes)	tetramethylsilane	—$Si(CH_3)_4$
Tol	tolyl	4-(Me)C_6H_4
TOSMIC	toluenesulfonylmethyl isocyanide	
TPAP	tetrapropylammonium perruthenate	
TPP and tpp ligand	triphenylphosphine	PPh_3
Tr	trityl	—CPh_3
TRIP	(R)-3,3′-bis(2,4,6-Triisopropylphenyl)-1,1′-binaphthyl-	
TROC	trichloroethyl chloroformate	
Ts(Tos)	tosyl = *p*-toluenesulfonyl	4-(Me)$C_6H_4SO_2$
UV	ultraviolet (spectroscopy)	
VCD	vibrational circular dichroism	
VDW	van der Waals	
vis	visible	

BIOGRAPHICAL STATEMENT

I was born in Detroit, Michigan, and moved to Madison Heights, Virginia, in 1957. I graduated from Amherst County High School in 1964. I worked at Old Dominion Box Factory for a year and then started college at Ferrum Jr. College in 1965. I graduated in 1967 with an A.A. and began studies at Virginia Tech later that year, graduating with a B.S. in Chemistry in 1969. I worked as a chemist at the Newport News Shipbuilding & Dry Dock Co., Newport News, Virginia, from 1969 until 1972. In 1972 I began studies in graduate school at Purdue University, West Lafayette, Indiana, working with Prof. Joseph Wolinsky. I graduated in 1977 with a Ph.D. in Organic Chemistry. I took a postdoctoral position at Arizona State University in Tempe, Arizona, working on the isolation of anti-cancer agents from marine animals with Prof. Bob Pettit. After one year, I took another postdoctoral position at MIT in Cambridge, Massachusetts, working on the synthesis of the anti-cancer drug bleomycin with Prof. Sidney Hecht.

I began my independent career as a assistant professor in the Chemistry department at the University of Connecticut (UCONN), Storrs, CT, in 1979. I received tenure in 1986, and spent six months on sabbatical in Belgium with Prof. Leon Ghosez at the Université Catholique de Louvain in Louvain la Neuve, Belgium. I was promoted to full professor in 1994 and have spent my entire career at UCONN. My research involved the synthesis of biologically interesting molecules. My most recent work involved the preparation of functionalized indocyanine dyes for the detection of hypoxic cancerous tumors (breast cancer), and also the synthesis of inflammatory lipids derived from the dental pathogen, *Porphyromonas gingivalis*. I have published 25 books and published 95 peer-reviewed research articles. I retired from UCONN in January 2017.

NEW FEATURES OF THE 8TH EDITION

- The book has been extensively rewritten.
- More than 5500 new references have been incorporated into the book, all from 2011–2017, and about 85–90% of all citations in the book taken from literature since 2000.
- New sections have been added, some old sections moved to new chapters, and some old sections combined with existing sections and replaced with new sections.
- Spartan molecular models continue to be included for selected molecules and intermediates and to replace arcane drawings of molecular orbitals wherever possible.
- Appendix B, which correlates reaction type with section numbers, has been completely revised and updated.
- A correlation table for conversion of reaction sections in the 8th edition to those that previously appeared in the 6th and 7th editions is included in the Preface.
- The Author Index has been completely updated and revised.

PART I

INTRODUCTION

This book contains 19 chapters. Chapters 1 to 9 may be thought of as an introduction to Part II. The first five chapters deal with the structure of organic compounds. These chapters discuss the kinds of bonding important in organic chemistry, the fundamental principles of conformation and stereochemistry of organic molecules, and reactive intermediates in organic chemistry. Chapters 6 to 9 are concerned with general principles of mechanism in organic chemistry, including acids and bases, photochemistry, sonochemistry and microwave irradiation, and finally the relationship between structure and reactivity. Chapters 10 to 19, which make up Part II, are directly concerned with the nature and the scope of organic reactions and their mechanisms.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

CHAPTER 1

Localized Chemical Bonding

Localized chemical bonding may be defined as bonding in which the electrons are shared by two and only two nuclei. Such bonding is the essential feature associated with the structure of organic molecules.[1] Chapter 2 will discuss *delocalized bonding*, in which electrons are shared by more than two nuclei.

1.A. COVALENT BONDING[2]

Wave mechanics is based on the fundamental principle that electrons behave as waves (e.g., they can be diffracted). Consequently, a wave equation can be written for electrons, in the same sense that light waves, sound waves, and so on can be described by wave equations. The equation that serves as a mathematical model for electrons is known as the *Schrödinger equation*, which for a one-electron system is:

$$\frac{\delta^2\psi}{\delta x^2} + \frac{\delta^2\psi}{\delta y^2} + \frac{\delta^2\psi}{\delta z^2} + \frac{8\pi^2 m}{h^2}(E - V)\,\psi = 0$$

where m is the mass of the electron, E is its total energy, V is its potential energy, and h is Planck's constant. In physical terms, the function Ψ expresses the square root of the probability of finding the electron at any position defined by the coordinates x, y, and z, where the origin is at the nucleus. The equation is similar, but more complicated, for systems containing more than one electron.

The Schrödinger equation is a differential equation, so solutions to it are themselves equations; however, the solutions are not differential equations but simple equations for which graphs can be drawn. Such graphs are essentially three-dimensional (3D) pictures

[1] See Hoffmann, R.; Schleyer, P.v.R.; Schaefer III, H.F. *Angew. Chem. Int. Ed.* ***2008***, *47*, 7164.

[2] This treatment of orbitals is simplified by necessity. For more detailed treatments of orbital theory, as applied to organic chemistry, see Matthews, P.S.C. *Quantum Chemistry of Atoms and Molecules*, Cambridge University Press, Cambridge, ***1986***; Clark, T. *A Handbook of Computational Chemistry*, Wiley, NY, ***1985***; Albright, T.A.; Burdett, J.K.; Whangbo, M. *Orbital Interactions in Chemistry*, Wiley, NY, ***1985***; MacWeeny, R.M. *Coulson's Valence*, Oxford University Press, Oxford, ***1980***; Murrell, J.N.; Kettle, S.F.A; Tedder, J.M. *The Chemical Bond*, Wiley, NY, ***1978***; Dewar, M.J.S.; Dougherty. R.C. *The PMO Theory of Organic Chemistry*, Plenum, NY, ***1975***; Zimmerman, H.E. *Quantum Mechanics for Organic Chemists*, Academic Press, NY, ***1975***; Borden, W.T. *Modern Molecular Orbital Theory for Organic Chemists*, Prentice-Hall, Englewood Cliffs, NJ, ***1975***.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

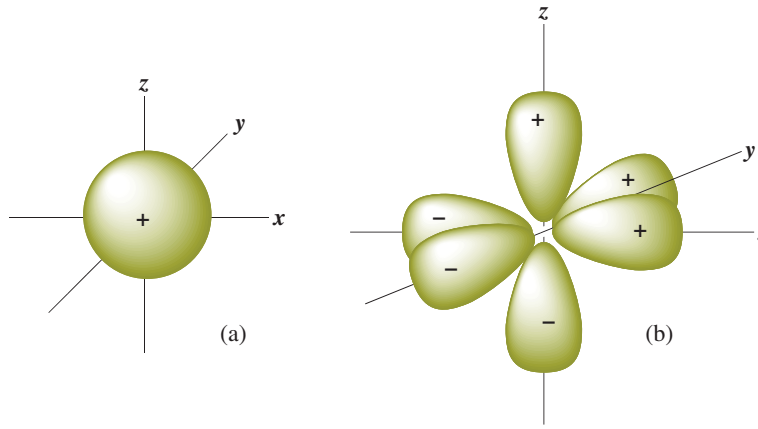


FIGURE 1.1. (*a*) The 1*s* orbital. (*b*) The three degenerate 2*p* orbitals.

that show the electron density, and these pictures are representations of *orbitals*, which are electron clouds. Most students are familiar with the shapes of the *s* and *p* atomic orbitals (Figure 1.1).[3] Note that each *p* orbital has a *node*: a region in space where the probability of finding the electron is extremely small.[4] Also note that in Figure 1.1 some lobes of the orbitals are labeled (+) and others (−). These signs do not refer to positive or negative *charges*, since both lobes of an electron cloud must be negatively charged, but rather refer to the signs of the wave function Ψ. When a node separates two parts of an orbital, a point of zero electron density, Ψ, always has opposite signs on the two sides of the node. According to the *Pauli exclusion principle*, no more than two electrons can be present in any orbital, and they must have opposite spins.

Unfortunately, the Schrödinger equation can be solved exactly only for one-electron systems, such as the hydrogen atom. If it could be solved exactly for molecules containing two or more electrons,[5] a precise picture of the shape of the orbitals available to each electron (especially for the important ground state) would become available, as well as the energy for each orbital. Since exact solutions are not available, drastic approximations must be made. There are two chief general methods of approximation: the molecular-orbital method and the valence-bond method.

In the molecular-orbital method, bonding is considered to arise from the overlap of atomic orbitals. When any number of atomic orbitals overlap, they combine to form an equal number of new orbitals, called *molecular* orbitals. Molecular orbitals differ from atomic orbitals in that an electron cloud effectively surrounds the nuclei of two or more atoms, rather than just one atom. In other words, the electrons are shared by more than one

[3] The argument has been proposed that hybrid atomic orbitals should not be taught in a chemistry curriculum. See Grushow, A. *J. Chem. Educ.* ***2011***, *88*, 860.

[4] When wave-mechanical calculations are made according to the Schrödinger equation, the probability of finding the electron in a node is zero, but this treatment ignores relativistic considerations. When such considerations are applied, Dirac has shown that nodes do have a very small electron density: Powell, R.E. *J. Chem. Educ.* ***1968***, *45*, 558. See also, Ellison, F.O.; Hollingsworth, C.A. *J. Chem. Educ.* ***1976***, *53*, 767; McKelvey, D.R. *J. Chem. Educ.* ***1983***, *60*, 112; Nelson, P.G. *J. Chem. Educ.* ***1990***, *67*, 643. For a general review of relativistic effects on chemical structures, see Pyykkö, P. *Chem. Rev.* ***1988***, *88*, 563.

[5] See Roothaan, C.C.J.; Weiss, A.W. *Rev. Mod. Phys.* ***1960***, *32*, 194; Kolos, W.; Roothaan, C.C.J. *Rev. Mod. Phys.* ***1960***, *32*, 219. See Clark, R.G.; Stewart, E.T. *Q. Rev. Chem. Soc.* ***1970***, *24*, 95.

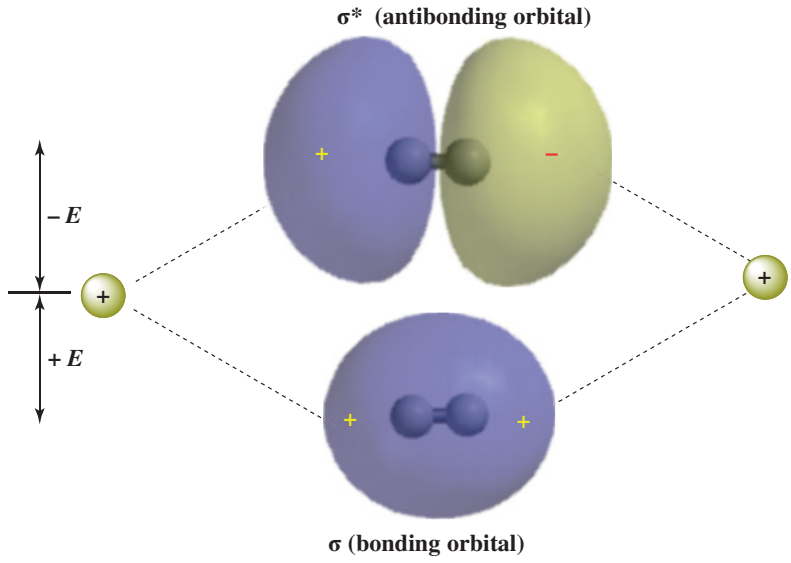


FIGURE 1.2. Overlap of two 1*s* orbitals gives rise to a σ orbital and a σ* orbital.

atom rather than being localized on a single atom. In localized bonding for a single covalent bond, the number of atomic orbitals that overlap is two (each containing one electron), so that two molecular orbitals are generated. One of these, called a *bonding orbital*, has a lower energy than the original atomic orbitals, otherwise a bond would not form, and the other, called an *antibonding orbital*, has a higher energy. Orbitals of lower energy fill first. Since the two original atomic orbitals each held one electron, both of these electrons will reside in the new *molecular bonding orbital*, which is lower in energy. Remember that *any orbital can hold only two electrons*. The higher energy antibonding orbital remains empty in the ground state.

The strength of a bond is determined by the amount of electron density that resides between the two nuclei. The greater the overlap of the orbitals, the stronger the bond, but total overlap is prevented by repulsion between the nuclei. Determining the electron density at the carbon atom, although difficult, is important for the stability of a molecule. One method to determine this parameter is quantum theory using the atomic charges and volumes of carbon atoms,[6] as these are good descriptors of electron depletion and are indicative of the stability and reactivity of a molecule.

Figure 1.2 shows the bonding and antibonding orbitals that arise by the overlap of two 1*s* electrons. Note that since the antibonding orbital has a node between the nuclei, there is practically no electron density in that area, so that this orbital cannot be expected to bond very well. When the centers of electron density are on the axis common to the two nuclei, the molecular orbitals formed by the overlap of two atomic orbitals are called σ (*sigma*) orbitals, and the bonds are called σ bonds. The corresponding antibonding orbitals are designated σ*. Sigma orbitals may be formed by the overlap of any of the atomic orbitals (*s*, *p*, *d*, or *f*), whether the same or different, not only by the overlap of two *s* orbitals. However, the two lobes that overlap must have the same sign: a positive *s* orbital can form a bond only by

[6] Kržan, A.; Mavri, J. *J. Org. Chem.* ***2011***, *76*, 1891.

overlapping with another positive *s* orbital or with a positive lobe of a *p*, *d*, or *f* orbital. Any σ molecular orbital may be represented as approximately ellipsoidal in shape.

Orbitals are frequently designated by their symmetry properties. The σ orbital of hydrogen is often written ψ_g. The *g* stands for *gerade*. A *gerade* orbital is one in which the sign on the orbital does not change when it is inverted through its center of symmetry. The σ* orbital is *ungerade* (designated ψ_u). An *ungerade* orbital changes sign when inverted through its center of symmetry.

In molecular-orbital calculations, the *linear combination of atomic orbitals* (known as LCAO) generates a wave function from a linear combination of overlapped atomic orbitals. Addition of the atomic orbitals gives the bonding molecular orbital:

$$\psi = c_A\psi_A + c_B\psi_B \tag{1-1}$$

The functions ψ_A and ψ_B are the functions for the atomic orbitals of atoms A and B, respectively, and c_A and c_B represent weighting factors. Subtraction is also a linear combination:

$$\psi = c_A\psi_A - c_B\psi_B \tag{1-2}$$

This gives rise to the antibonding molecular orbital.

In the valence-bond method, a wave equation is written for each of the various possible electronic structures that a molecule may have (each of these is called a *canonical form*), and the total ψ is obtained by summation of as many of these as seem plausible, each with its weighting factor:

$$\psi = c_1\psi_1 + c_2\psi_2 + \cdots \tag{1-3}$$

This resembles Eq. (1-1), but here each ψ represents a wave equation for an imaginary canonical form and each *c* is the amount contributed to the total picture by that form. For example, a wave function can be written for each of the following canonical forms of the hydrogen molecule:[7]

$$\mathrm{H{-}H} \qquad \mathrm{H{:}^-H^+} \qquad \mathrm{^+HH{:}^-}$$

Values for *c* in each method are obtained by solving the equation for various values of each *c*, and choosing the solution of lowest energy. In practice, both methods give similar solutions for molecules that contain only localized electrons, and these are in agreement with the Lewis structures long familiar to the organic chemist. Delocalized systems are considered in Chapter 2. It is noted that orbital functions can indeed be reconstructed from measured data using several different approaches. However, the results are often less accurate than those achieved with purely theoretical methods.[8]

[7] In this book, a pair of electrons in a bond is represented by a straight line.

[8] Schwarz, W.H.E. *Angew. Chem. Int. Ed.* ***2006***, *45*, 1508. For the ball-in-box model, see Pierrefixe, S.C.A.H.; Guerra, C.F.; Bickelhaupt, F.M. *Chem. Eur. J.* ***2008***, *14*, 819; Pierrefixe, S.C.A.H.; Bickelhaupt, F.M. *J. Phys. Chem. A.* ***2008***, *112*, 12816.

1.B. MULTIPLE VALENCE

A univalent atom has only one orbital available for bonding. But atoms with a valence of 2 or more must form bonds by using at least two orbitals. An oxygen atom has two half-filled orbitals, giving it a valence of 2. It forms single bonds by the overlap of these with the orbitals of two other atoms. According to the principle of maximum overlap, the other two nuclei should form an angle of 90° with the oxygen nucleus, since the two available orbitals on oxygen are *p* orbitals, which are perpendicular. If this is correct, nitrogen, which has three mutually perpendicular *p* orbitals, would also have bond angles of 90° when it forms three single bonds. However, these are not the observed bond angles. The bond angles are 104°27′ in water and 106°46′ in ammonia.[9] For alcohols and ethers the angles are even larger (Sec. 1.K). A discussion of this difference in bond angles will be deferred to Section 1.K, but it is important to note that covalent compounds do have definite bond angles. Although the atoms are continuously vibrating, the mean position is the same for each molecule of a given compound.

1.C. HYBRIDIZATION

Consider the case of mercury. Its electronic structure is:

$$[\mathbf{Xe}\,\text{core}]\,4f^{14}5d^{10}6s^2$$

Although it has no half-filled orbitals, it has a valence of 2 and forms two covalent bonds. This bonding can be explained by imagining that one of the 6*s* electrons is promoted to a vacant 6*p* orbital to give the excited configuration:

$$[\mathbf{Xe}\,\text{core}]\,4f^{14}5d^{10}6s^{1}6p^{1}$$

In this state, the atom has two half-filled orbitals, but they are not equivalent. If bonding were to occur by the overlap of these orbitals with the orbitals of external atoms, the two bonds would not be equivalent. The bond formed from the 6*p* orbital would be more stable than the one formed from the 6*s* orbital, since a larger amount of overlap is possible with the former. A more stable situation is achieved when, in the course of bond formation, the 6*s* and 6*p* orbitals combine to form two new orbitals that *are* equivalent; these are shown in Figure 1.3.

The new molecular orbitals are a mixture of the two original orbitals, so they are called *hybrid orbitals*.[10] Each orbital is a merger of an *s* orbital and a *p* orbital and is called an *sp* orbital. *Note that only lobes of the same sign can overlap*. The *sp* orbitals, each of which consists of a large lobe and a very small one, arise only in the bonding process and do not represent a possible structure for the free atom. An example is the mercury atom, which forms its two bonds by overlapping each of the large lobes shown in Figure 1.3 with an orbital from an external atom. The orbital of this external atom may be any of the atomic orbitals previously considered (*s*, *p*, *d*, or *f*), or it may be another hybrid orbital. In any of

[9] Bent, H.A. *Chem. Rev.* ***1961***, *61*, 275, see p. 277.
[10] See Alabugin, I.V.; Bresch, S.; Gomes, G.d.P. *J. Phys. Org. Chem.* ***2015***, *28*, 147.

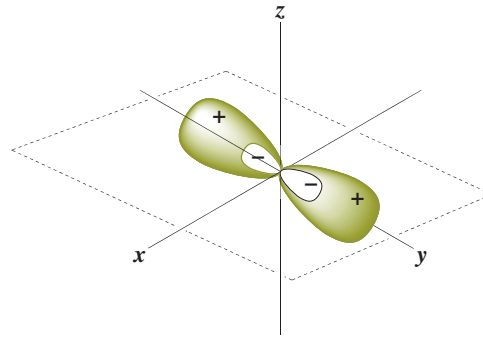


FIGURE 1.3. The two *sp* orbitals formed by mercury.

these cases, the molecular orbital that arises is called a σ orbital since it fits the previous definition of a σ orbital.

In general, equivalent orbitals lie as far away from each other as possible because of mutual repulsion, so two *sp* orbitals form an angle of 180°. In other words, an atom that forms only two σ bonds uses two *sp* orbitals. $HgCl_2$, for example, should be a linear molecule, and it is. This kind of hybridization is called *digonal hybridization*. An *sp* hybrid orbital forms a stronger covalent bond than either an *s* or a *p* orbital because it extends out in space in the direction of the other atom's orbital farther than the *s* or the *p* and permits greater overlap. Compare $HgCl_2$ with water (OH_2). It is known that the shape of $HgCl_2$ is linear, but water is angular. This fact suggests that the hybrid orbitals utilized by oxygen in water are different from those used by mercury in $HgCl_2$.

Many other kinds of hybridization are possible. Consider boron, which has the electronic configuration $1s^2 2s^2 2p^1$ yet has a valence of 3. Boron has only three valence electrons available to form bonds, hence the valence of 3. Any hybridization model must take this into account. As before, imagine promotion of an electron and hybridization:

$$1s^2 2s^2 2p^1 \xrightarrow{\text{promotion}} 1s^2 2s^1 2p_x^1 2p_y^1 \xrightarrow{\text{hybridization}} 1s^2 (2sp^2)^3$$

In this case, there are three equivalent hybrid orbitals, each called sp^2 (*trigonal hybridization*). This method of designating hybrid orbitals is perhaps unfortunate since nonhybrid orbitals are designated by single letters, but it must be kept in mind that *each* of the three orbitals is called sp^2. The key is to understand that an atom forms two σ bonds for *sp* hybridization and three σ bonds for sp^2 hybridization. The sp^2 hybrid orbitals just noted are shown in Figure 1.4. The three axes are all in one plane and point to the corners of an equilateral triangle. This accords with the known structure of BF_3, a planar molecule with angles of 120°.

Another type of hybrid orbital is possible, formed by atoms that can form four σ bonds. Carbon is an important atom that can form four single bonds (four σ bonds). Imagine promotion of an electron and hybridization that leads to:

$$1s^2 2s^2 2p_x^1 2p_y^1 \xrightarrow{\text{promotion}} 1s^2 2s^1 2p_x^1 2p_y^1 2p_z^1 \xrightarrow{\text{hybridization}} 1s^2 (2sp^3)^4$$

There are four equivalent molecular orbitals connected to a central locus, each called sp^3, and mutual electron repulsion leads to a shape in which *the orbitals point to the corners of a regular tetrahedron* (Figure 1.4). A typical molecule is methane, CH_4, and assuming

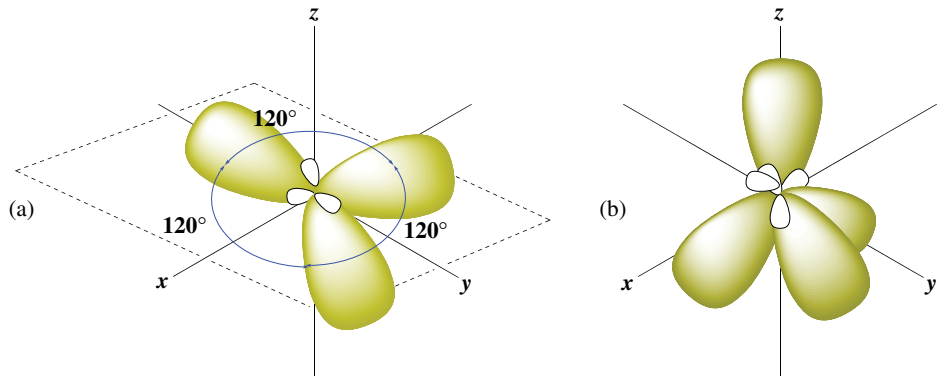


FIGURE 1.4. (*a*) The three sp^2 and (*b*) the four sp^3 orbitals.

that carbon forms four bonds with sp^3 hybrid orbitals, the bond angles of methane would thus be expected to be 109°28′. Indeed, those are the angles of a regular tetrahedron. *In reality, electrons are not "promoted" in atomic orbitals but atomic orbitals are different from molecular orbitals, such as those found in methane*. The model of promoting an electron is a mathematical device to describe molecular orbitals using the atomic orbitals. With the realization that electrons are not really "promoted", it is important to remember that the hybridization model is just that, a *model*, so the VSEPR (valence shell electron pair repulsion) model[11] can be used to show electron distribution, and molecules will form the strongest bonds possible using available orbitals.

The hybrid orbitals discussed in this section stem from only one possible approximate solution of the Schrödinger equation. The *s* and the three *p* atomic orbitals used to form sp^3 orbitals, for example, can be combined in other equally valid ways. As will be seen in Section 1.E, the four C—H bonds of methane do not always behave as if they are equivalent. Bickelhaupt[8] has proposed an alternative approach to the bonding in carbon, which suggests that the maximum coordination number of carbon cannot exceed four because it is too small to allow more than four substituents to approach and form the appropriate bonds.

1.D. MULTIPLE BONDS

If ethene ($H_2C{=}CH_2$); the old name is ethylene) is examined in terms of the molecular-orbital concepts discussed so far, each carbon has three σ bonds (see Figure 1.5), one to each of the three atoms. Therefore, sp^2 orbitals are used to form those three bonds. These sp^2 orbitals arise from hybridization of the $2s^1$, $2p_x^1$, and $2p_y^1$ electrons after promotion of electrons (Sec. 1.C). In general, any carbon atom that is bonded to only three different atoms uses sp^2 orbitals for this bonding. The three σ bonds of ethene are identified as one to each of two hydrogen atoms and one to the other carbon. Each carbon therefore has another electron in the $2p_z$ orbital that is perpendicular to the plane of the sp^2 orbitals. The two parallel $2p_z$ orbitals, one on each of the two adjacent carbon atoms, can overlap sideways to generate a bonding and an antibonding orbital (Figure 1.5). In the ground state, both electrons go into the bonding orbital and the antibonding orbital remains vacant. In other words, a new bond

[11] Smith, M.B. *Organic Chemistry. An Acid–Base Approach*, 2nd ed., CRC Press, Boca Raton, FL, ***2016***, pp. 66–67.

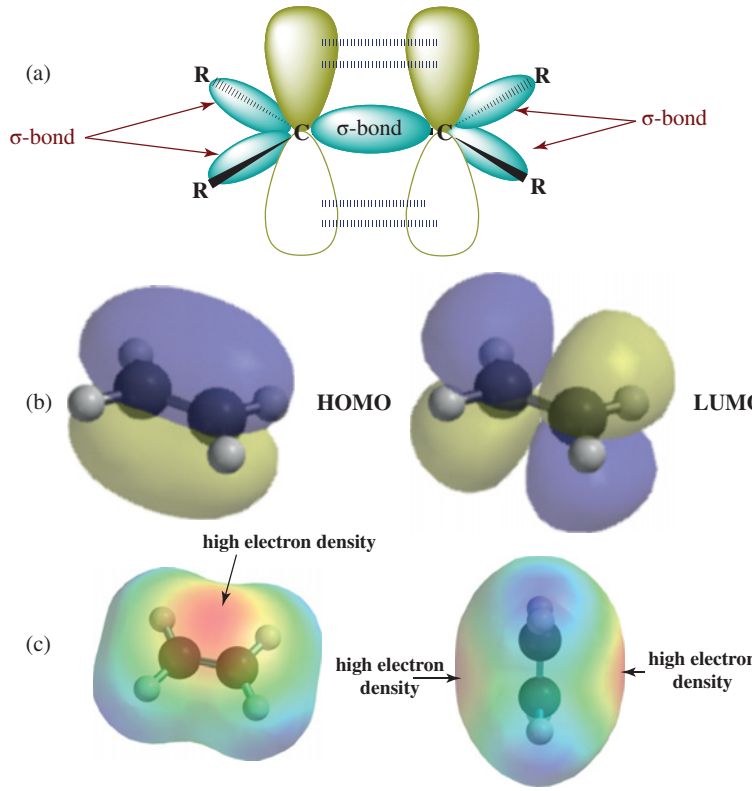


FIGURE 1.5. Overlapping *p* orbitals form a π orbital and a π* orbital. The σ orbitals are shown in (*a*). The π orbitals are shown in (*b*) as the HOMO (on the left) and the LUMO (on the right). In (*c*) the electron potential map of ethene shows the concentration of electron density above and below the plane of the atoms, consistent with a π bond.

is formed, but it is formed by sideways overlap of adjacent *p* orbitals rather than direct overlap of σ orbitals. Molecular orbitals formed by the overlap of atomic orbitals whose axes are parallel are called π *orbitals* if they are bonding and π* if they are antibonding.

In this picture of ethene, there are two bonds connecting the adjacent carbon atoms, but the two orbitals that make up the double bond are not equivalent.[12] In other words, the two bonds are different one from the other. The σ orbital is ellipsoidal and symmetrical about the C—C axis, the familiar σ bond. The π orbital is in the shape of two ellipsoids, one above the plane and one below, and forms the second bond, a π bond. The plane itself represents a node for the π orbital. In order for the *p* orbitals to maintain maximum overlap, they must be parallel. Since both a σ bond and the π bond connect the two carbon atoms, free rotation is not possible about the double bond. In other words, overlap of the two *p* orbitals does not allow one H—C—H plane to rotate with respect to the other; i.e., *the π bond would have to disappear*. With two sp^2 hybrid carbon atoms in ethene, the six atoms associated with the double bond ($H_2C{=}CH_2$) are in a plane with angles that should be ~120°. Double bonds are shorter than the corresponding single bonds because maximum stability is obtained when

[12] For an alternative representation, see Pauling, L. *Theoretical Organic Chemistry, The Kekulé Symposium*; Butterworth: London, ***1959***, pp. 2–5; Palke, W.E. *J. Am. Chem. Soc.* ***1986***, *108*, 6543.

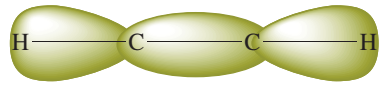


FIGURE 1.6. The σ electrons of ethyne.

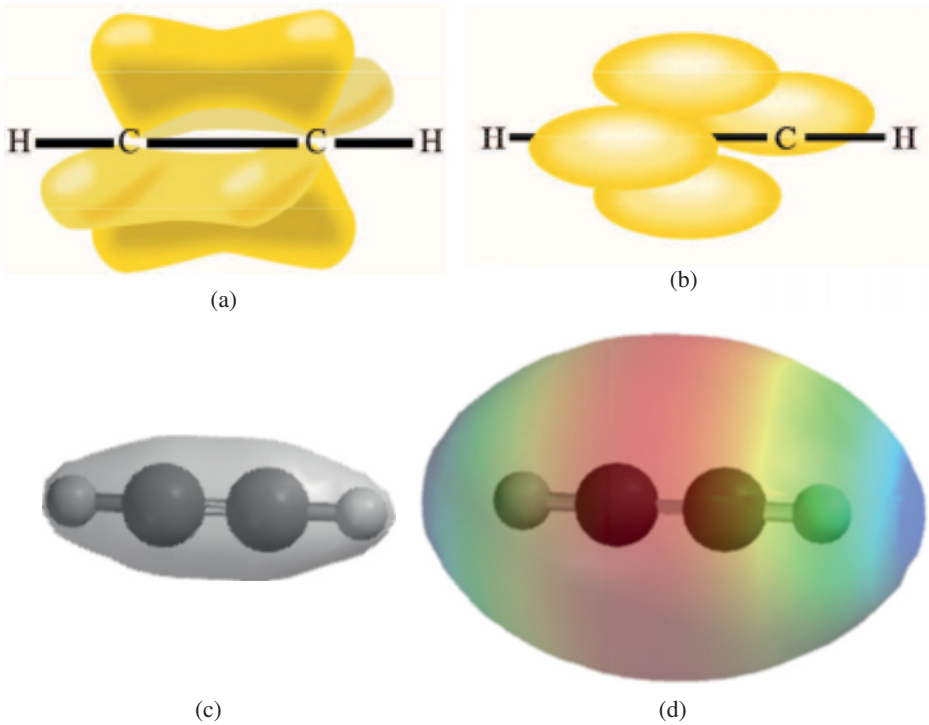


FIGURE 1.7. (*a*) The overlap of mutually perpendicular π orbitals. (*b*) Two orthogonal π bonds. (*c*) The electron density map of ethyne. Note the concentration of electron density along a line between the nuclei of each atom, consistent with overlap of σ orbitals in a triple bond. (*d*) Electron potential map of ethyne showing the concentration of electron density between the carbon atoms, consistent with two orthogonal π bonds.

the *p* orbitals overlap as much as possible (Sec. 1.J). Double bonds between carbon and oxygen (C═O) or carbon and nitrogen (C═N) similarly consist of one σ orbital and one π orbital.

When carbon is connected to another carbon atom by a triple bond, as in ethyne (HC≡CH; the common name is acetylene), each carbon is connected to only two other atoms by a σ bond and hence uses *sp* hybridization. This fact requires that the four atoms of acetylene (2H and 2C) are in a straight line (Figure 1.6).[13] Each carbon has two *p* orbitals remaining, with one electron in each. These orbitals are perpendicular to each other and also to the C─C axis. The mutually perpendicular *p* orbitals overlap in the manner shown in Figure 1.7a to form two orthogonal π orbitals, as shown in Figure 1.7b. A triple bond is

[13] See Simonetta, M.; Gavezzotti, A., in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, Wiley, NY, ***1978***, pp. 1–56; Dale, J., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 3–96.

thus composed of one σ orbital and two π orbitals. The electron density map of ethyne in shown in Figure 1.7c and shows a concentration of electron density along a line between the nuclei of each atom, consistent with overlap of σ orbitals in a triple bond. In Figure 1.7d the concentration of electron density is shown to be surrounding the space between the carbon atoms, consistent with two orthogonal π bonds. Triple bonds between carbon and nitrogen can be represented in a similar manner, C≡N.

For most organic molecules, double and triple bonds typically involve the first-row elements carbon, nitrogen, and oxygen.[14] Second-row elements tend to form weaker π bonds than do the first-row elements,[15] so multiple bonds are less common and compounds containing them are generally less stable.[16] Compounds with C=S bonds are known, for example, and C=S compounds are generally much less stable than the corresponding C=O compounds (however, see *pπ–dπ* bonding in Sec. 2.H). Stable compounds with Si=C and Si=Si bonds are rare, but examples have been reported,[17] including a pair of *cis* and *trans* Si=Si isomers.[18]

There is at least one report of a so-called two-electron, four-center C—C bond for the dimer of tetracyanoethylene.[19] While such multi-center bonding is not formally an example of the multiple bonding described in this section, it constitutes a different type of bonding when compared to the simple C—C bonds described earlier.

1.E. PHOTOELECTRON SPECTROSCOPY

Based on the hybridization model, methane is expected to have four equivalent σ bonds. Indeed, the four bonds of methane are equivalent according to most physical and chemical methods of detection. The *nuclear magnetic resonance* (NMR) and the *infrared* (IR) spectra of methane show *no* peaks that can be attributed to different kinds of C—H bonds. However, there is one physical technique that shows that the eight valence electrons of methane can be differentiated. In this technique, called *photoelectron spectroscopy* (PES),[20] a molecule or a free atom is bombarded with vacuum *ultraviolet* (UV) radiation, causing an electron to

[14] For a review of metal–metal multiple bonds, see Cotton, F.A. *J. Chem. Educ.* ***1983***, *60*, 713.

[15] For discussions, see Schmidt, M.W.; Truong, P.N.; Gordon, M.S. *J. Am. Chem. Soc.* ***1987***, *109*, 5217; Schleyer, P.v.R.; Kost, D. *J. Am. Chem. Soc.* ***1988***, *110*, 2105.

[16] For double bonds between carbon and elements other than C, N, S, or O, see Jutzi, P. *Angew. Chem. Int. Ed.* ***1975***, *14*, 232; Raabe, G.; Michl, J. *Chem. Rev.* ***1985***, *85*, 419 (Si only); Wiberg, N. *J. Organomet. Chem.* ***1984***, *273*, 141 (Si only); Gordon, M.S. *Mol. Struct. Energ.* ***1986***, *1*, 101. For reviews of C=P and C≡P bonds, see Regitz, M. *Chem. Rev.* ***1990***, *90*, 191; Appel, R.; Knoll, F. *Adv. Inorg. Chem.* ***1989***, *33*, 259; Markovski, L.N.; Romanenko, V.D. *Tetrahedron* ***1989***, *45*, 6019.

[17] For Si=C bonds, see Fink, M.J.; DeYoung, D.J.; West, R.; Michl, J. *J. Am. Chem. Soc.* ***1983***, *105*, 1070; Fink, M.J.; Michalczyk, M.J.; Haller, K.J.; West, R.; Michl, J. *Organometallics* ***1984***, *3*, 793; West, R. *Pure Appl. Chem.* ***1984***, *56*, 163; Masamune, S.; Eriyama, Y.; Kawase, T. *Angew. Chem. Int. Ed.* ***1987***, *26*, 584; Shepherd, B.D.; Campana, C.F.; West, R. *Heteroat. Chem.* ***1990***, *1*, 1.

[18] Michalczyk, M.J.; West, R.; Michl, J. *J. Am. Chem. Soc.* ***1984***, *106*, 821, *Organometallics* ***1985***, *4*, 826.

[19] Miller, J.S.; Novoa, J.J. *Acc. Chem. Res*. ***2007***, *40*, 189.

[20] See Ballard, R.E. *Photoelectron Spectroscopy and Molecular Orbital Theory*, Wiley, NY, ***1978***; Rabalais, J.W. *Principles of Ultraviolet Photoelectron Spectroscopy*, Wiley, NY, ***1977***; Baker, A.D.; Betteridge, D. *Photoelectron Spectroscopy*, Pergamon, Elmsford, NY, ***1972***; Turner, D.W.; Baker, A.D.; Baker, C.; Brundle, C.R. *High Resolution Molecular Photoelectron Spectroscopy*, Wiley, NY, ***1970***. For reviews, see Westwood, N.P.C. *Chem. Soc. Rev.* ***1989***, *18*, 317; Baker, C.; Brundle, C.R.; Thompson, M. *Chem. Soc. Rev.* ***1972***, *1*, 355; Bock, H.; Ramsey, B.G. *Angew. Chem. Int. Ed.* ***1973***, *12*, 734; Turner, D.W. *Adv. Phys. Org. Chem.* ***1966***, *4*, 31. For the IUPAC descriptive classification of various electron spectroscopy techniques, see Porter, H.Q.; Turner, D.W. *Pure Appl. Chem.* ***1987***, *59*, 1343.

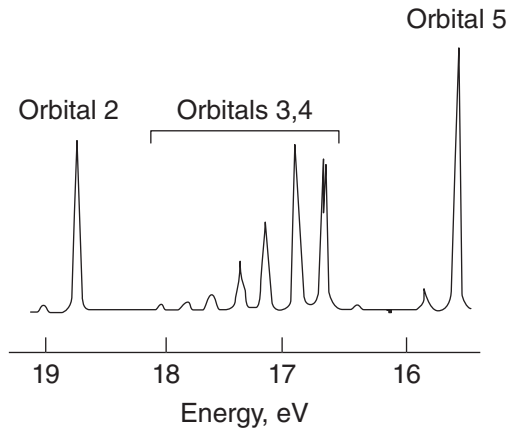


FIGURE 1.8. Photoelectron spectrum of N_2.[22] [Reprinted with permission from Brundle, C.R.; Robin M.B. in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods, Vol. 1*, Academic Press, NY, ***1971***, p. 18. Copyright © 1971, with permission of C. Richard Brundle, ***2012***.]

be ejected. The energy of the ejected electron can be measured, and the difference between the energy of the radiation used and that of the ejected electron is the *ionization potential* of that electron. A molecule that contains several electrons of differing energies can lose any one of them as long as its ionization potential is less than the energy of the radiation used. A single molecule loses only one electron; the loss of two electrons by any individual molecule almost never occurs. Since electrons reside in orbitals, a photoelectron spectrum consists of a series of bands, *each corresponding to an orbital of a different energy*. The spectrum gives a direct experimental picture of all orbitals that are present, and they are ejected in ascending order of their energies, provided that radiation of sufficiently high energy is used.[21] Broad bands usually correspond to strongly bonding electrons and narrow bands to weakly bonding or nonbonding electrons.

Using photoelectron spectroscopy, it is possible to probe the validity of the hybridization model for bonding. Dinitrogen, N_2, is a typical diatomic molecule and the photoelectron spectrum is shown in Figure 1.8.[22] The N_2 molecule has the electronic structure shown in Figure 1.9 using the VSPER model. In this model, the two 2*s* orbitals of the nitrogen atoms combine to give the two orbitals marked 1 (bonding) and 2 (antibonding), while the six 2*p* orbitals combine to give six orbitals, three of which (marked 3, 4, and 5) are bonding. The three antibonding orbitals (not shown in Figure 1.9) are unoccupied. Electrons ejected from orbital 1 are not found in Figure 1.8 because the ionization potential of these electrons is greater than the energy of the light used (they can be seen when higher-energy light is used). The broad band in Figure 1.8 corresponds to the four electrons in the degenerate orbitals 3 and 4. The individual peaks within this band are caused by different vibrational levels (see Chapter 7). The triple bond of N_2 is therefore composed of these two orbitals and orbital 1. The bands corresponding to orbitals 2 and 5 are narrow; hence these orbitals contribute little to the bonding and may be regarded as the two unshared pairs of N̈≡N̈. Note that this

[21] The correlation is not perfect, but the limitations do not seriously detract from the usefulness of the method. The technique is not limited to vacuum UV radiation. Higher energy radiation can also be used.

[22] From Brundle, C.R.; Robin, M.B., in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods, Vol. 3*, Academic Press, NY, ***1971***, p. 18.

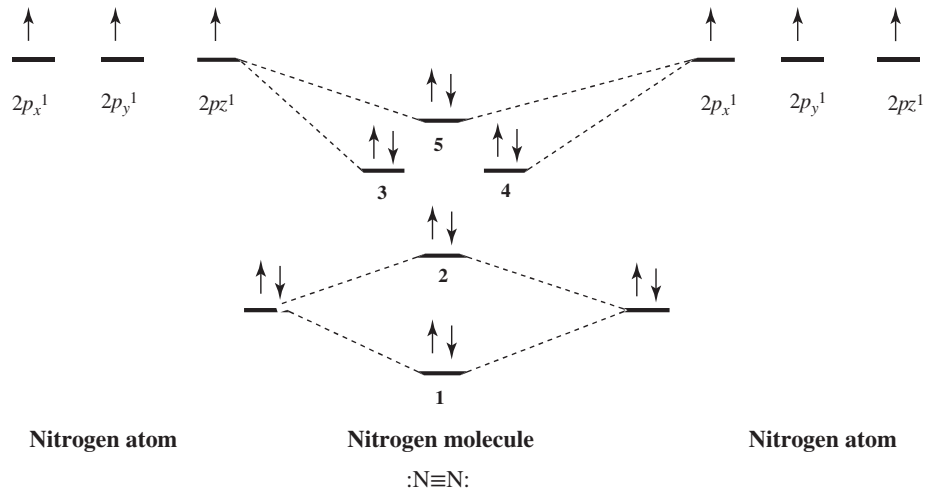


FIGURE 1.9. Electronic structure of N_2 (inner-shell electrons omitted).

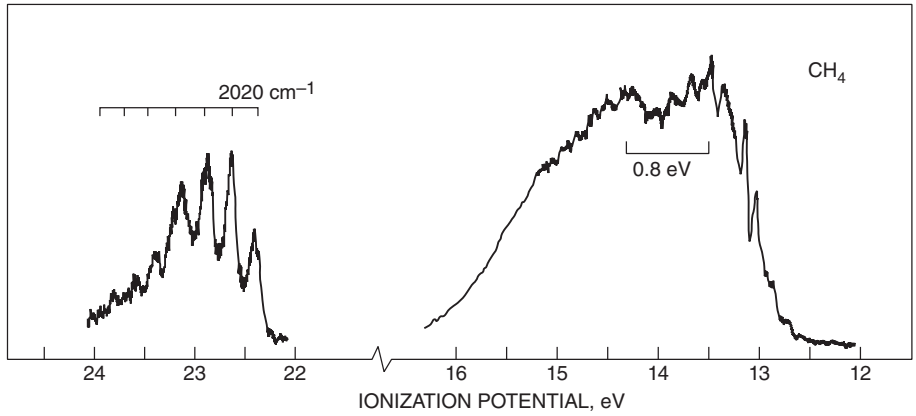


FIGURE 1.10. Photoelectron spectroscopy scan of methane.[23] [Reprinted with permission from Brundle, C.R.; Robin, M.B. *Journal of Chemical Physics* ***1970****, 53*, 2196. Copyright © 1970, American Institute of Physics.]

result is contrary to that expected from a naive consideration of orbital overlaps, where it would be expected that the two unshared pairs would be those of orbitals 1 and 2, resulting from the overlap of the filled 2*s* orbitals, and that the triple bond would be composed of orbitals 3, 4, and 5, resulting from overlap of the *p* orbitals. This example is one illustration of the value of photoelectron spectroscopy.

The photoelectron spectrum of methane[23] in Figure 1.10 shows two bands,[24] at ∼23 and 14 eV, and not the single band expected from the equivalency of the four C—H bonds. Indeed, Figure 1.10 suggests that carbon uses two available orbitals to form four bonds and

[23] Brundle, C.R.; Robin, M.B.; Basch, H. *J. Chem. Phys.* ***1970***, *53*, 2196; Baker, A.D.; Betteridge, D.; Kemp, N.R.; Kirby, R.E. *J. Mol. Struct.* ***1971***, *8*, 75; Potts, A.W.; Price, W.C. *Proc. R. Soc. London, Ser A* ***1972***, *326*, 165.
[24] A third band, at 290 eV, caused by the 1*s* electrons of carbon, can also be found if radiation of sufficiently high energy is used.

the electrons in the bonds are distributed between carbon and the four atoms involved in the bonds. Remember that the hybridization model predicts four identical σ bonds made by overlap of four identical hybrid orbitals. The band at 23 eV comes from two electrons in a low-energy level (called the a_1 level), which can be regarded as arising from a combination of the 2*s* orbital of carbon with an appropriate combination of hydrogen 1*s* orbitals. The band at 14 eV comes from six electrons in a triply degenerate level (the t_2 level), arising from a combination of the three 2*p* orbitals of carbon with other combinations of 1*s* hydrogen orbitals. As mentioned above, most physical and chemical processes cannot distinguish these levels, but photoelectron spectroscopy can. This spectrum suggests that the traditional sp^3 hybridization model does not explain phenomena involving ionized molecules (e.g., the $CH_4^{+\bullet}$ radical ion, which is left behind when an electron is ejected from methane). For these phenomena it is necessary to use other combinations of atomic orbitals (Sec. 1.C). Since methane is known to form a tetrahedral array of atoms about carbon, a different bonding model assumes that the four σ bonds are formed by the best overlap of *s* and *p* orbitals of carbon with the orbital of each of the four atoms approaching at the angles of a regular tetrahedron. Such tetrahedral approach of the atoms allows the 2*s* and all three 2*p* orbitals of carbon for overlap. Overlap with the available orbitals of the carbon atom will form the best bonds possible. The overlap of an atom with the 2*s* orbitals and all three 2*p* orbitals is consistent with the sp^3 hybrid description. Such a model is not real, of course, since an elemental carbon atom does not form bonds with four individual atoms to form a molecule in this manner. However, this model is an alternative to the hybridization model used for methane. The photoelectron spectra of many other organic molecules are known as well,[25] including monocyclic alkenes, in which bands <10 eV are due to π-orbital ionization and those >10 eV originate from ionization of σ orbitals only.[26]

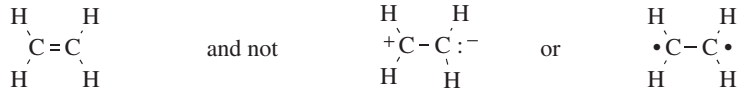
1.F. ELECTRONIC STRUCTURES OF MOLECULES

For each molecule, ion, or free radical that has only localized electrons, it is possible to draw an electronic formula, called a *Lewis structure*, which shows the location of these electrons. Only the valence electrons are shown. Valence electrons may be found in covalent bonds connecting two atoms or they may be unshared.[27] Drawing these structures correctly is essential, since the position of electrons changes in the course of a reaction, and it is necessary to know where the electrons are initially before one can follow where they are going. To this end, the following rules operate:

1. The total number of valence electrons in the molecule (or ion or free radical) must be the sum of all outer-shell electrons "contributed" to the molecule by each atom plus the negative charge or minus the positive charge, for the case of ions. Thus, for H_2SO_4, there are 2 (one for each hydrogen) +6 (for the sulfur) +24 (6 for each oxygen) = 32; while for SO_4^{2-}, the number is also 32, since each atom "contributes" 6 plus 2 for the negative charge.

[25] Robinson, J.W. *Practical Handbook of Spectroscopy*, CRC Press, Boca Raton, FL ***1991***, p. 178.
[26] Novak, I.; Potts, A.W. *Tetrahedron* ***1997***, *53*, 14713.
[27] It has been argued that although the Lewis picture of two electrons making up a covalent bond may work well for organic compounds, it cannot be successfully applied to the majority of inorganic compounds: Jørgensen, C.K. *Top. Curr. Chem.* ***1984***, *124*, 1.

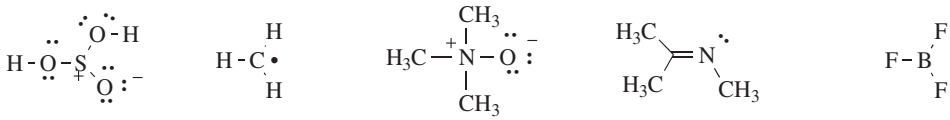
2. Once the number of valence electrons has been ascertained, it is necessary to determine which of them are found in covalent bonds and which are unshared. Unshared electrons (either a single electron or a pair) form part of the outer shell of just one atom, but electrons in a covalent bond are part of the outer shell of both atoms of the bond. *First-row atoms* (B, C, N, O, F) *can have a maximum of eight valence electrons*, and usually have this number, although some cases are known where a first-row atom has only six or seven. Where there is a choice between a structure that has six or seven electrons around a first-row atom and one in which all such atoms have an octet, the structure based on the octet is generally lower in energy and the one that is observed. For example, ethene is:



There are a few exceptions. For the molecule O_2, the structure Ȯ—Ȯ: has a lower energy than Ö═Ö:. Although first-row atoms are limited to eight valence electrons, this is not so for second-row atoms, which can accommodate 10 or even 12 because empty *d* orbitals may be utilized.[28] For example, PCl_5 and SF_6 are stable compounds, and the hybridization model can be used to explain this fact. In SF_6, one *s* electron and one *p* electron from the ground state $3s^2 3p^4$ of the sulfur are promoted to empty *d* orbitals, and the six orbitals hybridize to give six sp^3d^2 orbitals, which point to the corners of a regular octahedron.

3. It is customary to show the formal charge on each atom. For this purpose, an atom is considered to "own" all unshared electrons, but only *one-half of the electrons in covalent bonds*. The sum of electrons that thus "belong" to an atom is compared with the number "contributed" by the atom. An excess belonging to the atom results in a negative charge, and a deficiency results in a positive charge. The total of the formal charges on all atoms equals the charge on the whole molecule or ion. Note that the counting procedure is not the same for determining formal charge as for determining the number of valence electrons. For both purposes an atom "owns" all unshared electrons, but for outer-shell purposes it "owns" both the electrons of the covalent bond, while for formal-charge purposes it "owns" only one-half of these electrons.

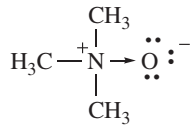
Examples of electronic structures are:



A coordinate-covalent bond (sometimes called a dative bond), represented by an arrow, is one in which both electrons come from the same atom; that is, the bond can be regarded as

[28] For a review concerning sulfur compounds with a valence shell larger than eight, see Salmond, W.G. *Q. Rev. Chem. Soc.* ***1968***, *22*, 235.

being formed by the overlap of an orbital containing two electrons with an empty orbital. Thus trimethylamine *N*-oxide would be represented:



For a coordinate-covalent bond the rule concerning formal charge is amended, so that both electrons count for the donor and neither for the recipient. Thus the nitrogen and oxygen atoms of trimethylamine *N*-oxide bear no formal charges. However, it is apparent that the electronic picture is exactly the same as the picture of trimethylamine *N*-oxide given just above, and there is a choice of drawing an arrowhead or a charge separation. Some compounds, for example, amine *N*-oxides, must be drawn one way or the other. It is usually simpler to use charge separation. It is noted that the electronic descriptions of molecules, especially complex molecules, is much more complicated, in large part due to the ultra-fast dynamics that characterize such molecules. One method has been developed, called attosecond electron dynamics,[29] and may allow the investigation and understanding of complex ultrafast dynamics in large molecular systems.

1.G. ELECTRONEGATIVITY

When two atoms are the same and have the same substituents, the electron cloud that bonds the two atoms is symmetrical (with respect to the plane that is the perpendicular bisector of the bond), but when two atoms are not the same, the electron cloud that bonds those two atoms is not symmetrical. In other words, a symmetrical electron cloud typically occurs when there is a bond between two identical atoms, and an unsymmetrical electron cloud occurs when there are two different atoms. When there are two different atoms, and one is more electronegative (the tendency of an atom to acquire electrons) than the other, the electron cloud is necessarily distorted toward the atom (nucleus plus electrons) that maintains the greater attraction for the cloud. This attraction is called *electronegativity*;[30] and it is greatest for atoms in the upper-right corner of the periodic table and lowest for atoms in the lower-left corner. Thus a bond between fluorine and carbon (C—F) shows distortion of the electron cloud associated with the bond toward the atom with the greater electronegativity. In other words, there is a higher probability of finding the electrons near the fluorine than near the carbon. Such a bond is said to be *polarized*, and the C—F bond is an example of a polarized covalent bond. The polarization gives the fluorine a partial negative charge (shown by the symbol $\delta-$) and the carbon a partial positive charge (shown by the symbol $\delta+$). This distortion of electron density is called an *induced dipole*.

A number of attempts have been made to set up quantitative tables of electronegativity that will indicate the direction and extent of electron-cloud distortion for a bond between any pair of atoms. The most popular of these scales, devised by Pauling, is based on bond energies (Sec. 1.L) of diatomic molecules. It is rationalized that if the electron distribution

[29] Nisoli, M.; Decleva, P.; Calegari, F.; Palacios, A.; Martín, F. *Chem. Rev.* ***2017***, *117*, 10760.

[30] For a collection of articles on this topic, see Sen, K.D.; Jørgensen, C.K. *Electronegativity* (Vol. 6 of *Structure and Bonding*); Springer, NY, ***1987***. For a review, see Batsanov, S.S. *Russ. Chem. Rev.* ***1968***, *37*, 332.

TABLE 1.1 Some group electronegativities relative to H = 2.176[31]

CH_3	2.472	CCl_3	2.666
CH_3CH_2	2.482	C_6H_5	2.717
CH_2Cl	2.538	CF_3	2.985
CBr_3	2.561	C≡N	3.208
$CHCl_2$	2.602	NO_2	3.421

Reprinted with permission from Inamoto, N.; Masuda, S. *Chem. Lett.* ***1982***, 1003. Copyright © 1982 The Chemical Society of Japan.

were symmetrical in a molecule A—B, the bond energy would be the mean of the energies of A—A and B—B, since in these cases the cloud must be undistorted. If the actual bond energy of A—B is higher than this (and it usually is), it is the result of the partial charges (the charges attract each other and make a stronger bond, which requires more energy to break). It is necessary to assign a value to one element arbitrarily (F = 4.0). Then the electronegativity of another is obtained from the difference between the actual energy of A—B and the mean of A—A and B—B (this difference is called Δ) by the formula:

$$x_A - x_B = \sqrt{\frac{\Delta}{23.06}}$$

where x_A and x_B are the electronegativities of the known and unknown atoms and 23.06 is an arbitrary constant. The electronegativities of several atoms have been calculated using the Pauling scale[32] and the Sanderson scale.[33] Using the Pauling scale, F = 4.0, O = 3.5, Cl and N = 3.0, Br = 2.8, S, I, and C = 2.5, and H and P = 2.1.

Other treatments[34] have led to scales that are based on different principles, for example, the average of the ionization potential and the electron affinity,[35] the average one-electron energy of valence-shell electrons in ground-state free atoms,[36] or the "compactness" of an atom's electron cloud.[28] In some of these treatments electronegativities can be calculated for different valence states, for different hybridizations (e.g., *sp* carbon atoms are more electronegative than sp^2, which are still more electronegative than sp^3),[37] and even differently for primary, secondary, and tertiary carbon atoms. Also, electronegativity values can be calculated for groups rather than atoms (Table 1.1).[38] A new descriptor Q has been described

[31] A magnetically anisotropic group is one that is not equally magnetized along all three axes. The most common such groups are benzene rings (Sec. 2.I) and triple bonds.

[32] Taken from Pauling, L. *The Nature of the Chemical Bond*, 3rd ed., Cornell University Press, Ithaca, NY, 1960, p. 93, except for the value for Na, which is from Sanderson, R.T. *J. Am. Chem. Soc.* ***1983***, *105*, 2259; *J. Chem. Educ.* ***1988***, *65*, 112, 223.

[33] See Sanderson, R.T. *J. Am. Chem. Soc.* ***1983***, *105*, 2259; *J. Chem. Educ.* ***1988***, *65*, 112, 223.

[34] See Huheey, J.E. *Inorganic Chemistry,* 3rd ed., Harper and Row, NY, ***1983***, pp. 146–148; Mullay, J., in Sen, K.D.; Jørgensen, C.K. *Electronegativity (*Vol. 6 of *Structure and Bonding*), Springer, NY, ***1987***, p. 9.

[35] Hinze, J.; Jaffé, H.H. *J. Am. Chem. Soc.* ***1962***, *84*, 540; Rienstra-Kiracofe, J.C.; Tschumper, G.S.; Schaefer III, H.F.; Nandi, S.; Ellison, G.B. *Chem. Rev.* ***2002***, *102*, 231.

[36] Allen, L.C. *J. Am. Chem. Soc.* ***1989***, *111*, 9003.

[37] Walsh, A.D. *Discuss. Faraday Soc.* ***1947***, *2*, 18; Bergmann, D.; Hinze, J., in Sen, K.D.; Jørgensen, C.K. *Electronegativity (*Vol. 6 of *Structure and Bonding*), Springer, NY, ***1987***, pp. 146–190.

[38] Inamoto, N.; Masuda, S. *Chem. Lett.* ***1982***, 1003. See also, Bratsch, S.G. *J. Chem. Educ.* ***1988***, *65*, 223; Mullay, J. *J. Am. Chem. Soc.* ***1985***, *107*, 7271; Zefirov, N.S.; Kirpichenok, M.A.; Izmailov, F.F.; Trofimov, M.I. *Dokl. Chem.* ***1987***, *296*, 440; Boyd, R.J.; Edgecombe, K.E. *J. Am. Chem. Soc.* ***1988***, *110*, 4182.

that when plotted versus the bond energy, separates nicely a wide variety of bonding types, covalent, polar and increasingly ionic, metallogenic, electrostatic, charge-shift bonds, and dispersion interactions.[39]

Electronegativity information can be obtained from NMR spectra. In the absence of a magnetically anisotropic group,[31] the chemical shift of a ^{1}H or a ^{13}C nucleus is approximately proportional to the electron density around it and hence to the electronegativity of the atom or group to which it is attached. The greater the electronegativity of the atom or group, the lower the electron density around the proton, and the further downfield the chemical shift (relative to tetramethylsilane, TMS, as zero ppm). An example of the use of this correlation is found in the variation of chemical shift of the *ring* protons in the series toluene, ethylbenzene, isopropylbenzene, *tert*-butylbenzene (there is a magnetically anisotropic group here, but its effect should be constant throughout the series). The electron density surrounding the ring protons decreases[40] in the order given.[41] However, this type of correlation is by no means perfect, since all the measurements are made in a powerful field, which itself may affect the electron density distribution. Coupling constants between the two protons of a system ─CH─CH─X have also been found to depend on the electronegativity of X.[42]

When the difference in electronegativity between two atoms is great, the electron density in an orbital may be effectively localized on only one nucleus. Such a bond is called an *ionic bond*, which arises naturally out of the previous discussion. It is possible to view polarized covalent bonds as intermediate between ionic and covalent. With this view, the extent of electron-cloud distortion is expressed as the percent ionic character of a bond. In this model, there is a continuous gradation from ionic to covalent bonds.

1.H. DIPOLE MOMENT

The *dipole moment* is a property of a molecule that results from charge separations like those discussed above. However, it is not possible to measure the dipole moment of an individual bond within a molecule. Only the total moment of the molecule may be measured, and it is the vectorial sum of the individual bond moments.[43] These individual moments are roughly the same from molecule to molecule,[44] but this constancy is by no means universal. Thus, from the dipole moments of toluene and nitrobenzene (Figure 1.11)[45] the moment of *p*-nitrotoluene is predicted to be ~4.36 D. The actual value of 4.39 D is reasonable. However, the moment of *p*-cresol (1.57 D) is different from the predicted value of 1.11 D. In

[39] Rahm, M.; Hoffmann, R. *J. Am. Chem. Soc.* ***2016***, *138*, 3731.

[40] This order is opposite to that expected from the field effect (Sec. 1.I). It is an example of the *Baker–Nathan order* (Sec. 2.M).

[41] Moodie, R.B.; Connor, T.M.; Stewart, R. *Can. J. Chem.* ***1960***, *38*, 626.

[42] Williamson, K.L. *J. Am. Chem. Soc.* ***1963***, *85*, 516; Laszlo, P.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1963***, *85*, 2709; Niwa, J. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2192.

[43] See Exner, O. *Dipole Moments in Organic Chemistry*, Georg Thieme Publishers, Stuttgart, ***1975***; McClellan, A.L. *Tables of Experimental Dipole Moments*, Vol. 1, W.H. Freeman, San Francisco, ***1963***, Vol. 2, Rahara Enterprises, El Cerrito, CA, ***1974***.

[44] For example, see Koudelka, J.; Exner, O. *Collect. Czech. Chem. Commun.* ***1985***, *50*, 188, 200.

[45] The values for toluene, nitrobenzene, and *p*-nitrotoluene are from MacClellan, A.L. *Tables of Experimental Dipole Moments*, Vol. 1, W.H. Freeman, San Francisco, ***1963***; Vol. 2, Rahara Enterprises, El Cerrito, CA, ***1974***. The values for phenol and *p*-cresol were determined by Goode, E.V.; Ibbitson, D.A. *J. Chem. Soc.* ***1960***, 4265.

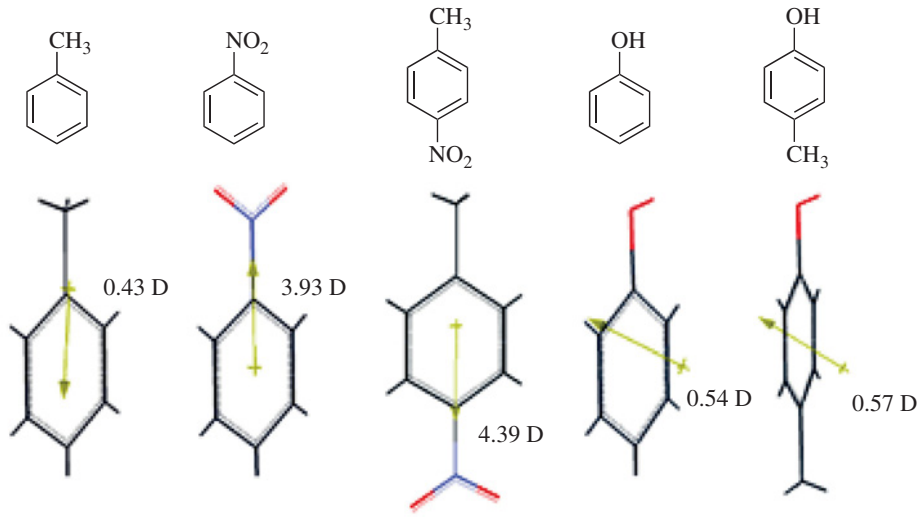


FIGURE 1.11. Some dipole moments, in Debye units, measured in benzene. In each 3D model, the arrow indicates the direction of the dipole moment for the molecule, pointing to the negative pole.[47]

some cases, molecules may have substantial individual bond moments but no total moments at all because the individual moments are canceled out by the overall symmetry of the molecule. Some examples are CCl_4, *trans*-1,2-dibromoethene, and *p*-dinitrobenzene.

Because of the small difference between the electronegativities of carbon and hydrogen, alkanes have very small dipole moments, so small that they are difficult to measure. For example, the dipole moment of isobutane is 0.132 D[46] and that of propane is 0.085 D.[47] Of course, methane and ethane, because of their symmetry, have no dipole moments.[48] It is known that simple alkanes with more highly branched carbon skeletons are more stable than their straight-chain isomers.[49] Few organic molecules have dipole moments >7 D. The most polar compound that has been reported is 5,6-diaminobenzene-1,2,3,4-tetracarbonitrile, which has a measured dipole moment of 14.1 D.[50]

1.I. INDUCTIVE AND FIELD EFFECTS

The C—C bond in ethane has no polarity because it connects two equivalent atoms with identical electronegativities. The presence of a more electronegative atom attached to one of the carbon atoms will lead to bond polarization however, in what is known as an *induced*

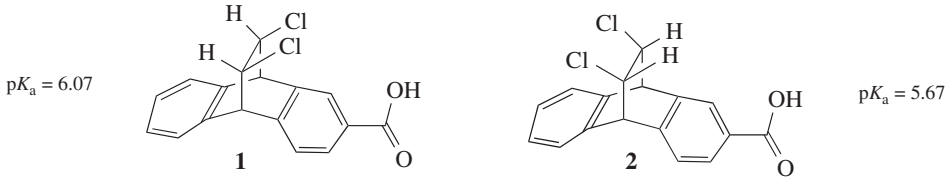
[46] Lide Jr., D.R.; Mann, D.E. *J. Chem. Phys.* ***1958***, *29*, 914.
[47] Muenter, J.S.; Laurie, V.W. *J. Chem. Phys.* ***1966***, *45*, 855.
[48] Actually, symmetrical tetrahedral molecules like methane do have extremely small dipole moments, caused by centrifugal distortion effects; these moments are so small that they can be ignored for all practical purposes. For CH_4 μ is $\sim 5.4 \times 10^{-6}$ D: Ozier, I. *Phys. Rev. Lett.* ***1971***, *27*, 1329; Rosenberg, A.; Ozier, I.; Kudian, A.K. *J. Chem. Phys.* ***1972***, *57*, 568.
[49] McKee, W.C.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***2013***, *135*, 13008.
[50] Wudarczyk, J.; Papamokos, G.; Margaritis, V.; Schollmeyer, D.; Hinkel, F.; Baumgarten, M.; Floudas, G.; Mîllen, K. *Angew. Chem. Int. Ed.* ***2016***, *55*, 3220.

dipole (Sec. 1.G). The C—C bond in chloroethane, for example, is polarized by the presence of the electronegative chlorine atom.

$$^{2}\overset{\delta+}{CH_3} \rightarrow {}^{1}\overset{\delta+}{CH_3} \longrightarrow \longrightarrow \overset{\delta-}{Cl}$$

This polarization is actually the sum of two effects. In the first of these, the C-1 atom is deprived of some of its electron density by the greater electronegativity of Cl, and this effect is partially compensated by drawing the C—C electrons closer to itself. The result is a polarization of the C—C bond and a slightly positive charge on the C-2 atom: an induced dipole. This polarization of one bond caused by the polarization of an adjacent bond is known as an *inductive effect*. The effect is greatest for adjacent bonds but may also be felt farther away; thus the polarization of the C—C bond causes a (slight) polarization of the three methyl C—H bonds. As a practical matter, the effect is negligible if the polarizing group is more than three bonds away.

The other effect operates not through bonds, but directly through space or solvent molecules, and is called a *field effect*.[51] It is often very difficult to separate the two kinds of effect, but a number of cases have been reported, generally by taking advantage of the fact that the field effect depends on the geometry of the molecule but the inductive effect depends only on the nature of the bonds. For example, in isomers **1** and **2**[52] the inductive effect of the chlorine atoms on the position of the electrons in the COOH group (and hence on the acidity, see Chapter 8) should be the same since the same bonds intervene. The field effect is different, however, because the chlorine atoms are closer in space to the COOH in **1** than they are in **2**. Thus, a comparison of the acidity of **1** and **2** should reveal whether a field effect is truly operating. The evidence obtained from such experiments is overwhelming that field effects are much more important than inductive effects.[53] In most cases, the two types of effect are considered together; in this book, they will not be separated but will use the name *field effect* to refer to their combined action.[54] Note that the field effect for **1** may be viewed as internal hydrogen bonding (Sec. 3.A).



Functional groups can be classified as electron-withdrawing (−*I*) or electron-donating (+*I*) groups relative to hydrogen. This means, for example, that NO_2, a −*I* group, will draw

[51] Roberts, J.D.; Moreland, Jr., W.T. *J. Am. Chem. Soc.* ***1953***, *75*, 2167.

[52] See Grubbs, E.J.; Fitzgerald, R.; Phillips, R.E.; Petty, R. *Tetrahedron* ***1971***, *27*, 935.

[53] See Schneider, H.; Becker, N. *J. Phys. Org. Chem.* ***1989***, *2*, 214; Bowden, K.; Ghadir, K.D.F. *J. Chem. Soc., Perkin Trans. 2* ***1990***, 1333. Also see Exner, O.; Fiedler, P. *Collect. Czech. Chem. Commun.* ***1980***, *45*, 1251; Li, Y.; Schuster, G.B. *J. Org. Chem.* ***1987***, *52*, 3975.

[54] There has been some question as to whether it is even meaningful to maintain the distinction between the two types of effect: see Grob, C.A. *Helv. Chim. Acta* ***1985***, *68*, 882; Lenoir, D.; Frank, R.M. *Chem. Ber.* ***1985***, *118*, 753; Sacher, E. *Tetrahedron Lett.* ***1986***, *27*, 4683.

TABLE 1.2[55] **Field effects of various groups relative to hydrogen**[a]

$+I$		$-I$	
O^-	NR_3^+	COOH	OR
COO^-	SR_2^+	F	COR
CR_3	NH_3^+	Cl	SH
CHR_2	NO_2	Br	SR
CH_2R	SO_2R	I	OH
CH_3	CN	OAr	C≡CR
D	SO_2Ar	COOR	Ar
			C≡CR

[a]The groups are listed approximately in order of decreasing strength for both $-I$ and $+I$ groups.

electrons to itself more than a hydrogen atom would if it occupied the same position in the molecule.

$$O_2N \longleftarrow \longleftarrow CH_2 \longleftarrow Ph$$
$$H{-}CH_2{-}Ph$$

Thus, in α-nitrotoluene, the electrons in the N—C bond are farther away from the carbon atom than the electrons in the H—C bond of toluene. Similarly, the electrons of the C—Ph bond are farther away from the ring in α-nitrotoluene than they are in toluene. Field effects are always comparison effects. For example, we compare the $-I$ or $+I$ effect of one group with another (usually hydrogen). Therefore, it may be said that, compared with hydrogen, the NO_2 group is electron withdrawing and the O^- group is electron donating or electron releasing. However, there is no actual donation or withdrawal of electrons but rather electron distortion or electron redistribution. While "withdrawing" and "releasing" terms are convenient to use, the terms merely represent a difference in the position of electrons due to the difference in electronegativity between H and NO_2 or between H and O^-.

Table 1.2 lists a number of the most common $-I$ and $+I$ groups.[56] It can be seen that, compared with hydrogen, most groups are electron withdrawing. The only electron-donating groups are those with a formal negative charge (but not even all of these) and atoms of low electronegativity (Si,[57] Mg, etc., and perhaps alkyl groups). Alkyl groups[55] were formerly regarded as electron donating, but many examples of behavior have been found that can be interpreted only by the conclusion that alkyl groups are electron withdrawing compared with hydrogen.[58] In accord with this is the value of 2.472 for the group electronegativity of CH_3 (Table 1.1) compared with 2.176 for H. When an alkyl group is attached to an unsaturated or trivalent carbon (or other atom), its behavior is best explained by assuming it is $+I$ (e.g., Secs. 5.A.ii, 5.B.i, 8.E, and 11.B.i), but when an alkyl group is connected to a

[55] See Levitt, L.S.; Widing, H.F. *Prog. Phys. Org. Chem.* ***1976***, *12*, 119. See Tandon, R.; Tobias, A. Nigst, T.A.; Zipse, H. *Eur. J. Org. Chem.* ***2013***, 5423.

[56] See also, Ceppi, E.; Eckhardt, W.; Grob, C.A. *Tetrahedron Lett.* ***1973***, 3627.

[57] For a review of field and other effects of silicon-containing groups, see Bassindale, A.R.; Taylor, P.G., in Patai, S.; Rappoport, Z. *The Chemistry of Organic Silicon Compounds*, pt. 2, Wiley, NY, ***1989***, pp. 893–963.

[58] See Sebastian, J.F. *J. Chem. Educ.* ***1971***, *48*, 97.

saturated atom, the results are not as clear, and alkyl groups seem to be $+I$ in some cases and $-I$ in others[59] (see also, Sec. 8.F). When connected to a positive carbon, alkyl groups are clearly electron releasing.

It is clear that the field-effect order of alkyl groups attached to unsaturated systems is tertiary > secondary > primary > CH_3, but this order is not always maintained when the groups are attached to saturated systems. Deuterium is electron donating with respect to hydrogen.[60] Other things being equal, atoms with *sp* bonding generally have a greater electron-withdrawing power than those with sp^2 bonding, which in turn have more electron-withdrawing power than those with sp^3 bonding.[61] This observation accounts for the fact that aryl, vinylic, and alkynyl groups are $-I$. Field effects always decrease with increasing distance, and in most cases (except when a very powerful $+I$ or $-I$ group is involved), cause very little difference in a bond four bonds away or more. There is evidence that field effects can be affected by the solvent.[62]

For discussions of field effects on acid and base strength and on reactivity, see Chapters 8 and 9, respectively.

1.J. BOND DISTANCES[63]

The distances between atoms in a molecule are characteristic properties of the molecule and can give information if compared with the same bond in different molecules. The chief methods of determining bond distances and angles are X-ray diffraction (only for solids), electron diffraction (only for gases), and spectroscopic methods, especially microwave spectroscopy. The distance between the atoms of a bond is not constant since the molecule is always vibrating. The measurements obtained are therefore average values, so that different methods give different results.[64] However, this must be taken into account only when fine distinctions are made.

Measurements vary in accuracy, but indications are that similar bonds have fairly constant lengths from one molecule to the next. While exceptions are known,[65] the variation is generally less than 1%. Table 1.3 shows distances for single bonds between two sp^3 carbons. However, an analysis of C—OR bond distances in >2000 ethers and carboxylic esters

[59] See Wahl Jr., G.H.; Peterson Jr., M.R. *J. Am. Chem. Soc.* ***1970***, *92*, 7238; Minot, C.; Eisenstein, O.; Hiberty, P.C.; Anh, N.T. *Bull. Soc. Chim. Fr.* ***1980***, II-119.

[60] Streitwieser Jr., A.; Klein, H.S. *J. Am. Chem. Soc.* ***1963***, *85*, 2759.

[61] Bent, H.A. *Chem. Rev.* ***1961***, *61*, 275, p. 281.

[62] See Laurence, C.; Berthelot, M.; Lucon, M.; Helbert, M.; Morris, D.G.; Gal, J. *J. Chem. Soc., Perkin Trans. 2* ***1984***, 705.

[63] For tables of bond distances and angles, see Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* ***1987***, S1–S19 (follows p. 1914); Tables of Interatomic Distances and Configurations in Molecules and Ions *Chem. Soc. Spec. Publ.* No. 11, ***1958***; Interatomic Distances Supplement *Chem. Soc. Spec. Publ*. No. 18, ***1965***; Harmony, M.D.; Laurie, V.W.; Kuczkowski, R.L.; Schwendeman, R.H.; Ramsay, D.A.; Lovas, F.J.; Lafferty, W.J.; Maki, A.G. *J. Phys. Chem. Ref. Data* ***1979***, *8*, 619–721. See Lathan, W.A.; Curtiss, L.A.; Hehre, W.J.; Lisle, J.B.; Pople, J.A. *Prog. Phys. Org. Chem.* ***1974***, *11*, 175; Topsom, R.D. *Prog. Phys. Org. Chem.* ***1987***, *16*, 85.

[64] Burkert, U.; Allinger, N.L. *Molecular Mechanics*, ACS Monograph 177, American Chemical Society, Washington, ***1982***, pp. 6–9; Whiffen, D.H. *Chem. Ber.* ***1971***, *7*, 57–61; Stals, J. *Rev. Pure Appl. Chem.* ***1970***, *20*, 1 (pp. 2–5).

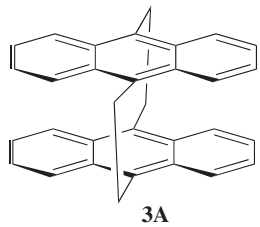
[65] Schleyer, P.v.R.; Bremer, M. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1226.

TABLE 1.3 Bond lengths between sp^3 carbons in some compounds

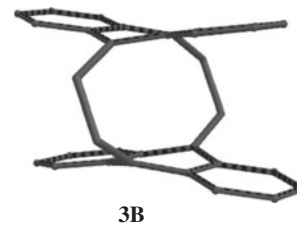
C—C Bond in	Reference	Bond Length (Å)
Diamond	66	1.544
C_2H_6	67	1.5324 ± 0.0011
C_2H_5Cl	68	1.5495 ± 0.0005
C_3H_8	69	1.532 ± 0.003
Cyclohexane	70	1.540 ± 0.015
tert-Butyl chloride	71	1.532
n-Butane to *n*-heptane	72	1.531–1.534
Isobutane	73	1.535 ± 0.001

Reprinted with permission from Ceppi, E.; Eckhardt, W.; Grob, C.A. *Tetrahedron Lett.* ***1973***, 3627, Copyright © 1973, with permission from Elsevier Science.

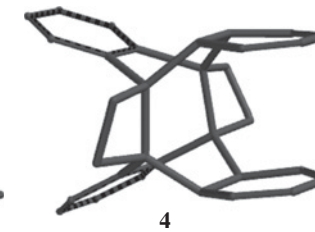
(all with sp^3 carbons) shows that this distance increases with increasing electron withdrawal in the R group and as the C changes from primary to secondary to tertiary.[74] For these compounds, mean bond lengths of the various types ranged from 1.418 to 1.475 Å. Certain substituents can also influence bond length. The presence of a silyl substituent β to a C—O (ester) linkage can lengthen the C—O, thereby weakening it.[75] This is believed to result from σ–σ* interactions in which the C—Si σ bonding orbital acts as the donor and the C—O σ* orbitals acts as the receptor.



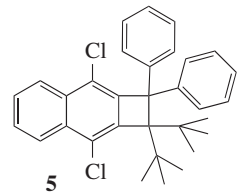
3A



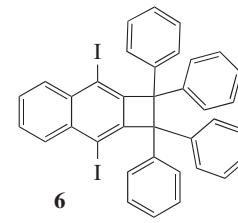
3B



4



5



6

[66] Lonsdale, K. *Phil. Trans. R. Soc. London* ***1947***, *A240*, 219.
[67] Bartell, L.S.; Higginbotham, H.K. *J. Chem. Phys.* ***1965***, *42*, 851.
[68] Wagner, R.S.; Dailey, B.P. *J. Chem. Phys.* ***1957***, *26*, 1588.
[69] Iijima, T. *Bull. Chem. Soc. Jpn.* ***1972***, *45*, 1291.
[70] For tables of interatomic distances, see ref. 63.
[71] Momany, F.A.; Bonham, R.A.; Druelinger, M.L. *J. Am. Chem. Soc.* ***1963***, *85*, 3075. Also see, Lide Jr., D.R.; Jen, M. *J. Chem. Phys.* ***1963***, *38*, 1504.
[72] Bonham, R.A.; Bartell, L.S.; Kohl, D.A. *J. Am. Chem. Soc.* ***1959***, *81*, 4765.
[73] Hilderbrandt, R.L.; Wieser, J.D. *J. Mol. Struct.* ***1973***, *15*, 27.
[74] Allen, F.H.; Kirby, A.J. *J. Am. Chem. Soc.* ***1984***, *106*, 6197; Jones, P.G.; Kirby, A.J. *J. Am. Chem. Soc.* ***1984***, *106*, 6207.
[75] White, J.M.; Robertson, G.B. *J. Org. Chem.* ***1992***, *57*, 4638.

Bond distances for some important bond types are given in Table 1.4.[76] Although a typical C—C single bond has a bond length of ~1.54 Å, certain molecules are known that have significantly longer bond lengths.[77] Calculations have been done for unstable molecules

TABLE 1.4[76] Bond distances[a]

Bond Type	Length, Å	Typical Compounds
C—C		
sp^3–sp^3	1.53	
sp^3–sp^2	1.51	Acetaldehyde, toluene, propene
sp^3–sp	1.47	Acetonitrile, propyne
sp^2–sp^2	1.48	Butadiene, glyoxal, biphenyl
sp^2–sp	1.43	Acrylonitrile, vinylacetylene
sp–sp	1.38	Cyanoacetylene, butadiyne
C═C		
sp^2–sp^2	1.32	Ethylene
sp^2–sp	1.31	Ketene, allenes
sp–sp[78]	1.28	Butatriene, carbon suboxide
C≡C[79]		
sp–sp	1.18	Ethyne
C—H[80]		
sp^3–**H**	1.09	Methane
sp^2–**H**	1.08	Benzene, ethene
sp–**H**[81]	1.08	HCN, ethyne
C—O		
sp^3–**O**	1.43	Dimethyl ether, ethanol
sp^2–**O**	1.34	Formic acid
C═O		
sp^2–**O**	1.21	Formaldehyde, formic acid
sp–**O**[71]	1.16	CO_2
C—N		
sp^3–**N**	1.47	Methylamine
sp^2–**N**	1.38	Formamide
C═N		
sp^2–**N**	1.28	Oximes, imines
C≡N		
sp–**N**	1.14	HCN
C—S		
sp^3–**S**	1.82	Methanethiol
sp^2–**S**	1.75	Diphenyl sulfide
sp–**S**	1.68	CH_3SCN
C═S		
sp–**S**	1.67	CS_2

[76] Except where noted, values are from Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* ***1987***, S1–S19 (follows p. 1914). In this source, values are given to three significant figures.

[77] Kaupp, G.; Boy, J. *Angew. Chem. Int. Ed.* ***1997***, *36*, 48.

[78] Costain, C.C.; Stoicheff, B.P. *J. Chem. Phys.* ***1959***, *30*, 777.

[79] For a full discussion of alkyne bond distances, see Simonetta, M.; Gavezzotti, A., in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, Wiley, NY, ***1978***.

[80] See Henry, B.R. *Acc. Chem. Res.* ***1987***, *20*, 429.

[81] Bartell, L.S.; Roth, E.A.; Hollowell, C.D.; Kuchitsu, K.; Young Jr., J.E. *J. Chem. Phys.* ***1965***, *42*, 2683.

TABLE 1.4 (*Continued*)

C–halogen[82]	F	Cl	Br	I
sp^3–halogen	1.40	1.79	1.97	2.16
sp^2–halogen	1.34	1.73	1.88	2.10
sp–halogen	1.27[83]	1.63	1.79[84]	1.99[84]

[a]The values given are average lengths and do not necessarily apply exactly to the compounds mentioned.[84] Reproduced from Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1987***, S1–S19 with permission from the Royal Society of Chemistry.

that showed them to have long bond lengths, and an analysis of the X-ray structure for a photoisomer (**4**) of [2.2]-tetrabenzoparacyclophane, **3A** (also see Sec. 2.G), showed a C—C bond length of 1.77 Å.[85,86] Note that **3A** is shown as the molecular model **3B** for comparison with photoisomer **4**, which has the two four-membered ring moieties. Long bond lengths have been observed in stable molecules such as benzocyclobutane derivatives.[86] A bond length of 1.729 Å was reliably measured in 1,1-di-*tert*-butyl-2,2-diphenyl-3,8-dichlorocyclobutan[*b*]naphthalene, **5**.[87] X-ray analysis of several of these derivations confirmed the presence of long C—C bonds, with **6** having a confirmed bond length of 1.734 Å.[88]

A theoretical study has been reported, using computer simulation to apply encapsulation, strapping back, and stiffening to "squeeze" C—C bonds, leading to shorter bonds than would be observed if hybridization and conjugative effects operated alone.[89] The additional strain caused by threefold symmetric geometry constraints is believed responsible for this effect rather than changes in hybridization alone, as postulated by others.[90]

There are indications that a C—D bond is slightly shorter than a corresponding C—H bond. Thus, electron-diffraction measurements of C_2H_6 and C_2D_6 showed a C—H bond distance of 1.1122 ± 0.0012 Å and a C—D distance of 1.1071 ± 0.0012 Å.[81]

As seen in Table 1.4, carbon bonds are shortened by increasing *s* character. This is most often explained by the fact that, as the percentage of *s* character in a hybrid orbital increases, the orbital becomes more like an *s* orbital and hence is held more tightly by the nucleus than an orbital with less *s* character. However, other explanations have also been offered (Sec. 2.C), and the matter is not completely settled. In general, molecules with one π bond (X═X) have shorter bond distances when compared to single bonds (X—X), and molecules with two π bonds (X≡X) have even shorter bond lengths. Indeed, the bond length clearly decreases in the molecules $H_3C—CH_3$, $H_2C═CH_2$, and HC≡CH, with C—C bond lengths

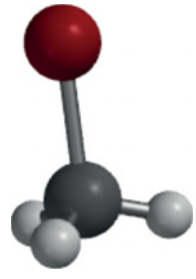
[82] For reviews of carbon–halogen bonds, see Trotter, J., in Patai, S. *The Chemistry of the Carbon–Halogen Bond, pt. 1*; Wiley, NY, ***1973***, pp. 49–62; Mikhailov, B.M. *Russ. Chem. Rev.* ***1971***, *40*, 983.
[83] Lide Jr., D.R. *Tetrahedron* ***1962***, *17*, 125.
[84] Rajput, A.S.; Chandra, S. *Bull. Chem. Soc. Jpn.* ***1966***, *39*, 1854.
[85] Ehrenberg, M. *Acta Crystallogr.* ***1966***, *20*, 182.
[86] Toda, F.; Tanaka, K.; Stein, Z.; Goldberg, I. *Acta Crystallogr., Sect. C* ***1996***, *52*, 177.
[87] Toda, F.; Tanaka, K.; Watanabe, M.; Taura, K.; Miyahara, I.; Nakai, T.; Hirotsu, K. *J. Org. Chem.* ***1999***, *64*, 3102.
[88] Tanaka, K.; Takamoto, N.; Tezuka, Y.; Kato, M.; Toda, F. *Tetrahedron* ***2001***, *57*, 3761.
[89] Huntley, D.R.; Markopoulos, G.; Donovan, P.M.; Scott, L.T.; Hoffmann, R. *Angew. Chem. Int. Ed.* ***2005***, *44*, 7549.
[90] See Tanaka, M.; Sekiguchi, A. *Angew. Chem. Int. Ed.* ***2005***, *44*, 5821.

of 1.538 Å, 1.338 Å, and 1.203 Å.[91] There is work that suggests the absence of σ bonds may play a role in producing short bond distances in molecules that contain only π bonds.[92] This suggests that σ bonds prevent π bonds from adopting their optimal shorter distances. Such bonds occur in some organometallic compounds.

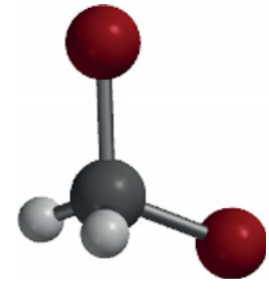
1.K. BOND ANGLES

The bond angles of sp^3 carbon should be the tetrahedral angle 109°28′ when the four atoms or groups are relatively small and identical, as in methane, neopentane, or carbon tetrachloride (Sec. 1.E). As atoms or groups become larger, bond angles are distorted to accommodate the larger size of the attached units. In most cases the angles deviate only a little from the pure tetrahedral value unless two or more units are very large. Molecular models **7–9** illustrate this phenomenon. The H—C—H bond angles in methane (**7**) are calculated for the model to be 109.47°, whereas the Br—C—H bond angle in **8** is calculated to be 108.08° and the Br—C—Br bond angle in **9** is calculated to be 113.38°. Note that the C—Br bond length is longer than the C—H bond lengths. As the bond angles expand to accommodate the larger atoms, the H—C—H bond angles in **8** and **9** must compress to a smaller angle. In 2-bromopropane, the methyl group can be compared with a H atom in bromomethane (**8**), so methyl replaces H, and the C—C—Br angle is 114.2°.[93]

7



8



9

Variations are generally found from the ideal values of 120° and 180° for sp^2 and *sp* carbons, respectively. These deviations occur because of slightly different hybridizations, that is, a carbon bonded to four other atoms hybridizes one *s* and three *p* orbitals, but the four hybrid orbitals thus formed are generally not exactly equivalent, nor does each contain exactly 25% *s* and 75% *p* character. Because the four atoms have (in the most general case) different electronegativities, each makes its own demand for electrons from the carbon atom.[94] The carbon atom supplies more *p* character when it is bonded to more electronegative atoms, so that in chloromethane, for example, the bond to chlorine has somewhat more than 75% *p* character, which of course requires that the other three bonds have somewhat less, since there are only three *p* orbitals (and one *s*) to be divided among the four hybrid

[91] Vannes, G.J.H.; Vos, A. *Acta Crystallogr. Sect. B* ***1978***, *B34*, 1947; Vannes, G.J.H.; Vos, A. *Acta Crystallogr. Sect. B* ***1979***, *B35*, 2593; McMullan, R.K.; Kvick, A. *Acta Crystallogr. Sect. B* ***1992***, *B48*, 726.
[92] Jemmis, E.D.; Pathak, B.; King, R.B.; Schaefer III, H.F. *Chem. Commun.* ***2006***, 2164.
[93] Schwendeman, R.H.; Tobiason, F.L. *J. Chem. Phys.* ***1965***, *43*, 201.
[94] For a review of this concept, see Bingel, W.A.; Lüttke, W. *Angew. Chem. Int. Ed.* ***1981***, *20*, 899.

TABLE 1.5 Oxygen, sulfur, and nitrogen bond angles in some compounds

Angle	Value	Compound	Ref.
H—O—H	104°27′	Water	9
C—O—H	107–109°	Methanol	70
C—O—C	111°43′	Dimethyl ether	95
C—O—C	124° ± 5°	Diphenyl ether	96
H—S—H	92.1°	Hydrogen sulfide	84
C—S—H	99.4°	Methanethiol	84
C—S—C	99.1°	Dimethyl sulfide	97
H—N—H	106°46′	Ammonia	9
H—N—H	106°	Methylamine	98
C—N—H	112°	Methylamine	91
C—N—C	108.7°	Trimethylamine	99

Reproduced from Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1972***, S1–S19 with permission from the Royal Society of Chemistry.

orbitals.[100] Of course, in strained molecules, such as **3–6**, the bond angles may be greatly distorted from the ideal values (also see Sec. 4.Q).

For molecules that contain oxygen and nitrogen, angles of 90° are predicted from p^2 bonding. However, as seen in Section 1.B, the angles of water and ammonia are much larger than this, as are the angles of other organic molecules that contain oxygen and nitrogen (Table 1.5). In fact, they are much closer to the tetrahedral angle of 109°28′ than to 90°. These facts have led to the suggestion that in these compounds oxygen and nitrogen use sp^3 bonding. Using the hybridization model, these atoms are said to form bonds by the overlap of two (or three) *p* orbitals with 1*s* orbitals of the hydrogen atoms, which means that they hybridize their 2*s* and 2*p* orbitals to form four sp^3 orbitals and then use only two (or three) of these for bonding with hydrogen, with the others remaining occupied by unshared pairs (also called *lone pairs*). If this description is valid, and it is generally accepted by most chemists today,[101] it becomes necessary to explain why the angles of these two compounds are in fact not 109°28′ but a few degrees smaller. One explanation that has been offered is that the unshared electron pair actually has a greater steric requirement (Sec. 4.Q) than the electrons in a bond, since there is no second nucleus to draw away some of the electron density and the bonds are thus crowded together. However, most evidence is that unshared pairs have smaller steric requirements than bonds[102] and the explanation

[95] Blukis, V.; Kasai, P.H.; Myers, R.J. *J. Chem. Phys.* ***1963***, *38*, 2753.
[96] Abrahams, S.C. *Q. Rev. Chem. Soc.* ***1956***, *10*, 407.
[97] Iijima, T.; Tsuchiya, S.; Kimura, M. *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 2564.
[98] Lide, Jr., D.R. *J. Chem. Phys.* ***1957***, *27*, 343.
[99] Lide, Jr., D.R.; Mann, D.E. *J. Chem. Phys.* ***1958***, *28*, 572.
[100] This assumption has been challenged: see Pomerantz, M.; Liebman, J.F. *Tetrahedron Lett*. ***1975***, 2385.
[101] An older theory holds that the bonding is indeed p^2, and that the increased angles come from repulsion of the hydrogen or carbon atoms. See Laing, M. *J. Chem. Educ.* ***1987***, *64*, 124.
[102] See Blackburne, I.D.; Katritzky, A.R.; Takeuchi, Y. *Acc. Chem. Res.* ***1975***, *8*, 300; Aaron, H.S.; Ferguson, C.P. *J. Am. Chem. Soc.* ***1976***, *98*, 7013; Anet, F.A.L.; Yavari, I. *J. Am. Chem. Soc.* ***1977***, *99*, 2794; Vierhapper, F.W.; Eliel, E.L. *J. Org. Chem.* ***1979***, *44*, 1081; Gust, D.; Fagan, M.W. *J. Org. Chem.* ***1980***, *45*, 2511. For other views, see Lambert, J.B.; Featherman, S.I. *Chem. Rev.* ***1975***, *75*, 611; Breuker, K.; Kos, N.J.; van der Plas, H.C.; van Veldhuizen, B. *J. Org. Chem.* ***1982***, *47*, 963.

most commonly accepted is that the hybridization is not pure sp^3. As seen above, an atom supplies more *p* character when it is bonded to more electronegative atoms. An unshared pair may be considered to be an "atom" of the lowest possible electronegativity, since there is no attracting power at all. Consequently, the unshared pairs have more *s* character and the bonds more *p* character than pure sp^3 orbitals, making the bonds somewhat more like p^2 bonds and reducing the angle. However, these arguments ignore the steric effect of the atoms or groups attached to oxygen or nitrogen. As seen in Table 1.5, oxygen, nitrogen, and sulfur angles generally increase with decreasing electronegativity of the substituents. Note that the explanation given above cannot explain why some of these angles are *greater* than the tetrahedral angle.

1.L. BOND ENERGIES[103]

There are two kinds of bond energy. The energy necessary to cleave a bond to give the constituent radicals is called the *dissociation energy*, *D*. For example, *D* for $H_2O \rightarrow HO + H$ is 118 kcal mol^{-1} (494 kJ mol^{-1}). However, this is not taken as the energy of the O—H bond in water, since *D* for H—O → H + O is 100 kcal mol^{-1} (418 kJ mol^{-1}). The average of these two values, 109 kcal mol^{-1} (456 kJ mol^{-1}), is taken as the *bond energy*, *E*. In diatomic molecules, of course, $D = E$.

The *D* values may be easy or difficult to measure, and they can be estimated by various techniques.[104] When properly applied, "Pauling's original electronegativity equation accurately describes homolytic bond dissociation enthalpies of common covalent bonds, including highly polar ones, with an average deviation of (1.5 kcal mol^{-1} [≈6.3 kJ mol^{-1}] from literature values)."[105] Whether measured or calculated, there is no question as to what *D* values mean. With *E* values the matter is not so simple. For methane, the total energy of conversion from CH_4 to C + 4 H (at 0 K) is 393 kcal mol^{-1} (1644 kJ mol^{-1}).[106] Consequently, *E* for the C—H bond in methane is 98 kcal mol^{-1} (411 kJ mol^{-1}) at 0 K. The more usual practice is not to measure the heat of atomization (i.e., the energy necessary to convert a compound to its atoms) directly but to calculate it from the heat of combustion. Such a calculation is shown in Figure 1.12.

Heats of combustion are very accurately known for hydrocarbons.[107] For methane the value at 25 °C is 212.8 kcal mol^{-1} (890.4 kJ mol^{-1}), which leads to a heat of atomization of 398.0 kcal mol^{-1} (1665 kJ mol^{-1}) or a value of *E* for the C—H bond at 25 °C of

[103] Blanksby, S.J.; Ellison, G.B. *Acc. Chem. Res.* ***2003***, *36*, 255. For reviews including methods of determination, see Wayner, D.D.M.; Griller, D. *Adv. Free Radical Chem. (Greenwich, Conn.)* ***1990***, *1*, 159; Kerr, J.A. *Chem. Rev.* ***1966***, *66*, 465; Wiberg, K.B., in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods*, Vol. 3, Academic Press, NY, ***1971***, pp. 207–245.

[104] Cohen, N.; Benson, S.W. *Chem. Rev.* ***1993***, *93*, 2419; Korth, H.-G.; Sicking, W. *J. Chem. Soc., Perkin Trans. 2* ***1997***, 715.

[105] Matsunaga, N.; Rogers, D.W.; Zavitsas, A.A. *J. Org. Chem,* ***2003***, *68*, 3158.

[106] For the four steps, *D* values are 101 to 102, 88, 124, and 80 kcal mol^{-1} (423–427, 368, 519, and 335 kJ mol^{-1}), respectively, though the middle values are much less reliable than the other two: Knox, B.E.; Palmer, H.B. *Chem. Rev.* ***1961***, *61*, 247; Brewer, R.G.; Kester, F.L. *J. Chem. Phys.* ***1964***, *40*, 812; Linevsky, M.J. *J. Chem. Phys.* ***1967***, *47*, 3485.

[107] See Cox, J.D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*, Academic Press, NY, ***1970***; Domalski, E.S. *J. Phys. Chem. Ref. Data* ***1972***, *1*, 221–277; Stull, D.R.; Westrum Jr., E.F.; Sinke, G.C. *The Chemical Thermodynamics of Organic Compounds*, Wiley, NY, ***1969***.

				kcal	kJ
$C_2H_{6\,(gas)}$	$+ 3.5\ O_2$	$= 2\ CO_{2\,(gas)}$	$+ 3\ H_2O_{\,(liq)}$	+372.9	+1560
	$2\ CO_{2\,(gas)}$	$= 2\ C_{(graphite)}$	$+ 2\ O_{2\,(gas)}$	–188.2	–787
	$3\ H_2O_{\,(liq)}$	$= 3\ H_{2\,(gas)}$	$+ 1.5\ O_{2\,(gas)}$	–204.9	–857
	$3\ H_{2\,(gas)}$	$= 6\ H_{\,(gas)}$		–312/5	–1308
	$2\ C_{(graphite)}$	$= 2\ C_{\,(gas)}$		–343.4	–1437
	$C_2H_{6\,(gas)}$	$= 6\ H_{\,(gas)}$	$+ 2\ C_{\,(gas)}$	–676.1 kcal	–2829 kJ

FIGURE 1.12 Calculation of the heat of atomization of ethane at 25 °C.

99.5 kcal mol^{-1} (416 kJ mol^{-1}). This method is fine for molecules like methane in which all the bonds are equivalent, but for more complicated molecules assumptions must be made. Thus for ethane, the heat of atomization at 25 °C is 676.1 kcal mol^{-1} or 2829 kJ mol^{-1} (Figure 1.12), and it must be decided how much of this energy is due to the C—C bond and how much to the six C—H bonds. Any assumption must be artificial, since there is no way of actually obtaining this information, and indeed the question has no real meaning. If the assumption is made that *E* for each of the C—H bonds is the same as *E* for the C—H bond in methane (99.5 kcal mol^{-1} or 416 kJ mol^{-1}), then 6×99.5 (or 416) = 597.0 (or 2498), leaving 79.1 kcal mol^{-1} (331 kJ mol^{-1}) for the C—C bond. However, a similar calculation for propane gives a value of 80.3 (or 336) for the C—C bond and for isobutane the value is 81.6 (or 341). A consideration of heats of atomization of isomers also illustrates the difficulty. The *E* values for the C—C bonds in pentane, isopentane, and neopentane, similarly calculated from heats of atomization, are (at 25 °C) 81.1, 81.8, and 82.4 kcal mol^{-1} (339, 342, 345 kJ mol^{-1}), respectively, even though all of them have twelve C—H bonds and four C—C bonds. The bond dissociation enthalpies for bridgehead C—H bonds have been determined.[108] The allylic C—H bond dissociation energy of cyclopropene was measured to be 104.4 kcal mol^{-1} (435 kJ mol^{-1}), and there is evidence that the radical is nonaromatic.[109]

These differences have been attributed to various factors caused by the introduction of new structural features. Thus isopentane (2-methylbutane) has a tertiary carbon whose C—H bond does not have exactly the same amount of *s* character as the C—H bond in pentane, which for that matter contains secondary carbons not possessed by methane. It is known that *D* values, which *can* be measured, are not the same for primary, secondary, and tertiary C—H bonds (see Table 5.2). There is also the steric factor (Sec. 4.Q). Hence it is certainly incorrect to use the value of 99.5 kcal mol^{-1} (416 kJ mol^{-1}) from methane as the *E* value for all C—H bonds. Several empirical equations have been devised that account for these factors; the total energy can be computed[110] if the proper set of parameters (one for each structural feature) is inserted. Of course, these parameters are originally calculated from the known total energies of some molecules that contain the structural feature.

The literature contains charts that take hybridization into account (thus an sp^3 C—H bond does not have the same energy as an sp^2 C—H bond).[111] Bond dissociation energies, both

[108] Fattahi, A.; Lis, L.; Tehrani, Z.A.; Marimanikkuppam, S.S.; Kass, S.R. *J. Org. Chem.* ***2012***, *77*, 1909.
[109] Tian, Z.; Lis, L.; Kass, S.R. *J. Org. Chem.* ***2013***, *78*, 12650.
[110] For a review, see Cox, J.D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*, Academic Press, NY, ***1970***, pp. 531–597. See also, Gasteiger, J.; Jacob, P.; Strauss, U. *Tetrahedron* ***1979***, *35*, 139.
[111] Cox, J.D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*, Academic Press, NY, ***1970***, pp. 531–597; Cox, J.D. *Tetrahedron* ***1962***, *18*, 1337.

calculated and experientially determined, are constantly being refined. Improved values are available for the O—O bond of peroxides,[112] the C—H bond in alkyl amines,[113] the N—H bond in aniline derivatives,[114] the N—H bond in protonated amines,[115] the O—H bond in phenols,[116] the C—H bond in alkenes,[117] amides, and ketones,[118] and in CH_2X_2 and CH_3X derivatives (X=COOR, C=O, SR, NO_2, etc.),[119] the O—H and S—H bonds of alcohols and thiols,[120] and the C—Si bond of aromatic silanes.[121] Solvent plays a role in the *E* values. When phenols bearing electron-releasing groups are in aqueous media, calculations show that the bond dissociation energies decrease due to hydrogen-bonding interactions with water molecules, while electron-withdrawing substituents on the phenol increase the bond dissociation energies.[122] The bond dissociation energy of 1-phenylcyclopropane was determined to be 93.0 kcal mol^{-1} (389.1 kJ mol^{-1}).[123]

Certain generalizations can be derived from bond energy data.

1. There is a correlation of bond strengths with bond distances. In general, *shorter bonds are stronger bonds*. Since it is known that increasing *s* character shortens bonds (Sec. 1.J), it follows that bond strengths increase with increasing *s* character. Calculations show that ring strain has a significant effect on bond dissociation energy, particularly the C—H bond of hydrocarbons, because it forces the compound to adopt an undesirable hybridization.[124]
2. Bonds become weaker moving down the periodic table. Compare C—O and C—S, or the carbon–halogen bonds C—F, C—Cl, C—Br, C—I. This is a consequence of the first generalization, since bond distances must increase going down the periodic table because the number of inner electrons increases. However, it is noted that "high-level *ab initio* molecular orbital calculations confirm that the effect of alkyl substituents on R—X bond dissociation energies varies according to the nature of X (the stabilizing influence of the ionic configurations to increase in the order Me < Et < *i*-Pr < *t*-Bu), accounting for the *increase* (rather than expected decrease) in the R—X bond dissociation energies with increasing alkylation in the R—OCH_3, R—OH, and R—F molecules. This effect of X has been explained in terms of the increasing contribution of the ionic R^+X^- configuration for electronegative X substituents."[125]

[112] Bach, R.D.; Ayala, P.Y.; Schlegel, H.B. *J. Am. Chem. Soc.* ***1996***, *118*, 12758.
[113] Wayner, D.D.M.; Clark, K.B.; Rauk, A.; Yu, D.; Armstrong, D.A. *J. Am. Chem. Soc.* ***1997***, *119*, 8925. For the α C—H bond of tertiary amines, see Dombrowski, G.W.; Dinnocenzo, J.P.; Farid, S.; Goodman, J.L.; Gould, I.R. *J. Org. Chem.* ***1999***, *64*, 427.
[114] Bordwell, F.G.; Zhang, X.-M.; Cheng, J.-P. *J. Org. Chem.* ***1993***, *58*, 6410. See also, Li, Z.; Cheng, J.-P. *J. Org. Chem.* ***2003***, *68*, 7350.
[115] Liu, W.-Z.; Bordwell, F.G. *J. Org. Chem.* ***1996***, *61*, 4778.
[116] Lucarini, M.; Pedrielli, P.; Pedulli, G.F.; Cabiddu, S.; Fattuoni, C. *J. Org. Chem.* ***1996***, *61*, 9259. For the O—H *E* of polymethylphenols, see de Heer, M.I.; Korth, H.-G.; Mulder, P. *J. Org. Chem.* ***1999***, *64*, 6969.
[117] Zhang, X.-M. *J. Org. Chem.* ***1998***, *63*, 1872. See Langler, R.F. *Aust. J. Chem.* ***2011***, *64*, 324.
[118] Bordwell, F.G.; Zhang, X.-M.; Filler, R. *J. Org. Chem.* ***1993***, *58*, 6067.
[119] Brocks, J.J.; Beckhaus, H.-D.; Beckwith, A.L.J.; Rüchardt, C. *J. Org. Chem.* ***1998***, *63*, 1935.
[120] Hadad, C.M.; Rablen, P.R.; Wiberg, K.B. *J. Org. Chem.* ***1998***, *63*, 8668.
[121] Cheng, Y.-H.; Zhao, X.; Song, K.-S.; Liu, L.; Guo, Q.-X. *J. Org. Chem.* ***2002***, *67*, 6638.
[122] Guerra, M.; Amorati, R.; Pedulli, G.F. *J. Org. Chem.* ***2004***, *69*, 5460.
[123] Fattahi, A.; Lis, L.; Kass, S.R. *J. Org. Chem.* ***2016***, *81*, 9175.
[124] Feng, Y.; Liu, L.; Wang, J.-T.; Zhao, S.-W.; Guo, Q.X. *J. Org. Chem.* ***2004***, *69*, 3129; Song, K.-S.; Liu, L.; Guo, Q.X. *Tetrahedron* ***2004***, *60*, 9909. See De Lio, A.M.; Durfey, B.L.; Gilbert, T.M. *J. Org. Chem.* ***2015***, *80*, 10234.
[125] Coote, M.L.; Pross, A.; Radom, L. *Org. Lett.* ***2003***, *5*, 4689.

3. Double bonds are both shorter and stronger than the corresponding single bonds, but not twice as strong, because π overlap is less than σ overlap. This means that a σ bond is stronger than a π bond. The difference in energy between a single bond, say C—C, and the corresponding double bond is the amount of energy necessary to cause rotation around the double bond.[126]

Calculations suggest that covalent bond strength and also equilibrium bond length are not determined by maximum overlap of the σ valence orbitals, as described in previous sections.[127] Rather, orbital interactions, Pauli repulsion, and quasi-classical electrostatic attraction determine both.

Solvents are thought to play a role in bond dissociation energy of molecules, as noted for phenol above, and also for intermediates (see Chapter 5). It has been assumed that the solvation enthalpies were small and they have been largely ignored in calculations involving various reactions. Solvent effects on the bond dissociation energy of a molecule may arise from the difference in solvation enthalpies between the molecule and the key intermediate. For radical reactions that involve polar molecules, the radical–solvent interaction may be larger.[128]

The relation of energy and bond length has been discussed.[129] It is noted that the bond energy of the C—S bond[130] is 61 kcal mol^{-1} (255 kJ mol^{-1}), that of the C—N bond[131] is 69–75 kcal mol^{-1} (290–315 kJ mol^{-1}), and a reported value for the O—O bond[132] is 42.9 kcal mol^{-1} (179.6 ± 4.5 kJ mol^{-1}).

[126] See Miller, S.I. *J. Chem. Educ.* ***1978***, *55*, 778.
[127] Krapp, A.; Bickelhaupt, F.M.; Frenking, G. *Chemistry: European J.* ***2006***, *12*, 9196.
[128] Borges dos Santos, R.M.; Costa Cabral, B.J.; Martinho Simões, J.A. *Pure Appl. Chem.* ***2007***, *79*, 1369.
[129] Lovering, E.G.; Laidler, K.J. *Can. J. Chem.* ***1960***, *38*, 2367; Levi, G.I.; Balandin, A.A. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* ***1960***, 149.
[130] Grelbig, T.; Pötter, B.; Seppelt, K. *Chem. Ber.* ***1987***, *120*, 815.
[131] Bedford, A.F.; Edmondson, P.B.; Mortimer, C.T. *J. Chem. Soc.* ***1962***, 2927.
[132] The average of the values obtained was ΔH° (O—O). dos Santos, R.M.B.; Muralha, V.S.F.; Correia, C.F.; Simões, J.A.M. *J. Am. Chem. Soc.* ***2001***, *123*, 12670.

CHAPTER 2

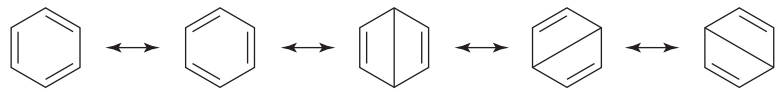
Delocalized Chemical Bonding

Although the bonding of many compounds can be adequately described by a single Lewis structure (Sec. 1.F), this is insufficient for many other compounds. Such compounds contain one or more bonding orbitals that are not restricted to two atoms, but rather they are spread out over three or more atoms. Such bonding is said to be *delocalized*.[1] In other words, the bonding electrons are dispersed over several atoms rather than localized on one atom. This chapter will discuss those compounds that must be represented in this way.

The two chief general methods of approximately solving the wave equation, discussed in Chapter 1, are also used for compounds containing delocalized bonds.[2] In the valence-bond method, several possible Lewis structures (called *canonical forms*) are drawn, and the molecule is taken to be a weighted average of them. Each Ψ in Eq. (1-3) from Chapter 1 represents one of these structures. Therefore:

$$\psi = c_1\psi_1 + c_1\psi_1 + \cdots$$

is the representation of a real structure as a weighted average of two or more canonical forms, which is called *resonance*. For benzene the canonical forms are drawn as **1** and **2**. Double-headed arrows (↔) are used to indicate resonance. When the wave equation is solved, it is found that the energy value obtained by equal participation of **1** and **2** is lower than that for **1** or **2** alone. If **3**, **4**, and **5** (called *Dewar structures*) are also considered, the value is lower still. According to this method, **1** and **2** contribute 39% each to the actual molecule and the others 7.3% each.[3] The carbon–carbon bond order is 1.463 (not 1.5, which would be the case if only **1** and **2** contributed).



1 **2** **3** **4** **5**

In the valence-bond method, the *bond order* of a particular bond is the sum of the weights of those canonical forms in which the bonds is double plus 1 for the single bond that is

[1] See Wheland, G.W. *Resonance in Organic Chemistry*, Wiley, NY, ***1955***.

[2] There are other methods. See Streitwieser Jr., A. *Molecular Orbital Theory for Organic Chemists*, Wiley, NY, ***1961***, pp. 27–29; Hirst, D.M.; Linnett, J.W. *J. Chem. Soc.* ***1962***, 1035; Firestone, R.A. *J. Org. Chem.* ***1969***, *34*, 2621.

[3] Pullman, A. *Prog. Org. Chem.* ***1958***, *4*, 31, p. 33.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

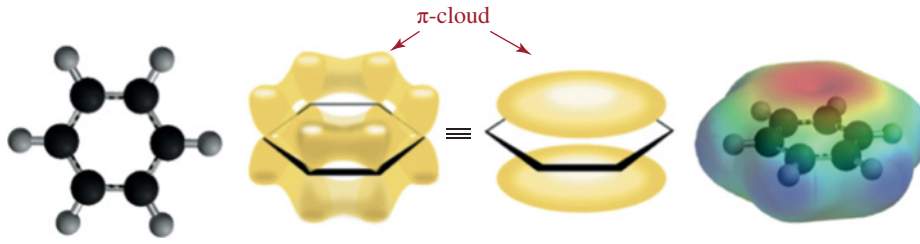


FIGURE 2.1. (a) Model of planar array of atoms in benzene. (b) The overlapping (delocalized) π cloud of benzene. (c) The electrostatic potential map of benzene, indicating the high concentration of electron density above and below the plane of the atoms, but in the center of the six-membered ring, consistent with the aromatic cloud.

present in all of them.[4] Thus, according to this picture, each C—C bond is not halfway between a single and a double bond but somewhat less. The energy of the actual molecule is obviously less than that of any one Lewis structure, since otherwise it would have one of those structures. The difference in energy between the actual molecule and the Lewis structure of lowest energy is called the *resonance energy*. Of course, the Lewis structures are not real, and their energies can only be estimated. Resonance in benzene is possible by overlap of the *p* orbitals, orthogonal to the plane of carbon and hydrogen atoms. This resonance is associated with the aromatic π cloud. Figure 2.1a shows the planar σ bond framework of benzene, and Figure 2.1b shows the overlapping *p* orbitals forming the aromatic π cloud. Figure 2.1c shows the electron potential map of benzene. Note the darker area above the middle of the ring that corresponds to high electron density, consistent with the high electron density of the aromatic π cloud.

2.A. MOLECULAR ORBITALS

While the resonance picture is often used to describe the structure of molecules, as structures become more complicated (e.g., naphthalene and pyridine), quantitative valence-bond calculations become much more difficult. Therefore, the molecular-orbital method is used much more often for the solution of wave equations.[5] Examination of benzene by this method (qualitatively) shows that each carbon atom, being connected to three other atoms, uses sp^2 orbitals to form σ bonds, so that all 12 atoms are in one plane. This method shows that each carbon has a remaining *p* orbital that contains one electron, and each orbital can overlap equally with the two adjacent *p* orbitals. This overlap of six orbitals (see Figure 2.2) produces six new orbitals, and the three lower energy orbitals of these are bonding. These three (called π orbitals) all occupy approximately the same space.[6] One of the three is of lower energy than the other two, which are degenerate. They each have the plane of the

[4] See Clarkson, D.; Coulson, C.A.; Goodwin, T.H. *Tetrahedron* ***1963***, *19*, 2153. See also Herndon, W.C.; Párkányi, C. *J. Chem. Educ.* ***1976***, *53*, 689.

[5] See Dewar, M.J.S. *Mol. Struct. Energ.* ***1988***, *5*, 1.

[6] Shaik, S.S.; Hiberty, P.C.; Lefour, J.; Ohanessian, G. *J. Am. Chem. Soc.* ***1987***, *109*, 363; Stanger, A.; Vollhardt, K.P.C. *J. Org. Chem.* ***1988***, *53*, 4889. See also, Jug, K.; Köster, A.M. *J. Am. Chem. Soc.* ***1990***, *112*, 6772; Aihara, J. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 1956.

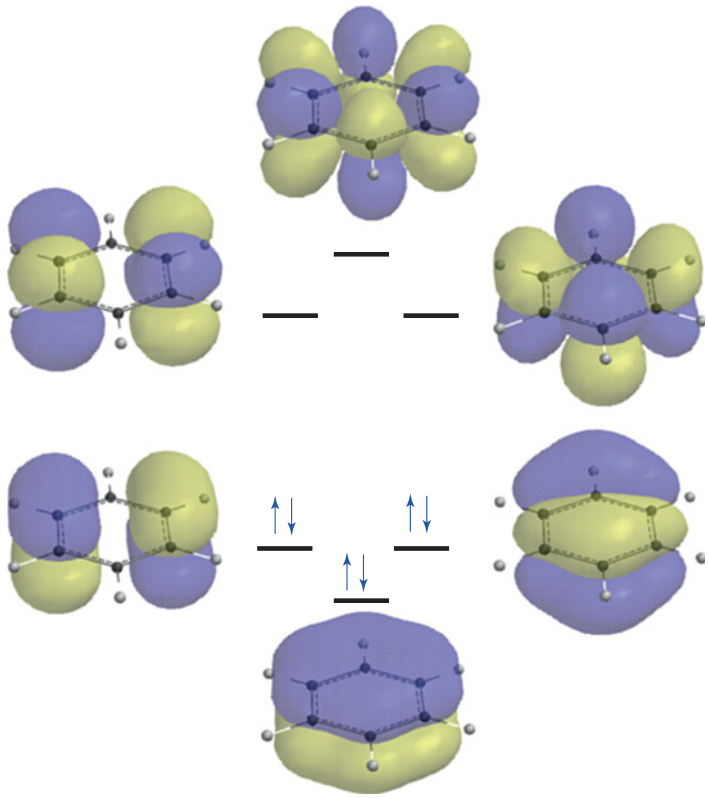


FIGURE 2.2. The molecular orbitals of benzene, showing the three bonding orbitals, as generated by Spartan.10, v.1.0.1.

ring as a node and so are in two parts, one above the plane and one below. The two orbitals of higher energy also have another node. The six electrons that occupy this torus-shaped cloud are called the *aromatic sextet*. A torus-shaped object is essentially a doughnut-shaped object. According to this explanation, the symmetrical hexagonal structure of benzene is caused by both the σ bonds and the π orbitals. Based on MO calculations, this symmetry is probably caused by the σ framework alone, and that the π system would favor three localized double bonds.[6] The carbon–carbon bond order for benzene, calculated by the molecular-orbital method, is 1.667.[7]

For planar unsaturated molecules that are aromatic, many molecular-orbital calculations (*MO calculations*) have been made by treating the σ and π electrons separately. It is assumed that the σ orbitals can be treated as localized bonds and the calculations involve only the π electrons. The first such calculations were made by Hückel, and such calculations are often called *Hückel molecular-orbital* (HMO) *calculations*.[8] Because electron–electron

[7] See Pullman, A. *Prog. Org. Chem.* ***1958***, *4*, 31, p. 36; Clarkson, D.; Coulson, C.A.; Goodwin, T.H. *Tetrahedron* ***1963***, *19*, 2153. For a MO picture of aromaticity, see Pierrefixe, S.C.A.H.; Bickelhaupt, F.M. *Chemistry: European J.* ***2007***, *13*, 6321.

[8] See Yates, K. *Hückel Molecular Orbital Theory*, Academic Press, NY, ***1978***; Coulson, C.A.; O'Leary, B.; Mallion, R.B. *Hückel Theory for Organic Chemists*, Academic Press, NY, ***1978***; Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row, NY, ***1987***, pp. 100–121.

repulsions are either neglected or averaged out in the HMO method, another approach, the *self-consistent field* (SCF), or *Hartree-Fock*, method, was devised.[9] Although these methods give many useful results for planar unsaturated and aromatic molecules, they are often unsuccessful for other molecules; it would obviously be better if all electrons, both σ and π, could be included in the calculations. The development of modern computers has now made this possible.[10] Many such calculations have been made[11] using a number of methods, among them an extension of the Hückel method[12] and the application of the SCF method to all valence electrons.[13]

One type of MO calculation that includes all electrons is called *ab initio*.[14] Despite the name (which means "from first principles") this type does involve some assumptions. Treatments that use certain simplifying assumptions (but still include all electrons) are called *semi-empirical* methods.[15] One of the first of these was called CNDO (Complete Neglect of Differential Overlap),[16] but as computers have become more powerful, this has been superseded by more modern methods, including MINDO/3 (Modified Intermediate Neglect of Differential Overlap),[17] MNDO (Modified Neglect of Diatomic Overlap),[17] and AM1 (Austin Model 1), all of which were introduced by M.J. Dewar and co-workers.[18] There is also the PM3, or Parameterized Model number 3, which uses the same formalism and equations as the AM1 method, but AM1 takes some of the parameter values from spectroscopic measurements whereas PM3 treats them as optimizable values.[19] Semi-empirical calculations are generally regarded as less accurate than *ab initio* methods,[20] but are much faster and cheaper.[21] It is noted that modern computers make molecular-orbital calculations practical in modern organic chemistry.

Molecular-orbital calculations, whether by *ab initio* methods or by semi-empirical methods, can be used to obtain structures (bond distances and angles), energies (e.g., heats of formation), dipole moments, ionization energies, and other properties of molecules, ions, and radicals: not only of stable ones, but also of those so unstable that these properties

[9] Pople, J.A. *Trans. Faraday Soc.* ***1953***, *49*, 1375, *J. Phys. Chem.* ***1975***, *61*, 6; Dewar, M.J.S. *The Molecular Orbital Theory of Organic Chemistry*, McGraw-Hill, NY, ***1969***; Dewar, M.J.S., in *Aromaticity*, Chem. Soc. Spec. Pub. no. 21, ***1967***, pp. 177–215. See Merino, G.; Vela, A.; Heine, T. *Chem. Rev.* ***2005***, *105*, 3812; Poater, J.; Duran, M.; Solà, M.; Silvi, B. *Chem. Rev.* ***2005***, *105*, 3911.

[10] See Ramsden, C.A. *Chem. Ber.* ***1978***, *14*, 396; Hall, G.G. *Chem. Soc. Rev.* ***1973***, *2*, 21.

[11] See Herndon, W.C. *Prog. Phys. Org. Chem.* ***1972***, *9*, 99.

[12] Hoffmann, R. *J. Chem. Phys.* ***1963***, *39*, 1397. See Yates, K. *Hückel Molecular Orbital Theory*, Academic Press, NY, ***1978***, pp. 190–201.

[13] Dewar, M.J.S. *The Molecular Orbital Theory of Chemistry*, McGraw-Hill, NY, ***1969***; Jaffé, H.H. *Acc. Chem. Res.* ***1969***, *2*, 136; Kutzelnigg, W.; Del Re, G.; Berthier, G. *Fortschr. Chem. Forsch.* ***1971***, *22*, 1.

[14] Hehre, W.J.; Radom, L.; Schleyer, P.v.R.; Pople, J.A. *Ab Initio Molecular Orbital Theory*, Wiley, NY, ***1986***; Clark, T. *A Handbook of Computational Chemistry*, Wiley, NY, ***1985***, pp. 233–317; Richards, W.G.; Cooper, D.L. *Ab Initio Molecular Orbital Calculations for Chemists*, 2nd ed., Oxford University Press, Oxford, ***1983***.

[15] For a review, see Thiel, W. *Tetrahedron* ***1988***, *44*, 7393.

[16] Pople, J.A.; Segal, G.A. *J. Chem. Phys.* ***1965***, *43*, S136; ***1966***, *44*, 3289; Pople, J.A.; Beveridge, D.L. *Approximate Molecular Orbital Theory*; McGraw-Hill, NY, ***1970***.

[17] For a discussion of MNDO and MINDO/3, and a list of systems for which these methods have been used, with references, see Clark, T. *A Handbook of Computational Chemistry*, Wiley, NY, ***1985***, pp. 93–232. For a review of MINDO/3, see Lewis, D.F.V. *Chem. Rev.* ***1986***, *86*, 1111.

[18] See Dewar, M.J.S.; Zoebisch, E.G.; Healy, E.F.; Stewart, J.J.P. *J. Am. Chem. Soc.* ***1985***, *107*, 3902.

[19] Stewart, J.J.P. *J. Comput. Chem.* ***1989***, *10*, 209, 221.

[20] See however, Dewar, M.J.S.; Storch, D.M. *J. Am. Chem. Soc.* ***1985***, *107*, 3898.

[21] Clark, T. *A Handbook of Computational Chemistry*, Wiley, NY, ***1985***, p. 141.

cannot be obtained from experimental measurements.[22] Many of these calculations have been performed on transition states (Sec. 6.D); this is the only way to get this information, *since transition states are not directly observable*. Of course, it is not possible to check data obtained for unstable molecules and transition states against any experimental values, so that the reliability of the various MO methods for these cases is always a question. However, confidence in them increases when (i) different MO methods give similar results, and (ii) a particular MO method works well for cases that can be checked against experimental methods.[23]

Monte Carlo (MC) methods use a random approach to solve problems.[24] The MC approach can be applied to quantum mechanics problems, and the intersection of MC methods and quantum mechanics is generally referred to as quantum Monte Carlo (QMC).[25] The statistical nature of QMC calculations impose certain limitations, but progress in algorithms, enhanced computational power, and the inherent parallelism of QMC help overcome many of the limitations.

Both the valence-bond method and the molecular-orbital method show that there is delocalization in benzene. For example, each predicts that the six carbon–carbon bonds should have equal lengths, which is true. Since each method is useful for certain purposes, one or the other will be used as appropriate. Recent *ab initio*, SCF calculations confirm that the delocalization effect acts to strongly stabilize symmetric benzene, consistent with the concepts of classical resonance theory.[26] It is known that substituents influence the extent of resonance.[27]

2.B. BOND ENERGIES AND DISTANCES IN COMPOUNDS CONTAINING DELOCALIZED BONDS

If the energies of all the bonds in benzene are added, taking the values from a source like Table 1.7, the value for the heat of atomization is less than the experimentally determined value (Figure 2.3) of 1323 kcal mol^{-1} (5535 kJ mol^{-1}). If E values for a C═C double bond obtained from cyclohexene (148.8 kcal mol^{-1}; 622.6 kJ mol^{-1}) are used, a C—C single bond from cyclohexane (81.8 kcal mol^{-1}, 342 kJ mol^{-1}), and C—H bonds from methane (99.5 kcal mol^{-1}, 416 kJ mol^{-1}), a value of 1289 kcal mol^{-1} (5390 kJ mol^{-1}) is obtained for structures **1** or **2**. The resonance energy is 34 kcal mol^{-1} (145 kJ mol^{-1}), using this calculation. Of course, this is an arbitrary calculation since, in addition to the fact that a heat of atomization is calculated for a nonexistent structure (**1**), E values must be used that do not have a firm basis in reality. The actual C—H bond energy for benzene has been measured to be 113.5 ± 0.5 kcal mol^{-1} at 300 K and estimated to be 112.0 ± 0.6 kcal mol^{-1}

[22] Another method of calculating such properies is molecular mechanics (Sec. **4.P**).

[23] Dias, J.R. *Molecular Orbital Calculations Using Chemical Graph Theory*, Spring-Verlag, Berlin, ***1993***.

[24] Hammond, B.L.; Lester Jr., W.A.; Reynolds, P.J. *Monte Carlo Methods in Ab Initio Quantum Chemistry: Quantum Monte Carlo for Molecules*, World Scientific, Hackensack, NJ, ***1994***; Metropolis, N.; Ulam, S. *J. Am. Stat.* ***1949***, *44*, 335; Kalos, M.H. *Phys. Rev.* ***1962***, *128*, 1791.

[25] Austin, B.M.; Zubarev, D.Yu.; Lester Jr., W.A. *Chem. Rev.* ***2012***, *112*, 263.

[26] Glendening, E.D.; Faust, R.; Streitwieser, A.; Vollhardt, K.P.C.; Weinhold, F. *J. Am. Chem.Soc.* ***1993***, *115*, 10952.

[27] For an electrostatic scale of substituent resonance effects, see Sayyed, F.B.; Suresh, C.H. *Tetrahedron Lett.* ***2009***, *50*, 7351. For effects in 1,2-benzoquinones, also see Szatyłowicz, H.; Krygowski, T.M.; Palusiak, M.; Poater, J.; Solà, M. *J. Org. Chem.* ***2011***, *76*, 550.

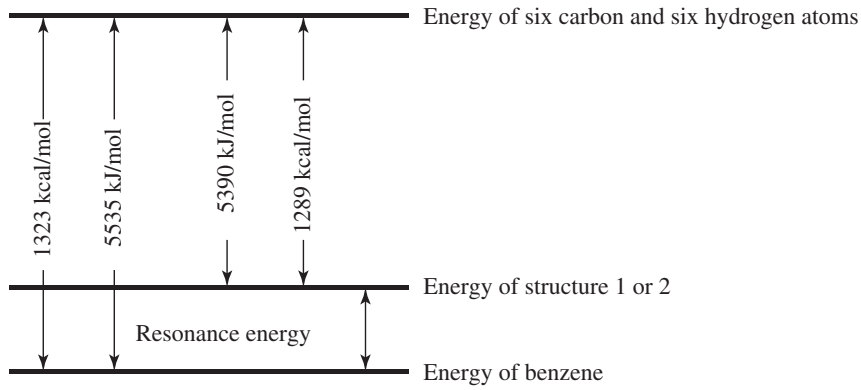


FIGURE 2.3. Resonance energy in benzene.

(469 kJ mol^{-1}) at 0 K.[28] The heat of atomization of a real molecule can be measured, but resonance energy can never be measured, only estimated, because only an intelligent guess can be made of the Lewis structure of lowest energy.

Another method frequently used for estimation of resonance energy involves measurements of heats of hydrogenation.[29] The heat of hydrogenation of cyclohexene is 28.6 kcal mol^{-1} (120 kJ mol^{-1}), so a hypothetical **1** or **2** with three double bonds is expected to have a heat of hydrogenation of about 85.8 kcal mol^{-1} (360 kJ mol^{-1}). Benzene has a measured heat of hydrogenation of 49.8 kcal mol^{-1} (208 kJ mol^{-1}), and the difference between the measured value and the expected value is the *resonance energy*, 36 kcal mol^{-1} (152 kJ mol^{-1}). By any calculation, the real molecule is more stable than a hypothetical **1** or **2**.

The energies of the six benzene orbitals can be calculated from HMO theory in terms of two quantities that are labeled α and β. The term α is the amount of energy possessed by an isolated 2*p* orbital before overlap, while β (called the *resonance integral*) is an energy unit expressing the degree of stabilization resulting from π orbital overlap. A negative value of β corresponds to stabilization, and the energies of the six orbitals are (from lowest to highest): $\alpha + 2\beta$, $\alpha + \beta$, $\alpha + \beta$, $\alpha - \beta$, $\alpha - \beta$, and $\alpha - 2\beta$.[30] The total energy of the three occupied orbitals is $6\alpha + 8\beta$, since there are two electrons in each orbital. The energy of an ordinary double bond is $\alpha + \beta$, so that structure **1** or **2** has an energy of $6\alpha + 6\beta$ and the resonance energy of benzene is 2β. Unfortunately, there is no convenient way to calculate the value of β from molecular-orbital theory. Benzene is given a value of β of about 18 kcal mol^{-1} (76 kJ mol^{-1}); this number is one-half of the resonance energy calculated from heats of combustion or hydrogenation. Using *ab initio* calculations, bond resonance energies for many aromatic hydrocarbons other than benzene have been reported.[31]

[28] Davico, G.E.; Bierbaum, V.M.; DePuy, C.H.; Ellison, G.B.; Squires, R.R. *J. Am. Chem. Soc.* ***1995***, *117*, 2590. See also, Pratt, D.A.; DiLabio, G.A.; Mulder, P.; Ingold, K.U. *Acc. Chem. Res.* ***2004***, *37*, 334.

[29] See Jensen, J.L. *Prog. Phys. Org. Chem.* ***1976***, *12*, 189.

[30] For the method for calculating these and similar results given in this chapter, see Higasi, K.; Baba, H.; Rembaum, A. *Quantum Organic Chemistry*, Interscience, NY, ***1965***. For values of calculated orbital energies and bond orders for many conjugated molecules, see Coulson, C.A.; Streitwieser Jr., A. *Dictionary of π Electron Calculations*, W.H. Freeman, San Francisco, ***1965***.

[31] Aihara, J-i. *J. Chem. Soc., Perkin Trans 2* ***1996***, 2185.

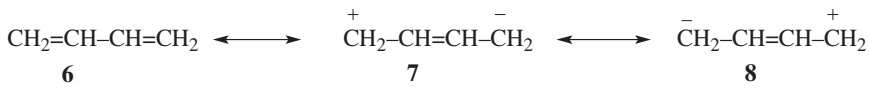
Isodesmic and homodesmotic reactions are frequently used for the study of aromaticity from the energetic point of view.[32] However, the energy of the reactions used experimentally, or in calculations, may reflect only the relative aromaticity of benzene and not its absolute aromaticity. New homodesmotic reactions based on radical systems predict an absolute aromaticity of 29.13 kcal mol^{-1} (121.9 kJ mol^{-1}) for benzene and an absolute antiaromaticity (Sec. 2.K.ii) of 40.28 kcal mol^{-1} (168.5 kJ mol^{-1}) for cyclobutadiene at the MP4(SDQ)/6-31G-(d,p) level.[33]

Compounds that exhibit delocalization are expected to have bond distances that lie between the values given in Table 1.5. This is the case for benzene, since the C—C bond distance is 1.40 Å,[34] which is between the 1.48 Å for an sp^2–sp^2 C—C single bond and the 1.32 Å of the sp^2–sp^2 C═C double bond.[35]

2.C. MOLECULES THAT HAVE DELOCALIZED BONDS

There are four main types of structure that exhibit delocalization.

1. *Double (or triple) bonds in conjugation*.[36] The double bonds in benzene are conjugated, of course, but conjugation exists in acyclic molecules such as buta-1,3-diene, **6**. In the molecular-orbital picture (Figure 2.4), the overlap of four orbitals gives two bonding orbitals that contain four electrons and two vacant antibonding orbitals. It can be seen that each orbital has one more node than the one of next lower energy. The energies of the four orbitals are (from lowest to highest): $\alpha + 1.618\beta$, $\alpha + 0.618\beta$, $\alpha - 0.618\beta$, and $\alpha - 1.618\beta$; hence the total energy of the two occupied orbitals is $4\alpha + 4.472\beta$. Since the energy of two isolated double bonds is $4\alpha + 4\beta$, the resonance energy by this calculation is 0.472β. In the resonance picture, structures **7** and **8** contribute.



6 **7** **8**

Despite the invocation of structures **7** and **8** in the resonance picture, buta-1,3-diene and similar conjugated systems are *not* considered to be resonance stabilized in the ground state. The bond order of the central bond should be > 1 and that of the other carbon–carbon bonds < 2, although neither predicts that the three bonds have

[32] George, P.; Trachtman, M.; Bock, C.W.; Brett, A.M. *J. Chem. Soc., Perkin Trans. 2* ***1976***, 1222; George, P.; Trachtman, M.; Bock, C.W.; Brett, A.M. *Tetrahedron* ***1976***, *32*, 317; George, P.; Trachtman, M.; Brett, A.M.; Bock, C.W. *J. Chem. Soc., Perkin Trans. 2* ***1977***, 1036.

[33] Suresh, C.H.; Koga, N. *J. Org. Chem.* ***2002***, *67*, 1965. The heat of hydrogenation of phenylcyclobutadiene is reported to be 57.4 ± 4.9 kcal mol^{-1} (240.3 kJ mol^{-1}); Fattahi, A.; Lis, L.; Kass, S.R. *J. Am. Chem. Soc.* ***2005***, *127*, 3065.

[34] Tamagawa, K.; Iijima, T.; Kimura, M. *J. Mol. Struct.* ***1976***, *30*, 243.

[35] The average C—C bond distance in aromatic rings is 1.38 Å: Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* ***1987***, p. S8.

[36] See Simmons, H.E. *Prog. Phys. Org. Chem.* ***1970***, *7*, 1; Popov, E.M.; Kogan, G.A. *Russ. Chem. Rev.* ***1968***, *37*, 119.

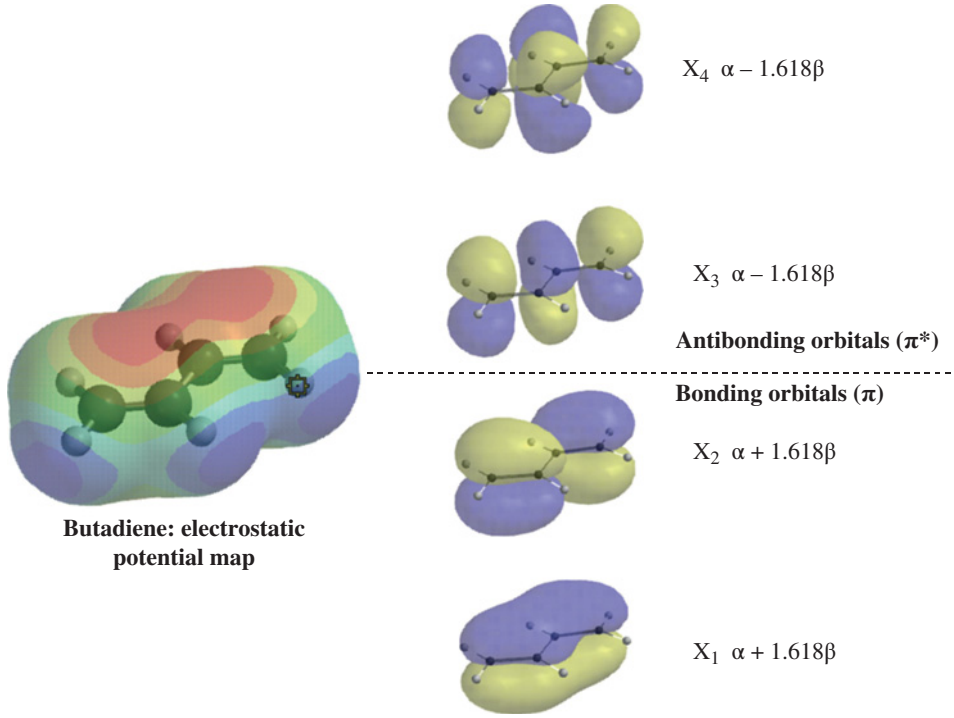


FIGURE 2.4. The four π orbitals of butadiene, formed by overlap of four *p* orbitals.

equal electron density. Molecular-orbital bond orders of 1.894 and 1.447 have been calculated.[37]

The existence of delocalization in buta-1,3-diene and similar molecules has been questioned. The bond lengths in buta-1,3-diene are 1.34 Å for the double bonds and 1.48 Å for the single bond.[38] Since a typical single-bond distance of a bond that is not adjacent to an unsaturated group is 1.53 Å (Sec. 1.J), the shorter single bond in butadiene could provide evidence for resonance. However, this shortening can also be explained by hybridization changes (Sec. 1.J); and other explanations have been offered.[39] Resonance energies for buta-1,3-dienes, calculated from heats of combustion or hydrogenation, are only about 4 kcal mol^{-1} (17 kJ mol^{-1}),[40] *but buta-1,3-diene is not resonance stabilized*. A calculation from heat of atomization data gives a resonance energy of 4.6 kcal mol^{-1} (19 kJ mol^{-1}) for *cis*-penta-1,3-diene, and −0.2 kcal mol^{-1} (−0.8 kJ mol^{-1}) for penta-1,4-diene. These two compounds, each of which possesses two double bonds, two C—C single bonds, and

[37] Coulson, C.A. *Proc. R. Soc. London, Ser. A* ***1939***, *169*, 413.
[38] Marais, D.J.; Sheppard, N.; Stoicheff, B.P. *Tetrahedron* ***1962***, *17*, 163.
[39] Politzer, P.; Harris, D.O. *Tetrahedron* ***1971***, *27*, 1567.
[40] For a discussion of so-called Y-aromaticity, and the relative stability of the butadienyl dication in relation to other dications, see Dworkin, A.; Naumann, R.; Seigfred, C.; Karty. J.M.; Mo, Y. *J. Org. Chem.* ***2005***, *70*, 7605; Kleinpeter, E.; Koch, A. *Tetrahedron.* ***2016***, *72*, 1675.

eight C—H bonds, would seem to offer a direct comparison of a conjugated with a nonconjugated compound, but they are nevertheless not strictly comparable. The former has three sp^3 C—H and five sp^2 C—H bonds, while the latter has two and six, respectively. Also, the two single C—C bonds of the 1,4-diene are both sp^2–sp^3 bonds, while in the 1,3-diene, one is sp^2–sp^3 and the other sp^2–sp^2. Therefore, it may be that some of the already small value of 4 kcal mol^{-1} (17 kJ mol^{-1}) is not resonance energy but arises from differing energies of bonds of different hybridization.[41] As noted above, buta-1,3-diene and related molecules are considered not to be resonance stabilized in the ground state.

Although bond distances fail to show it and the resonance energy is low, buta-1,3-diene is planar,[42] which has been taken as an indication that there is some delocalization. Similar effects are found in other conjugated systems (e.g., C=C—C=O[43] and C=C—C=N), in longer systems with three or more multiple bonds in conjugation, and where double or triple bonds are conjugated with aromatic rings. Diynes such as buta-1,3-diyne are also conjugated molecules and, based on calculations, Rogers et al. reported that the conjugation stabilization is zero.[44] Later calculations concluded that consideration of hyperconjugative interactions (Sec. 2.M) provides a more refined measure of conjugative stabilization.[45] When this measure is used, the conjugation energies of the isomerization and hydrogenation reactions considered agree with a conjugative stabilization of 9.3 (± 0.5) kcal mol^{-1} for diynes and 8.2 (± 0.1) kcal mol^{-1} for dienes.

2. *Double (or triple) bonds in conjugation with a p orbital on an adjacent atom.* When a *p* orbital is on an atom adjacent to a double bond, there are three parallel *p* orbitals that overlap. As previously noted, it is a general rule that the overlap of *n* atomic orbitals creates *n* molecular orbitals, so overlap of a *p* orbital with an adjacent double bond gives rise to three new orbitals, as shown in Figure 2.5. The middle orbital is a *nonbonding orbital* of zero bonding energy. The central carbon atom does not participate in the nonbonding orbital.

   There are three cases: the original *p* orbital may have contained two, one, or no electrons: e.g., the allylic carbanion, free radical, and cation differ from each other in that the nonbonding orbital is filled, half-filled, or empty. The double bond contributes two electrons, so the total number of electrons in the new orbitals will be four, three, or two, respectively. In vinyl chloride, CH_2=CH—Cl, the *p* orbital of the chlorine atom is filled, and still overlaps with the double bond (see **9**). The four electrons occupy the two molecular orbitals of lowest energies, an example of resonance

[41] For negative views on delocalization in butadiene and similar molecules, see Dewar, M.J.S.; Gleicher, G.J. *J. Am. Chem. Soc.* ***1965***, *87*, 692; Mikhailov, B.M. *J. Gen. Chem. USSR* ***1966***, *36*, 379. For positive views, see Miyazaki, T.; Shigetani, T.; Shinoda, H. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 1491; Altmann, J.A.; Reynolds, W.F. *J. Mol. Struct*, ***1977***, *36*, 149. In general, the negative argument is that resonance involving excited structures, such as **7** and **8**, is unimportant. See rule 6 in Sec. 2.E. See Popov, E.M.; Kogan, G.A. *Russ. Chem. Rev.* ***1968***, *37*, 119 (pp. 119–124).

[42] Wiberg, K.B.; Rosenberg, R.E.; Rablen, P.R. *J. Am. Chem. Soc.* ***1991***, *113*, 2890.

[43] See Patai, S.; Rappoport, Z. *The Chemistry of Enones*, two parts; Wiley, NY, ***1989***.

[44] Rogers, D.W.; Matsunaga, N.; McLafferty, F.J.; Zavitsas, A.A.; Liebman, J.F. *J. Org. Chem.* ***2004***, *69*, 7143.

[45] Jarowski, P.D.; Wodrich, M.D.; Wannere, C.S.; Schleyer, P.v.R.; Houk, K.N. *J. Am. Chem. Soc.* ***2004***, *126*, 15036.

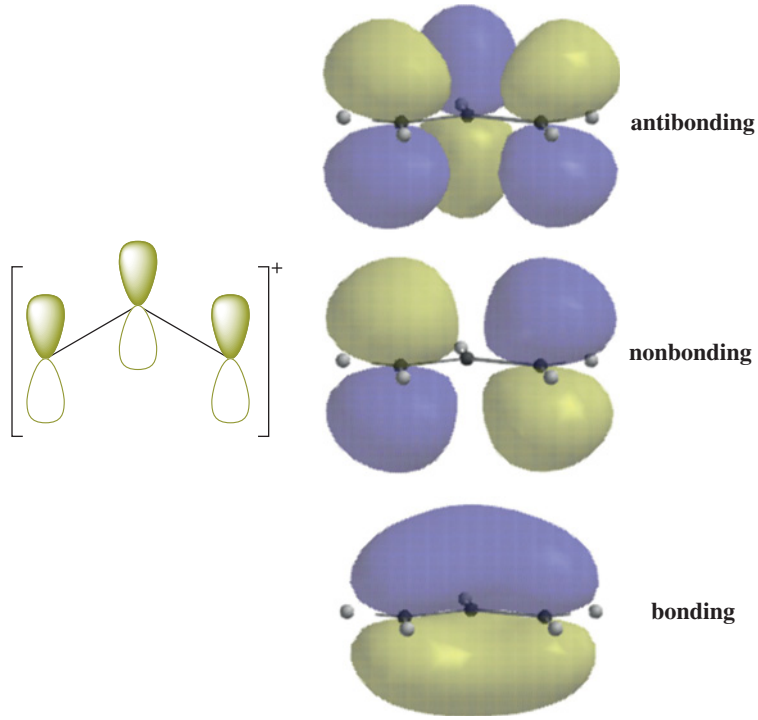
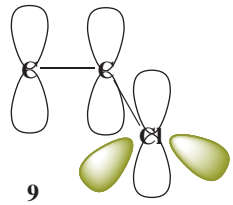


FIGURE 2.5. Three orbitals of an allylic carbocation, formed by overlap of three *p* orbitals.

involving overlap between unfilled orbitals and a *filled* orbital. Canonical forms for vinyl chloride are shown in **10** (Sec. 2.M).

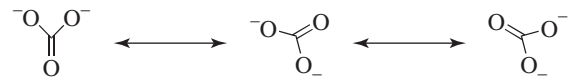


9

$$CH_2 = CH{-}Cl \longleftrightarrow {}^{-}CH_2{-}CH{=}Cl^{+}$$

10

Any system that contains an atom that has an unshared pair and is directly attached to a multiple-bond atom can show this type of delocalization. Resonance delocalization is more important with charged species such as the carbonate ion, and true resonance contributors can be drawn:

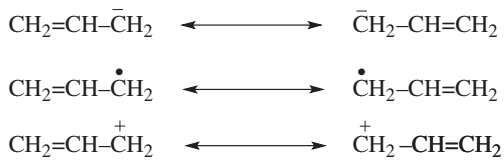


The resonance delocalization in allylic carbanions, for example $CH_2{=}CH{-}CH_2^{-}$, is another example.

The other two cases have a *p* orbital that contains only one electron (radicals) or no electrons (cations). Allylic free radicals have one electron in the nonbonding

orbital whereas this orbital is vacant in allylic cations and only the bonding orbital is occupied. Since this is an orbital of zero bonding energy, it follows that the bonding π energies of the three species relative to electrons in the 2*p* orbitals of free atoms are the same. The electrons in the nonbonding orbital do not contribute to the bonding energy, positively or negatively.[46]

The resonance picture best describes three species that are charged or contain an unshared electron with double bonds in conjugation with, respectively, an unshared pair, an unpaired electron, and an empty orbital as in the allyl cation (also see Chapter 5).



3. π-*Allyl and other* η *complexes.* In the presence of transition metals, delocalized electrons in allylic cations may be donated to the metal, resulting in stabilization.[47] In a carbon–metal bond such as $H_3C{-}Fe$, the carbon donates (shares) one electron with the metal, and is considered to be a one-electron donor. With a π bond such as that found in ethene, both electrons can be donated to the metal to form a complex such as **12** by reaction of Wilkinson's catalyst (**1**) with an alkene and hydrogen gas,[48] and the π bond is considered to be a two-electron donor. In these two cases, the electron donating ability of the group coordinated to the metal (the ligand) is indicated by terminology η^1, η^2, η^3, and so on, for a one-, two-, and three-electron donor, respectively.

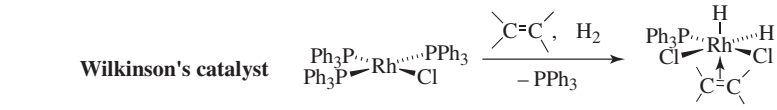
   Ligands are categorized as η ligands according to their ability to donate electrons to the metal. A hydrogen atom (as in **12**) or a halogen ligand (as in **11**) are η^1 ligands. An amine (NR_3), a phosphine (PR_3, as in **11**, **12**, and **16**), CO (as in **14** or **15**), an ether (OR_2) or a thioether (SR_2) are η^2 ligands. Hydrocarbon ligands include alkyl (as the methyl in **13**) or aryl with a carbon–metal bond (η^1), alkenes or carbenes (η^2, Sec. 3.C.i), π-allyl (η^3), conjugated dienes such as buta-1,3-diene (η^4), cyclopentadienyl (η^5, as in **13** and Sec. 2.I.ii), and arenes or benzene (η^6).[49] Note that in the formation of **12** from **11**, the two-electron donor alkene displaces a two-electron donor phosphine. Other typical complexes include chromium hexacarbonyl $Cr(CO)_6$ (**15**), with six η^2 CO ligands; η^6-$C_6H_6Cr(CO)_3$ (**15**), and *tetrakis*-triphenylphosphinopalladium(0), **16**, with four η^2 phosphine ligands.

[46] It has been argued that the geometry is forced upon allylic systems by the σ framework, and not the π system: Shaik, S.S.; Hiberty, P.C.; Ohanessian, G.; Lefour, J. *Nouv. J. Chim.*, ***1985***, *9*, 385. *ab initio* calculations suggest that the allyl cation has significant resonance stabilization, but the allyl anion has little stabilization: Wiberg, K.B.; Breneman, C.M.; LePage, T.J. *J. Am. Chem. Soc.* ***1990***, *112*, 61.

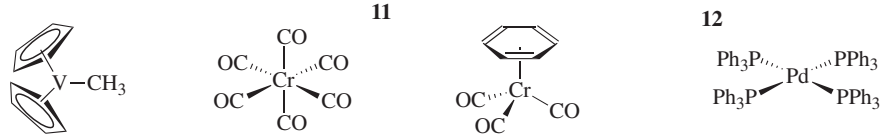
[47] Crabtree, R.H. *The Organometallic Chemistry of the Transition Metals*, Wiley-Interscience, NY, ***2005***; Hill, A.F. *Organotransition Metal Chemistry*, Wiley Interscience, Canberra, ***2002***.

[48] Jardine, F.H., Osborn, J.A.; Wilkinson, G.; Young, G.F. *Chem. Ind. (London)* ***1965***, 560; Imperial Chem. Ind. Ltd., *Neth. Appl. 6,602,062* [*Chem. Abstr.*, *66*: 10556y ***1967***]; Bennett, M.A.; Longstaff, P.A. *Chem. Ind.* ***1965***, 846.

[49] Davies, S.G. *Organotransition Metal Chemistry*, Pergamon, Oxford, ***1982***, p. 4.



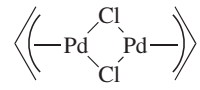
11 **12**



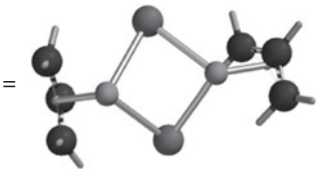
13 **14** **15** **16**

In the context of this section, the electron-delocalized ligand π-allyl is an η^3 donor and it is well known that allylic halides react with $PdCl_2$ to form a *bis*-η^3 complex **17** (see **18**).[50] Complexes such as **17** react with nucleophiles to give the corresponding coupling product (**10-60**).[51] The reactions of allylic acetates or carbons and catalytic amounts of Pd(0) compounds also lead to an η^3 complex that can react with nucleophiles.[52]

$[PdCl(\pi\text{-allyl})]_2 = [PdCl(\eta^2C_3H_5)]_2 =$



$=$



17 **18**

4. *Hyperconjugation*. The type of delocalization called *hyperconjugation* is discussed in Section 2.M.

Note that there are examples of delocalization that cannot be strictly classified as any of these types.

2.D. CROSS CONJUGATION[53]

In a cross-conjugated compound, three groups are present, two of which are not conjugated with each other, although each is conjugated with the third. Some examples are benzophenone (**19**), triene **20**,[54] and divinyl ether **21**. The molecular-orbital method shows that the overlap of six *p* orbitals in **21** (a member of a family of compounds known as dendralenes)[54] gives six molecular orbitals, and the three bonding orbitals are shown in Figure 2.6, along

[50] Trost, B.M.; Strege, P.E.; Weber, L.; Fullerton, T.J.; Dietsche, T.J. *J. Am. Chem. Soc.* ***1978***, *100*, 3407.
[51] Trost, B.M.; Weber, L.; Strege, P.E.; Fullerton, T.J.; Dietsche, T.J. *J. Am. Chem. Soc.*, ***1978*** *100*, 3416.
[52] Melpolder, J.B.; Heck, R.F. *J. Org. Chem.* ***1976***, *41*, 265; Trost, B.M.; Verhoeven, T.R. *J. Am. Chem. Soc.* ***1978***, *100*, 3435; Trost, B.M.; Verhoeven, T.R. *J. Am. Chem. Soc.* ***1980***, *102*, 4730.
[53] See Phelan, N.F.; Orchin, M. *J. Chem. Educ.* ***1968***, *45*, 633.
[54] For a review of such compounds, see Hopf, H. *Angew. Chem. Int. Ed.* ***1984***, *23*, 948.

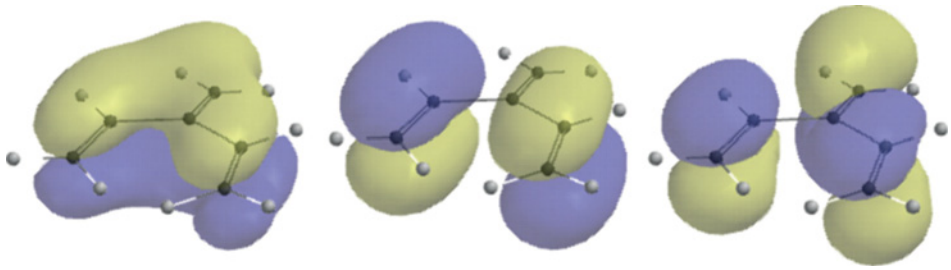
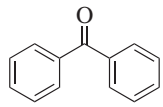
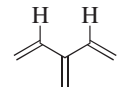


FIGURE 2.6. The three bonding orbitals of the dendralene, 3-methylenepenta-1,4-diene **(20)**.

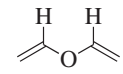
with their energies. Note that two of the carbon atoms do not participate in the $\alpha+\beta$ orbital.



19



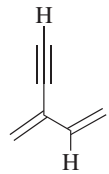
20



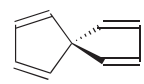
21

The total energy of the three occupied orbitals is $6\alpha+6.900\beta$, so the resonance energy is 0.900β. Molecular-orbital bond orders are 1.930 for the C-1,C-2 bond, 1.859 for the C-3,C-6 bond, and 1.363 for the C-2,C-3 bond.[53] Comparing these values with those for butadiene (Sec. 2.C), the C-1,C-2 bond contains more and the C-3,C-6 bond less double-bond character than the double bonds in buta-1,3-diene. The resonance picture supports this conclusion, since each C-1,C-2 bond is double in three of the five canonical forms, while the C-3,C-6 bond is double in only one. In most cases it is easier to treat cross-conjugated molecules by the molecular-orbital method than by the valence-bond method.

One consequence of this phenomenon is that the bond length of a cross-conjugated C=C unit is slightly longer than that of a non-cross-conjugated bond. In **22**, for example, the cross-conjugated bond is ~0.01 Å longer.[55] The conjugative effect of a C=C or C≡C unit can be measured for a conjugated enone: 4.2 kcal mol^{-1} (17.6 kJ mol^{-1}) for an ethenyl substituent but about 2.3 kcal mol^{-1} (9.6 kJ mol^{-1}) for an ethynyl substituent, which is more variable.[56]



22



23

24

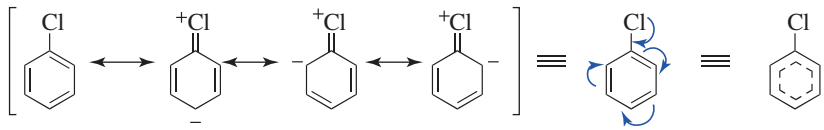
[55] Trætteberg, M.; Hopf, H. *Acta Chem. Scand. B* ***1994***, *48*, 989.
[56] Trætteberg, M.; Liebman, J.F.; Hulce, M.; Bohn, A.A.; Rogers, D.W. *J. Chem. Soc., Perkin Trans. 2* ***1997***, 1925.

The phenomenon of homoconjugation is related to cross conjugation in that there are C=C units in close proximity, but not conjugated one to the other. Homoconjugation arises when the termini of two orthogonal π systems are held in close proximity, as in compounds with a spiro-tetrahedral carbon atom.[57] Spiro[4.4]nonatetraene (**23**)[58] is an example and it is known that the HOMO (see **15.56**) of **23** is raised relative to cyclopentadiene, whereas the LUMO is unaffected[59] Another example is **24**, where there are bond length distortions caused by electronic interactions between the unsaturated bicyclic moiety and the cyclopropyl moiety.[60] It is assumed that cyclopropyl homoconjugation is responsible for this effect. There are also homoconjugation bonds that do not involve carbon, as observed between the Si=Si double bonds through the $SiMe_2$ unit in pentasila-1,4-diene.[61]

2.E. THE RULES OF RESONANCE

One way to express the actual structure of a molecule containing delocalized bonds is to draw several possible structures and to assume that the actual molecule is a hybrid of them. These structures are called canonical forms, but they are not real structures. In other words, the molecule does *not* rapidly shift between them and a given compound has a single actual structure. That structure is always the same all the time and is taken to be a weighted average of all the canonical forms. Drawing canonical forms and deriving the true structures from them is guided by certain rules, including:

1. All the canonical forms must be *bona fide* Lewis structures (Sec. 1.F). For example, none of them may have a carbon with five bonds.
2. The positions of the nuclei must be the same in all the structures. This means that when drawing the various canonical forms, the *electrons* are simply arranged in different ways. For this reason, shorthand ways of representing resonance are easy to devise:



25 **26**

Invoking hyperconjugation (Sec. 2.M), resonance interaction of chlorine with the benzene ring can be represented as shown in **25** or **26** and both representations have been used in the literature to save space. However, the curved-arrow method of **25** will not be used since arrows in this book are used to express the actual movement of electrons in reactions. Representations like **26** will be used occasionally, but more often one or more of the canonical forms will be used. The convention used in dashed-line formulas like **26** is that bonds that are present in all canonical forms are drawn as solid lines while bonds that are not present in all forms are drawn as dashed

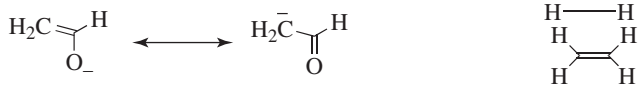
[57] See Durr, H.; Gleiter, R. *Angew. Chem. Int. Ed.* ***1978***, *17*, 559.
[58] For the synthesis of **23**, see Semmelhack, M.F.; Foos, J.S.; Katz, S. *J. Am. Chem. Soc.* ***1973***, *95*, 7325.
[59] Raman, J.V.; Nielsen, K.E.; Randall, L.H.; Burke, L.A.; Dmitrienko, G.I. *Tetrahedron Lett.* ***1994***, *35*, 5973.
[60] Haumann, T.; Benet-Buchholz, J.; Klärner, F.-G.; Boese, R. *Liebigs Ann. Chem.* ***1997***, 1429.
[61] Kosai, T.; Ishida, S.; Iwamoto, T. *J. Am. Chem. Soc.* ***2017***, *139*, 99.

lines. A downside of this model is that electron transfer in reactions associated with benzene rings is difficult to track. For this reason, one of the canonical forms is most often used, as mentioned. In most resonance, σ bonds are not involved, and only the π or unshared electrons are utilized. This means that writing one canonical form for a molecule allows the others to be written by merely moving π and unshared electrons.

3. All atoms taking part in the resonance, that is, covered by delocalized electrons, must lie in a plane or nearly so (Sec. 2.G). This, of course, does not apply to atoms that have the same bonding in all the canonical forms. Maximum overlap of the *p* orbitals leads to the planarity.
4. All canonical forms must have the same number of unpaired electrons. Thus the diradical structure $\bullet CH_2{-}CH{=}CH{-}CH_2\bullet$ is not a valid canonical form for butadiene.
5. The energy of the actual molecule is lower than that of any form, so delocalization is a stabilizing phenomenon.[62]
6. All canonical forms do not contribute equally to the true molecule. Each form contributes in proportion to its stability, the most stable form contributing most. Thus, for ethene, the form $^{+}CH_2{-}CH_2{}^{-}$ has such a high energy compared to $CH_2{=}CH_2$ that it essentially does not contribute at all. This argument was applied to buta-1,3-diene.[41] Equivalent canonical forms, such as **1** and **2**, contribute equally. The greater the number of significant structures that can be written and the more nearly equal they are, the greater the resonance energy, other things being equal.

It is not always easy to decide relative stabilities of imaginary structures; the chemist is often guided by intuition.[63] However, the following rules may be helpful:

1. Structures with more covalent bonds are ordinarily more stable than those with fewer (cf. **6** and **7**).
2. Stability is decreased by an increase in charge separation. Structures with formal charges are less stable than uncharged structures. Structures with more than two formal charges usually contribute very little. An especially unfavorable type of structure is one with two like charges on adjacent atoms.
3. Structures that carry a negative charge on a more electronegative atom are more stable than those in which the charge is on a less electronegative atom. Thus, enolate anion **27** is more stable than canonical form **28**. Similarly, positive charges are best carried on atoms of low electronegativity.



27 **28** **29**

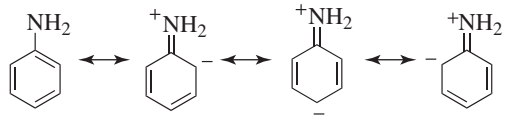
4. Structures with distorted bond angles or lengths are unstable, for example, contributor **29** for ethane.

[62] It has been argued that resonance is not a stabilizing phenomenon in all systems, especially in acyclic ions: Wiberg, K.B. *Chemtracts: Org. Chem.* ***1989***, *2*, 85. See also, Siggel, M.R.; Streitwieser Jr., A.; Thomas, T.D. *J. Am. Chem. Soc.* ***1988***, *110*, 8022; Thomas, T.D.; Carroll, T.X.; Siggel, M.R. *J. Org. Chem.* ***1988***, *53*, 1812.

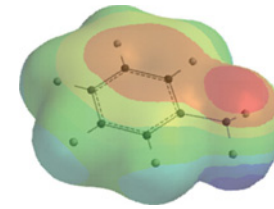
[63] A quantitative method for weighting canonical forms was proposed by Gasteiger, J.; Saller, H. *Angew. Chem. Int. Ed.* ***1985***, *24*, 687.

2.F. THE RESONANCE EFFECT

Resonance always results in a different distribution of electron density than would be the case if there were no resonance (i.e., the electrons are dispersed over several atoms rather than concentrated on one atom). For example, if **30** were the actual structure of aniline, the two unshared electrons of the nitrogen would reside entirely on that atom. The structure of **30** can be represented as a hybrid that includes contributions from the canonical forms shown, indicating that the electron density of the unshared pair does not reside entirely on the nitrogen, but is spread over the ring. However, as shown by the accompanying electron potential map for aniline, the charge distribution is such that most of the electron density resides on nitrogen. The decrease in electron density at one position (and corresponding increase elsewhere) means that the NH_2 contributes or donates electrons to the ring by a resonance effect ("electron releasing," although no actual contribution takes place), and is called the *resonance effect* or *mesomeric effect*. To emphasize the point, the canonical forms associated with **30** indicate electron release from the nitrogen to the benzene ring (the mesomeric effect), and do not necessarily indicate that there are four canonical forms. In ammonia, where resonance is absent, the unshared pair *is* located on the nitrogen atom. As with the field effect (Sec. 1.I), a certain molecule (in this case ammonia) may be thought of as a substrate and effects of substitution on the electron density may be studied. When one of the hydrogen atoms of the ammonia molecule is replaced by a benzene ring (to make aniline, **30**), the electrons are "withdrawn" from the ring by the resonance effect, just as when a methyl group replaces a hydrogen atom of benzene, electrons are "donated" by the field effect of the methyl. Note the increased electron density on the nitrogen in the model, as indicated by the darker area that is above the middle of the model as well and on the nitrogen (on the right side of the model) when compared to benzene in Figure 2.1b. The idea of donation or withdrawal merely arises from the comparison of a compound with a closely related one or comparison of a real compound with a canonical form.



30

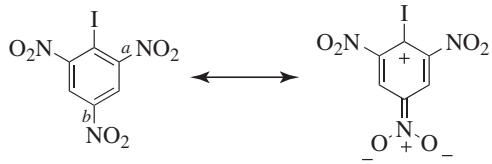


2.G. STERIC INHIBITION OF RESONANCE AND THE INFLUENCES OF STRAIN

Rule 3 given above (Sec. 2.E) states that all the atoms covered by delocalized electrons must lie in a plane or nearly so. Many examples are known where resonance is diminished or prevented because the atoms are sterically forced out of planarity. It is known that if para substituents are able to interact via the through-resonance mechanism, π-electron delocalization due to the substituent effects leads to an increase of stability.[64] If the substituents are both electron donating, there is a significant decrease in stability.

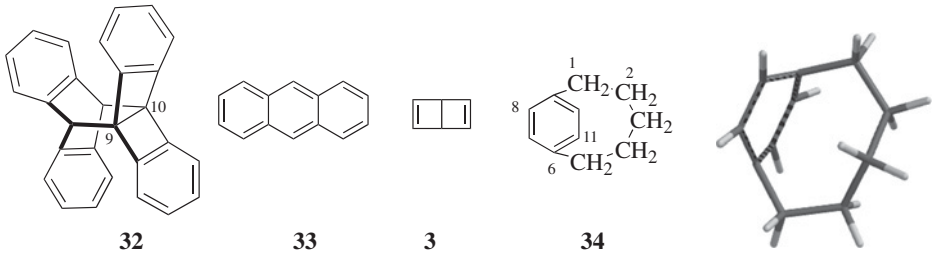
[64] Krygowski, T.M.; Stepień, B.T. *Chem. Rev.* ***2005***, *105*, 3482.

Bond lengths for the C—N bond linking the *o*- and *p*-nitro groups in picryl iodide (**31**) are quite different.[65] Distance *a* in **31** is 1.45 Å, whereas *b* is 1.35 Å. This phenomenon can be explained if the oxygen atoms of the *p*-nitro group are in the plane of the ring and thus in resonance with it, so that *b* has partial double-bond character, while the oxygen atoms of the *o*-nitro groups are forced out of the plane by the large iodine atom. In Section 2.M, it will be seen that the difference in bond length is associated with hyperconjugative effects, represented by the canonical form.



31

Compound **32** is recognized as a Dewar form of anthracene.[66] Dewar-benzene forms such as benzvalene (see **3** above) are recognized as possible valence isomers of benzene.[67] Since **33** is the actual structure of anthracene, it is reasonable to ask if **32** is a canonical structure? The answer is no, because the 9,10 substituents prevent the system from being planar, so **32** is the actual structure of the molecule and it is not in resonance with forms like **33**. This is a consequence of rule 2 (Sec. 2.E). In order for a **33**-like structure to contribute to resonance in **32**, the nuclei would have to be in the same positions in both forms. In anthracene itself (**33**), Dewar structures are thought to contribute to the structure however.



32 **33** **3** **34**

Even the benzene ring can be forced out of planarity.[68] In [5]paracyclophane[69] (**34**) the presence of a short bridge (this is the shortest para bridge known for a benzene ring) forces the benzene ring to become boat-shaped. The distortion in the benzene ring is apparent in the molecular model of **34** that is provided. The parent **34** has so far not proven stable enough for isolation, but a UV spectrum was obtained and showed that the benzene ring was aromatic,

[65] Wepster, B.M. *Prog. Stereochem.* ***1958***, *2*, 99, p. 125. Also see Exner, O.; Folli, U.; Marcaccioli, S.; Vivarelli, P. *J. Chem. Soc., Perkin Trans. 2* ***1983***, 757.

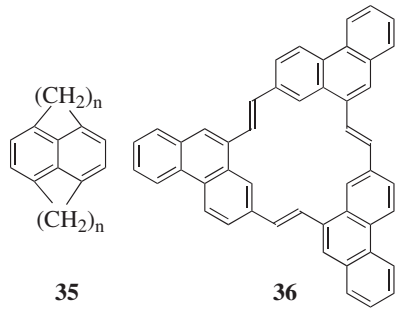
[66] Applequist, D.E.; Searle, R. *J. Am. Chem. Soc.* ***1964***, *86*, 1389.

[67] Cardillo, M.J.; Bauer, S.H. *J. Am. Chem. Soc.* ***1970***, *92*, 2399. See Hückel, E. *Elektrochem.* ***1937***, *43*, 752; van Tamelen, E. *Angew. Chem. Int. Ed.* ***1965***, *4*, 738; Viehe, H.G. *Angew. Chem. Int. Ed.* ***1965***, *4*, 746.

[68] See Ferguson, G.; Robertson, J.M. *Adv. Phys. Org. Chem.* ***1963***, *1*, 203. Hirst, E.S.; Jasti, R. *J. Org. Chem.* ***2012***, *77*, 10473.

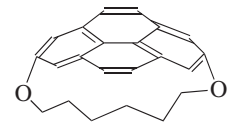
[69] For a monograph, see Keehn, P.M.; Rosenfeld, S.M. *Cyclophanes*, 2 Vols., Academic Press, NY, ***1983***. For reviews, see Bickelhaupt, F. *Pure Appl. Chem.* ***1990***, *62*, 373; Cram, D.J.; Cram, J.M. *Acc. Chem. Res.* ***1971***, *4*, 204; Vögtle, F.; Neumann, P. reviews in *Top. Curr. Chem.* ***1985***, *115*, 1.

despite the distortion.[70] The 8,11-dichloro analog of **34** is a stable solid, and X-ray diffraction showed that benzene ring to be boat-shaped, with one end of the boat bending ~27° out of the plane, and the other ~12°.[71] This compound too is aromatic, as shown by UV and NMR spectra. [6]Paracyclophanes are also bent,[72] but in [7]paracyclophanes the bridge is long enough so that the ring is only moderately distorted. Similarly, [*n,m*]paracyclophanes (**35**), where *n* and *m* are both 3 or less (the smallest yet prepared is [2.2]paracyclophane),[73] have bent (boat-shaped) benzene rings. All these compounds have properties that depart significantly from those of ordinary benzene compounds. Strained paracyclophanes exhibit both π and σ strain, and the effect of the two types of strain on the geometry is approximately additive.[74] In "belt" cyclophane **36**,[75] the molecule has a pyramidal structure with C_3 symmetry rather than the planar structure found in [18]annulene. 1,8-Dioxa[8](2,7)-pyrenophane (**37**)[76] is another severely distorted aromatic hydrocarbon (see **37A**), in which the bridge undergoes rapid pseudorotation (Sec. 4.O.iv). A recent study showed that despite substantial changes in the hybridization of carbon atoms involving changes in the σ-electron structure of pyrenephane such as **37**, the aromaticity of the system decreases slightly and regularly upon increasing the bend angle θ from 0° to 109.2°.[77] Heterocyclic paracyclophane analogs have been prepared, such as the [2.*n*](2,5)pyridinophanes.[78]

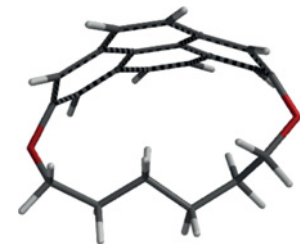


35

36



37



37A

There are many examples of molecules in which benzene rings are forced out of planarity, including 7-circulene (**38**),[79] 9,8-diphenyltetrabenz[*a,c,h,j*]anthracene (**39**),[80] and

[70] Kostermans, G.B.M.; de Wolf, W.E.; Bickelhaupt, F. *Tetrahedron Lett.* ***1986***, *27*, 1095; van Zijl, P.C.M.; Jenneskens, L.W.; Bastiaan, E.W.; MacLean, C.; de Wolf, W.E.; Bickelhaupt, F. *J. Am. Chem. Soc.* ***1986***, *108*, 1415; Rice, J.E.; Lee, T.J.; Remington, R.B.; Allen, W.D.; Clabo Jr., D.A.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1987***, *109*, 2902.

[71] Jenneskens, L.W.; Klamer, J.C.; de Boer, H.J.R.; de Wolf, W.H.; Bickelhaupt, F.; Stam, C.H. *Angew. Chem. Int. Ed.* ***1984***, *23*, 238.

[72] Tobe, Y.; Ueda, K.; Kakiuchi, K.; Odaira, Y.; Kai, Y.; Kasai, N. *Tetrahedron* ***1986***, *42*, 1851.

[73] For a computational study of [2.2]cyclophanes, see Caramori, G.F.; Galembeck, S.E.; Laali, K.K. *J. Org. Chem.* ***2005***, *70*, 3242. Also see Deslongchamps, G.; Deslongchamps, P. *Org. Biomol. Chem.* ***2011***, *9*, 5321.

[74] Stanger, A.; Ben-Mergui, N.; Perl, S. *Eur. J. Org. Chem.* ***2003***, 2709.

[75] Meier, H.; Müller, K. *Angew. Chem. Int. Ed.*, ***1995***, *34*, 1437.

[76] Bodwell, G.J.; Bridson, J.N.; Houghton, T.J.; Kennedy, J.W.J.; Mannion, M.R. *Angew. Chem. Int. Ed.*, ***1996***, *35*, 1320.

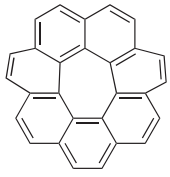
[77] See Bodwell, G.J.; Bridson, J.N.; Cyrański, M.K.; Kennedy, J.W.J.; Krygowski, T.M.; Mannion, M.R.; Miller, D.O. *J. Org. Chem.* ***2003***, *68*, 2089.

[78] Funaki, T.; Inokuma, S.; Ida, H.; Yonekura, T.; Nakamura, Y.; Nishimura, J. *Tetrahedron Lett.* ***2004***, *45*, 2393.

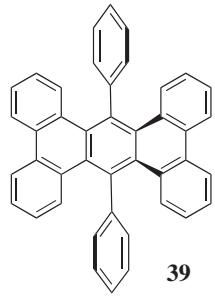
[79] Yamamoto, K.; Harada, T.; Okamoto, Y.; Chikamatsu, H.; Nakazaki, M.; Kai, Y.; Nakao, T.; Tanaka, M.; Harada, S.; Kasai, N. *J. Am. Chem. Soc.* ***1988***, *110*, 3578.

[80] Pascal Jr., R.A.; McMillan, W.D.; van Engen, D.; Eason, R.G. *J. Am. Chem. Soc.* ***1987***, *109*, 4660.

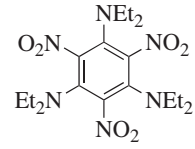
40[81] (see also, Sec. 4.Q.iv). These have been called tormented aromatic systems.[82] The "record" for twisting an aromatic π-electron system appears to be 9,10,11,12,13,14,15,16-octaphenyldibenzo[*a,c*]naphthacene (**41**),[83] which has an end-to-end twist of 105°. This was > 1.5 times greater than observed in any previous polyaromatic hydrocarbon. Perchlorotriphenylene has been reported in the literature and said to show severe molecular twisting; however, recent work suggests this molecule was not actually isolated, with perchlorofluorene-9-spirocyclohexa-2',5'-diene being formed instead.[84] The X-ray structure of the linear [3]phenylene (benzo[3,4]cyclobuta[1,2-*b*]biphenylene, **42**) has been obtained, and it shows a relatively large degree of bond alternation while the center distorts to a cyclic bis(allyl) frame.[85]



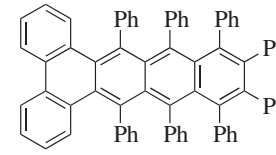
38



39

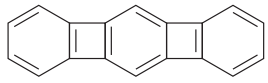


40

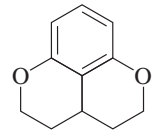


41

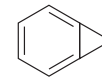
It is also possible to fuse strained rings on benzene, which induces great strain on the benzene ring. In **43**, the benzene ring is compressed by the saturated environment of the tetrahydropyran units and the strain leads to distortion of the benzene ring into a *boat* conformation.[86]



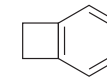
42



43



44



45

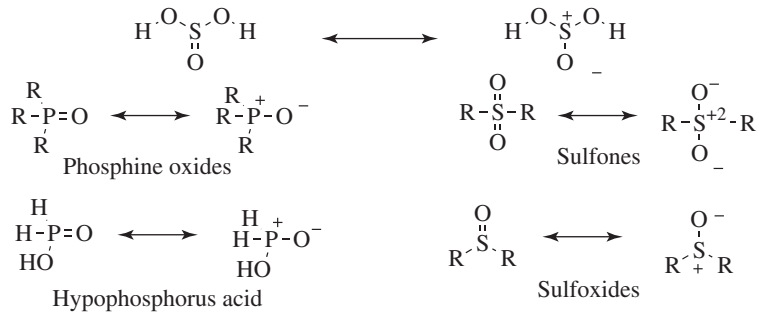
The term "strain-induced bond localization" was introduced in 1930 by Mills and Nixon[87] and is commonly referred to as the *Mills-Nixon effect* (Sec. 11.B.v). Ortho-fused aromatic compounds, such as benzocyclopropene (**44**), are known as cycloproparenes[88] and are highly strained. Benzocyclopropene (**44**) is a stable molecule with a strain energy of 68 kcal mol^{-1} (284.5 kJ mol^{-1}),[89] and the annellated bond is always the shortest, although

[81] Chance, J.M.; Kahr, B.; Buda, A.B.; Siegel, J.S. *J. Am. Chem. Soc.* ***1989***, *111*, 5940.
[82] Pascal Jr., R.A. *Pure Appl. Chem.* ***1993***, *65*, 105.
[83] Qiao, X.; Ho, D.M.; Pascal Jr., R.A. *Angew. Chem. Int. Ed.* ***1997***, *36*, 1531. Also see Menning, S.; Krämer, M.; Duckworth, A.; Rominger, F.; Beeby, A.; Dreuw. A.; Bunz, U.H.F. *J. Org. Chem.* ***2014***, *79*, 6571.
[84] Campbell, M.S.; Humphries, R.E.; Munn, N.M. *J. Org. Chem.* ***1992***, *57*, 641.
[85] Schleifenbaum, A.; Feeder, N.; Vollhardt, K.P.C. *Tetrahedron Lett.* ***2001***, *42*, 7329.
[86] Hall, G.G *J. Chem. Soc., Perkin Trans. 2* ***1993***, 1491.
[87] Mills, W.H.; Nixon, I.G. *J. Chem. Soc.* ***1930***, 2510.
[88] See Halton, B. *Chem. Rev.* ***2003***, *103*, 1327 and reviews cited therein.
[89] Apeloig, Y.; Arad, D. *J. Am. Chem. Soc.****1986***, *108*, 3241.

in benzocyclobutene (**45**) the adjacent bond is the shortest.[90] The bonds of annellation and those adjacent are strained. In cyclopropar enes, there is the expectation of partial aromatic bond localization, with bond length alternation in the aromatic ring.[91] When the bridging units are saturated, the benzene ring current is essentially unchanged, but annelation with one or more cyclobutadieno units disrupts the benzene ring current.[92] The chemistry of the cyclopropar enes is dominated by the influence of the high strain energy. When fused to a benzene ring, the bicyclo[1.1.0]butane unit also leads to strain-induced localization of aromatic π bonds.[93]

2.H. *pπ–dπ* BONDING: YLIDS

In Section 1.D it was stated that, in general, atoms of the second row of the periodic table do not form stable double bonds of the type discussed in Chapter 1 (π bonds formed by overlap of parallel *p* orbitals). However, there is another type of double bond that is particularly common for the second row atoms sulfur and phosphorus. Such a double bond is found in sulfurous acid, H_2SO_3. While the S=O double bond contains one *s* orbital, the second orbital is not a π orbital formed by overlap of half-filled *p* orbitals; instead it is formed by overlap of a filled *p* orbital from the oxygen with an empty *d* orbital from the sulfur. It is called a *pπ–dπ orbital*.[94] Note that this molecule may be represented by two canonical forms, but the bond is nevertheless localized, despite the resonance that is inherent to this structure. Some other examples of *pπ–dπ* bonding are the phosphine oxides, sulfones, hypophosphorus acid, and sulfoxides. Nitrogen analogs are known, but they are less stable than the phosphorus compounds because the resonance is lacking. For example, amine oxides, analogs of phosphine oxides, can only be written $R_3N^+—O^-$. The *pπ–dπ* canonical form is impossible since nitrogen is limited to eight outer-shell electrons.



[90] Boese, R.; Bläser, D.; Billups, W.E.; Haley, M.M.; Maulitz, A.H.; Mohler, D.L.; Vollhardt, K.P.C. *Angew. Chem. Int. Ed.* ***1994***, *33*, 313.

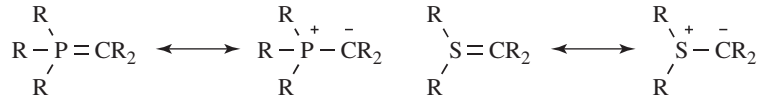
[91] Stanger, A. *J. Am. Chem. Soc.* ***1998***, *120*, 12034; Yáñez, O.M.O.; Eckert-Maksić, M.; Maksić, Z.B. *J. Org. Chem.* ***1995***, *60*, 1638; Eckert-Maksić, M.; Glasovac, Z.; Maksić, Z.B.; Zrinski, I. *J. Mol. Struct. (THEOCHEM)* ***1996***, *366*, 173; Baldridge, K.K.; Siegel, J.S. *J. Am. Chem. Soc.* ***1992***, *114*, 9583.

[92] Soncini, A.; Havenith, R.W.A.; Fowler, P.W.; Jenneskens, L.W.; Steiner, E. *J. Org. Chem.* ***2002***, *67*, 4753

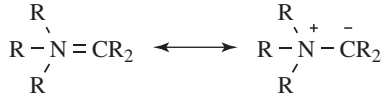
[93] Cohrs, C.; Reuchlein, H.; Musch, P.W.; Selinka, C.; Walfort, B.; Stalke, D.; Christl, M. *Eur. J. Org. Chem.* ***2003***, 901.

[94] For a monograph, see Kwart, H.; King, K. *d-Orbitals in the Chemistry of Silicon, Phosphorus, and Sulfur*, Springer, NY, ***1977***.

In all the examples given above an oxygen atom donates the electron pair and, indeed, oxygen is the most common such atom. In another important class of compounds, called *ylids*, this atom is carbon.[95] There are three common types of ylids: P,[96] S,[97] and N ylids,[98] although As,[99] Se, and so on, ylids are also known. Ylids may be defined as compounds in which a positively charged atom from group 15 or 16 of the periodic table is connected to a carbon atom carrying an unshared pair of electrons (+ and − charges on adjacent atoms). Because of *pπ–dπ* bonding, two canonical forms can be written for P and S, but there is only one for N ylids. Phosphorus ylids are much more stable than N ylids (see also **12-22**), which is one reason why N ylids tend to react more like carbanions (see **13-32** and **18-21**). While S ylids are generally less stable than P ylids, they are common.



Phosphorus ylids Sulfur ylids



Nitrogen ylids

In almost all compounds that have *pπ–dπ* bonds, the central atom is connected to four atoms or three atoms and an unshared pair, and the bonding is approximately tetrahedral. The *pπ–dπ* bond, therefore, does not greatly change the geometry of the molecule in contrast to the normal π bond, which changes an atom from tetrahedral to trigonal. Calculations show that nonstabilized phosphonium ylids have nonplanar ylid carbon geometries whereas stabilized ylids have planar ylid carbons.[100]

[95] See Johnson, A.W. *Ylid Chemistry*, Academic Press, NY, ***1966***; Morris, D.G., *Surv. Prog. Chem.* ***1983***, *10*, 189; Lowe, P.A. *Chem. Ind. (London)* ***1970***, 1070. See Padwa, A.; Hornbuckle, S.F. *Chem. Rev.* ***1991***, *91*, 263.

[96] Although the phosphorus ylid shown has three R groups on the phosphorus atom, other phosphorus ylids are known where other atoms, for example, oxygen, replace one or more of these R groups. When the three groups are all alkyl or aryl, the phosphorus ylid is also called a phosphorane.

[97] See Trost, B.M.; Melvin Jr., L.S. *Sulfur Ylids*, Academic Press, NY, ***1975***; Fava, A. in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*; Elsevier, NY, ***1985***, pp. 299–354; Belkin, Yu.V.; Polezhaeva, N.A. *Russ. Chem. Rev.* ***1981***, *50*, 481; Block, E. in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, part 2, Wiley, NY, ***1981***, pp. 680–702; Block, E. *Reactions of Organosulfur Compounds*; Academic Press, NY, ***1978***, pp. 91–127.

[98] For a review of nitrogen ylids, see Musker, W.K. *Fortschr. Chem. Forsch.* ***1970***, *14*, 295.

[99] For reviews of arsenic ylids, see Lloyd, D.; Gosney, I.; Ormiston, R.A. *Chem. Soc. Rev.* ***1987***, *16*, 45; Yaozeng, H.; Yanchang, S. *Adv. Organomet. Chem.* ***1982***, *20*, 115.

[100] Bachrach, S.M. *J. Org. Chem.* ***1992***, *57*, 4367.

2.I. AROMATICITY[101]

In the 19th century, it was recognized that aromatic compounds[102] differ greatly from unsaturated aliphatic compounds,[103] but for many years chemists were hard pressed to arrive at a mutually satisfactory definition of aromatic character.[104] Qualitatively, there has never been real disagreement. Definitions include statements that aromatic compounds are characterized by a special stability[105] and that they undergo substitution reactions more easily than addition reactions. These definitions are vague, however, and not easily applied to borderline cases. Definitions of aromaticity[106] must encompass molecules ranging from polycyclic conjugated hydrocarbons,[107] to heterocyclic compounds[108] of various ring sizes, to reactive intermediates. In 1925 Armit and Robinson[109] recognized that the aromatic properties of the benzene ring are related to the presence of a closed loop of electrons, the *aromatic sextet* (aromatic compounds are thus the archetypal examples of delocalized bonding), but determining whether rings other than the benzene ring possessed such a loop remained difficult. With the advent of magnetic techniques, most notably NMR, it is possible to determine experimentally whether or not a compound has a closed ring of electrons. Aromaticity can now be defined as the *ability to sustain an induced ring current*. A compound with this ability is called *diatropic*. Although this definition also has its flaws,[110] it is the one most commonly accepted today. There are several methods of determining whether a compound can sustain a ring current, but the most important one is based on NMR chemical

[101] Krygowski, T.M.; Cyrański, M.K. *Chem. Rev.* ***2001***, *101*, 1385; Katritzky, A.R.; Jug, K.; Oniciu, D.C. *Chem. Rev.* ***2001***, 1421; Fowler, P.W.; Lillington, M.; Olson, L.P. *Pure Appl. Chem.* ***2007***, *79*, 969. See also, Cyrański, M.K.; Krygowski, T.M.; Katritzky, A.R.; Schleyer, P.v.R. *J. Org. Chem.* ***2002***, *67*, 1333. For a discussion of excited state aromaticity and antiaromaticity, see Rosenberg, M.; Dahlstrand, C.; Kilså, K.; Ottosson, H. *Chem. Rev.* ***2014***, *114*, 5379.

[102] See Lloyd, D. *The Chemistry of Conjugated Cyclic Compounds*, Wiley, NY, ***1989***; *Non-Benzenoid Conjugated Carbocyclic Compounds*, Elsevier, NY, ***1984***; Garratt, P.J. *Aromaticity*, Wiley, NY, ***1986***; Balaban, A.T.; Banciu, M.; Ciorba, V. *Annulenes, Benzo-, Hetero-, Homo-Derivatives and their Valence Isomers*, 3 Vols., CRC Press, Boca Raton, FL, ***1987***; Badger, G.M. *Aromatic Character and Aromaticity*, Cambridge University Press, Cambridge, ***1969***; Snyder, J.P. *Nonbenzenoid Aromatics*, 2 Vols., Academic Press, NY, ***1969–1971***; Bergmann, E.D.; Pullman, B. *Aromaticity, Pseudo-Aromaticity, and Antiaromaticity*, Israel Academy of Sciences and Humanities, Jerusalem, ***1971***. See Gorelik, M.V. *Russ. Chem. Rev.* ***1990***, *59*, 116; Stevenson, G.R. *Mol. Struct. Energ.* ***1986***, *3*, 57; Figeys, H.P. *Top. Carbocyclic Chem.* ***1969***, *1*, 269; Garratt, P.J.; Sargent, M.V. papers in *Top. Curr. Chem.* ***1990***, 153 and *Pure Appl. Chem.* ***1980***, *52*, 1397.

[103] See Snyder, J.P., in Snyder, J.P. *Nonbenzenoid Aromatics*, Vol. 1, Academic Press, NY, ***1971***, pp. 1–31. See also, Balaban, A.T. *Pure Appl. Chem.* ***1980***, *52*, 1409.

[104] See Jones, A.J. *Pure Appl. Chem.* ***1968***, *18*, 253. For methods of assigning aromaticity, see Jug, K.; Köster, A.M. *J. Phys. Org. Chem.* ***1991***, *4*, 163; Zhou, Z.; Parr, R.G. *J. Am. Chem. Soc.* ***1989***, *111*, 7371; Katritzky, A.R.; Barczynski, P.; Musumarra, G.; Pisano, D.; Szafran, M. *J. Am. Chem. Soc.* ***1989***, *111*, 7. See also, Bird, C.W. *Tetrahedron* ***1985***, *41*, 1409; ***1986***, *42*, 89; ***1987***, *43*, 4725; Gleiter, R. Haberhauer, G. *Aromaticity and Other Conjugation Effects* Wiley-VCH, Weinheim, ***2012***.

[105] For a discussion of topological resonance energy (TRE), which is examined by graph theory, see Aihara, J. *Bull. Chem. Soc. Jpn.* ***2016***, *89*, 1425.

[106] For a critique of the concept of aromaticity, see Stanger, A. *Chem. Commun.* ***2009***, 1939.

[107] Randić, M. *Chem. Rev.* ***2003***, *103*, 3449. Sakai, S. *J. Phys. Org. Chem.* ***2014***, *27*, 555.

[108] Balaban, A.T.; Oniciu, D.C.; Katritzky, A.R. *Chem. Rev.* ***2004***, *104*, 2777.

[109] Armit, J.W.; Robinson, R. *J. Chem. Soc.* ***1925***, *127*, 1604.

[110] Jones, A.J. *Pure Appl. Chem.* ***1968***, *18*, 253 (pp. 266–274); Mallion, R.B. *Pure Appl. Chem.* ***1980***, 52, 1541. Also see, Schleyer, P.v.R.; Jiao, H. *Pure Appl. Chem.* ***1996***, *68*, 209. For a discussion of the relationship between Pauling resonance energy and ring current, see Havenith, R.W.A. *J. Org. Chem.* ***2006***, *71*, 3559.

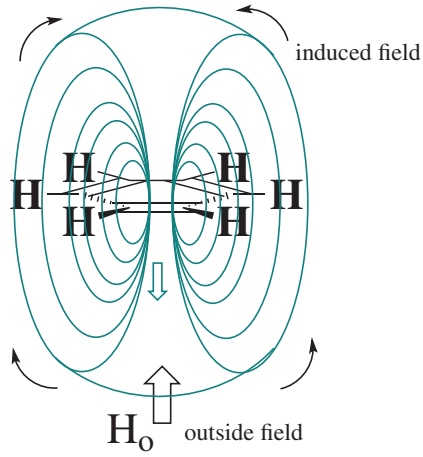


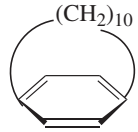
FIGURE 2.7. Ring current in benzene.

shifts.[111] Nucleus-independent chemical shift (NICS) analysis is a method used to identify local and global induced ring currents within multi-ring systems.[112] The NICS probes are positioned along the *x* axis and, if needed, along the *y* axis, at a constant height above the system under study. The change in the induced field along these axes allows the identification of ring currents.[112]

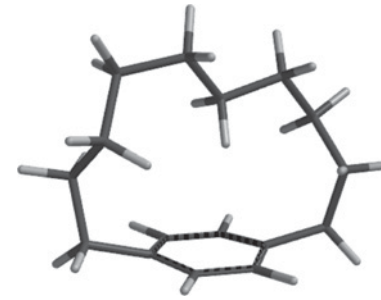
Water-soluble calix[4]resorcarenes (Sec. 3.C.ii) have been developed as enantioselective NMR shift reagents for aromatic compounds.[113] In order to understand this, it is necessary to remember that, as a general rule, the value of the chemical shift of a proton in an NMR spectrum depends on the electron density of its bond; the greater the density of the electron cloud surrounding or partially surrounding a proton, the more upfield is its chemical shift (a lower value of δ). However, this rule has several exceptions; one is for protons in the vicinity of an aromatic ring. When an external magnetic field is imposed upon an aromatic ring (as in an NMR instrument), the closed loop of aromatic electrons circulates in a diamagnetic ring current, which generates a field of its own (ring current; known as magnetic anisotropy).[114] As seen in Figure 2.7, this induced field curves around and in the area of the proton is parallel to the external field, so the field "seen" by the aromatic protons is greater than it would have been in the absence of the diamagnetic ring current. The protons are moved downfield (to higher δ) compared to where they would be if electron density were the only factor. Thus ordinary alkene hydrogen atoms are found at ∼5–6 δ, while the hydrogen atoms of benzene rings are located at ∼7–8 δ. However, if there were protons located above or within the ring, they would be subjected to a *decreased* field and should appear at lower δ values than normal CH_2 groups (normal δ for CH_2 is ∼1–2). The NMR spectrum of [10]paracyclophane

[111] Geuenich, D.; Hess, K.; Köhler, F.; Herges, R. *Chem. Rev.* ***2005***, *105*, 3758; Haddon, R.C.; Haddon, V.R.; Jackman, L.M. *Fortschr. Chem. Forsch.* ***1971***, *16*, 103; Dauben Jr., H.J.; Wilson, J.D.; Laity, J.L. in Snyder, J.P. *Nonbenzenoid Aromatics*, Vol. 2, Academic Press, NY, ***1971***, pp. 167–206.
[112] Gershoni-Poranne, R.; Stanger, A. *Chem. Eur. J.* ***2014***, *20*, 5673.
[113] Dignam, C.F.; Zopf, J.J.; Richards, C.J.; Wenzel, T.J. *J. Org. Chem.* ***2005***, *70*, 8071.
[114] See Baranac-Stojanović, M.; Koch, A.; Kleinpeter, E. *Chem. Eur. J.* ***2012***, *18*, 370.

(**46A**) showed that this was indeed the case,[115] and the CH_2 peaks were shifted to lower δ the closer they were to the middle of the chain. This fact that a portion of the methylene chain is positioned directly over the benzene ring is easier to see in the molecular model **46B**, and those protons are subject to the anisotropy shift.



46A



46B

It follows from this analysis that aromaticity can be determined from an NMR spectrum. If the protons attached to the ring are shifted downfield from the normal alkene region, it can be concluded that the molecule is diatropic and hence aromatic. In addition, if the compound has protons above or within the ring (see an example of the latter in Sec. 2.Kvi), then these will be shifted upfield if the compound is diatropic. However, local framework effects are important to aromaticity, and it has been argued that downfield chemical shifts of arene hydrogen atoms are not reliable indicators of aromaticity.[116] One drawback to this method is that it cannot be applied to compounds that have no protons in either category, for example, the dianion of squaric acid (Sec. 2.L). Unfortunately, ^{13}C NMR is of no help here, since these spectra do not show ring currents.[117]

Bickelhaupt has argued that "double-bond delocalization" actually refers to bond-length equalization.[117] The major effect is argued to be optimal sigma overlap, where the π electrons force the bonds to a somewhat shorter distance.[117] For antiaromatic systems, the π electrons are said to have a stronger localizing drive.[117]

It has been shown that when the nucleus independent chemical shifts for a set of aromatic and antiaromatic hydrocarbons are summed, there is a linear relationship with the magnetic susceptibility exaltation (the difference between the measured magnetic susceptibility of a compound and a calculated value based on group additivity tables) for neutral, cationic, and monoanionic species.[118] Aromatic and antiaromatic dianions show a similar relationship but with a different slope.[118] Antiaromatic dications and dianions can be used to evaluate the effectiveness of theoretical treatments of antiaromaticity such as the nucleus-independent chemical shift (NICS).[119]

[115] Waugh, J.S.; Fessenden, R.W. *J. Am. Chem. Soc.* ***1957***, *79*, 846. See also, Pascal, Jr., R.A.; Winans, C.G.; van Engen, D. *J. Am. Chem. Soc.* ***1989***, *111*, 3007.
[116] Wannere, C.S.; Corminboeuf, C.; Allen, W.D.; Schaefer III, H.F.; Schleyer, P.v.R. *Org. Lett.* ***2005***, *7*, 1457.
[117] See Günther, H.; Schmickler, H. *Pure Appl. Chem.* ***1975***, *44*, 807. See Pierrefixe, S.C.A.H.; Bickelhaupt, F.M. *Chem. Eur. J.* ***2007***, *13*, 6321; Pierrefixe, S.C.A.H.; Bickelhaupt, F.M. *J. Phys. Chem. A* ***2008***, *112*, 12816.
[118] Mills, N.S.; Llagostera, K.B. *J. Org. Chem.* ***2007***, *72*, 9163.
[119] Mills, N.S. *Pure Appl. Chem.* ***2012***, *84*, 1101.

It appears that there are both energetic and magnetic criteria for aromaticity. The so-called *circuit resonance energy*[120] is an important quantity that connects energetic and magnetic criteria of aromaticity. It is defined as a contribution of each cyclic path in a polycyclic π system to the aromatic stabilization energy. The individual circuit contributions to aromaticity from the magnetic response of a polycyclic system have been determined, and named circuit resonance energies, with the same sign and essentially the same magnitude as the corresponding cyclic conjugation energy defined by Bosanac and by Gutman.[121] Ring-current diamagnetism was taken as the tendency of a cyclic π system to retain aromatic stabilization energy of the individual circuits.

A controlled switching from the aromatic ground state of benzene to two different nonaromatic states, has been reported using a laser pulse.[122] The criterion of aromaticity in this experiment are the bond orders and Mulliken charges. The nonaromatic states show localized bonds and partial charges on the carbon atoms.[122] There are also so-called "contorted aromatics," so named due to steric congestion in their periphery that results in nonplanar structures.[123]

Antiaromatic systems exhibit a *paramagnetic* ring current,[124] which causes protons on the outside of the ring to be shifted *upfield* while any inner protons are shifted *downfield*, in sharp contrast to a diamagnetic ring current, which causes shifts in the opposite directions (see above). Compounds that sustain a paramagnetic ring current are called *paratropic*; and are prevalent in four- and eight-electron systems. As with aromaticity, antiaromaticity should be at a maximum when the molecule is planar and when bond distances are equal. The diamagnetic and paramagnetic effects of the ring currents associated with aromatic and antiaromatic compounds (i.e., shielding and deshielding of nuclei) can be measured by a simple and efficient criterion known as nucleus-independent chemical shift (NICS).[125] The aromatic–antiaromatic ring currents reflect the extra π effects that the molecules experience. The unique near-zero value of NICS at the cyclobutadiene ring center is due to cancellation by large and opposite anisotropic components.[126] The four-membered ring is puckered rather than planar, and this nonplanar preference is due to $\sigma \rightarrow \pi^*$ hyperconjugative interactions across the ring (Sec. 2.M).[127]

Apart from the experimental NMR techniques, there are at least four theoretical models for aromaticity that have been compared and evaluated for predictive ability.[128] The *Hess-Schaad model*[129] is good for predicting aromatic stability of benzenoid hydrocarbons, but does not predict reactivity. The *Herndon model*[130] is also good for predicting aromatic

[120] Aihara, J. *J. Am. Chem. Soc.* ***2006***, *128*, 2873.
[121] Gutman, I. *Monatsh. Chem.* ***2005***, *136*, 1055.; Bosanac, S.; Gutman, I. *Z. Naturforsch.* ***1977***, *32a*, 10; Gutman, I.; Bosanac, S. *Tetrahedron* ***1977***, *33*, 1809.
[122] Ulusoy, I.S.; Nest, M. *J. Am. Chem. Soc.* ***2011***, *133*, 20230.
[123] Nuckolls, C. *Acc. Chem. Res.* ***2015***, *48*, 267.
[124] Pople, J.A.; Untch, K.G. *J. Am. Chem. Soc.* ***1966***, *88*, 4811; Longuet-Higgins, H.C. in Garratt, P.J. *Aromaticity*, Wiley, NY, ***1986***, pp. 109–111.
[125] Schleyer, P.v.R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N.J.R.v.E. *J. Am. Chem. Soc.* ***1996***, *118*, 6317. For a discussion of low-lying electronic states, see Karadakov, P.B.; Hearnshaw, P.; Horner, K.E. *J. Org. Chem.* ***2016***, *81*, 11346.
[126] Schleyer, P.v.R.; Manoharan, M.; Wang, Z.-X.; Kiran, B.; Jiao, H.; Puchta, R.; Hommes, N.J.R.v.E. *Org. Lett.* ***2001***, *3*, 2465
[127] McKee, W.C.; Wu, J.I.; Hofmann, M.; Berndt, A.; Schleyer, P.v.R. *Org. Lett.* ***2012***, *14*, 5712.
[128] Plavšić, D.; Babić, D.; Nikolić, S.; Trinajstic, N. *Gazz. Chim. Ital.*, ***1993***, *123*, 243.
[129] Hess Jr., B.A.; Schaad, L.J. *J. Am. Chem. Soc.* ***1971***, *93*, 305.
[130] Herndon, W.C. *Isr. J. Chem.* ***1980***, *20*, 270.

stability, but is unreliable for benzenoidicity and does not predict reactivity. The *conjugated-circuit model*[131] is very good for predicting aromatic stability but not reactivity, and the *hardness model*[132] is best for predicting kinetic stability. Delocalization energy of π electrons has been used as an index for aromaticity in polycyclic aromatic hydrocarbons.[133] The claims for linear relationships between aromaticity and energetics, geometries, and magnetic criteria were said to be *invalid* for any representative set of heteroaromatics in which the number of heteroatoms varies.[134]

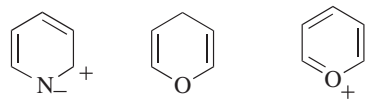
It should be emphasized that the old and new definitions of aromaticity are not necessarily parallel. If a compound is diatropic and therefore aromatic under the new definition, it is more stable than the canonical form of lowest energy, but this does not mean that it will be stable to air, light, or common reagents, since *this* stability is determined not by the resonance energy, but by the difference in free energy between the molecule and the transition states for the reactions involved; and these differences may be quite small, even if the resonance energy is large. A unified theory has been developed that relates ring currents, resonance energies, and aromatic character.[135] It is noted that aromaticity varies in magnitude relatively and sometimes absolutely with the molecular environment, which includes the polarity of the medium.[136]

The vast majority of aromatic compounds have a closed loop of six electrons in a ring (the aromatic sextet), and those compounds will be considered first.[137] Note that a "formula periodic table" for the benzenoid polyaromatic hydrocarbons has been developed.[138] The aromaticity of metal clusters is also important.[139]

2.I.i. Six-Membered Rings

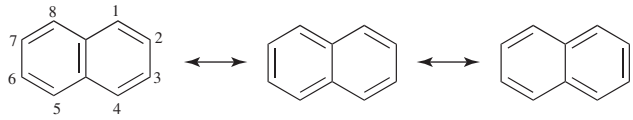
Not only is the benzene ring aromatic, but so are many heterocyclic analogs in which one or more heteroatoms replace carbon in the ring.[140] When nitrogen is the heteroatom, there is a sextet and there is an unshared electron pair on the nitrogen that does not participate in the aromaticity. Therefore, derivatives such as *N*-oxides or pyridinium ions are still aromatic. There are more significant canonical forms (e.g., **47**) for nitrogen heterocycles than for benzene. Where oxygen or sulfur is the heteroatom, it must be present in its ionic form (**49**) in order to possess the valence of 3 demanded for participation in such a system. Thus, pyran (**48**) is not aromatic, but the pyrylium ion (**49**) is.[141]

[131] Randić, M. *Chem. Phys. Lett.* ***1976***, *38*, 68.
[132] Zhou, Z.; Parr, R.G. *J. Am. Chem. Soc.* ***1989***, *111*, 7371; Zhou, Z.; Navangul, H.V. *J. Phys. Org. Chem.* ***1990***, *3*, 784.
[133] See Cyrański, M.K. *Chem. Rev.* ***2005***, *105*, 3773.
[134] Katritzky, A.R.; Karelson, M.; Sild, S.; Krygowski, T.M.; Jug, K. *J. Org. Chem.* ***1998***, *63*, 5228.
[135] Haddon, R.C. *J. Am. Chem. Soc.* ***1979***, *101*, 1722; Haddon, R.C.; Fukunaga, T. *Tetrahedron Lett.* ***1980***, *21*, 1191.
[136] Katritzky, A.R.; Karelson, M.; Wells, A.P. *J. Org. Chem.* ***1996***, *61*, 1619.
[137] Values of molecular-orbital energies for many aromatic systems, calculated by the HMO method, are given in Coulson, C.A.; Streitwieser Jr., A. *A Dictonary of π Electron Calculations*, W.H. Freeman, San Francisco, ***1965***. Values calculated by a variation of the SCF method are given by Dewar, M.J.S.; Trinajstic, N. *Collect. Czech. Chem. Commun.* ***1970***, *35*, 3136, 3484.
[138] Dias, J.R. *Chemistry in Britain* ***1994***, 384.
[139] *Aromaticity and Metal Clusters (Atoms, Molecules, and Clusters)* Chattaraj, P.K. (Ed), CRC Press, Boca Raton, FL. ***2010***.
[140] See Katritzky, A.R.; Karelson, M.; Malhotra, N. *Heterocycles* ***1991***, *32*, 127.
[141] See Balaban, A.T.; Schroth, W.; Fischer, G. *Adv. Heterocycl. Chem.* ***1969***, *10*, 241.



47 **48** **49**

In systems of fused six-membered aromatic rings,[142] the principal canonical forms are usually not all equivalent. Naphthalene, **50**, has a central double bond and is thus different from the other two canonical forms, which are equivalent to each other.[143] For naphthalene, these are the only forms that can be drawn without consideration of Dewar forms or those with charge separation.[144] If it is assumed that the three forms contribute equally, the 1,2 bond has more double-bond character than the 2,3 bond. Molecular-orbital calculations show bond orders of 1.724 and 1.603, respectively (cf. benzene, 1.667). In agreement with these predictions, the 1,2 and 2,3 bond distances are 1.36 Å and 1.415 Å, respectively,[145] and ozone (**19-09** and **15-54**) preferentially attacks the 1,2 bond.[146] This nonequivalency of bonds, called *partial bond fixation*,[147] is found in nearly all fused aromatic systems. It is noted that a strained naphthalene derivative has been prepared in which one benzene ring is fused to two bicyclic systems. In this new naphthalene derivative, one six-membered ring has equalized bond lengths but the other ring has alternating bond lengths.[148] The aromaticity of cation, anion and ion-radical derivatives of naphthalene and other arenes has also been calculated.[149] A six-membered ring with a circle is often used to indicate an aromatic system, but Kekulé structures having the C=C units rather than a circle are used most often in this book. This statement is made here because one circle can be used for benzene, but it would be misleading to use two circles for naphthalene, for example, because that would imply 12 aromatic electrons, when naphthalene has only 10.[150]



50

[142] See Gutman, I.; Cyvin, S.J. *Introduction to the Theory of Benzenoid Hydrocarbons*, Springer, NY, ***1989***; Dias, J.R. *Handbook of Polycyclic Hydrocarbons, Part A: Benzenoid Hydrocarbons*, Elsevier, NY, ***1987***; Clar, E. *Polycyclic Hydrocarbons*, 2 Vols., Academic Press, NY, ***1964***. For a "periodic table" that systematizes fused aromatic hydrocarbons, see Dias, J.R. *Acc. Chem. Res.* ***1985***, *18*, 241; *Top. Curr. Chem.* ***1990***, *253*, 123; *J. Phys. Org. Chem.* ***1990***, *3*, 765.

[143] See Fuji, Z.; Xiaofeng, G.; Rongsi, C. *Top. Curr. Chem.* ***1990***, *153*, 181; Wenchen, H.; Wenjie, H. *Top. Curr. Chem.* ***1990***, *153*, 195; Sheng, R. *Top. Curr. Chem.* ***1990***, *153*, 211; Rongsi, C.; Cyvin, S.J.; Cyvin, B.N.; Brunvoll, J.; Klein, D.J. *Top. Curr. Chem.* ***1990***, *153*, 227, and references cited in these papers. For a monograph, see Cyvin, S.J.; Gutman, I. *Kekulé Structures in Benzenoid Hydrocarbons*, Springer, NY, ***1988***.

[144] Sironi, M.; Cooper, D.L.; Gerratt, J.; Raimondi, M. *J. Chem. Soc., Chem. Commun.* ***1989***, 675.

[145] Cruickshank, D.W.J. *Tetrahedron* ***1962***, *17*, 155.

[146] Kooyman, E.C. *Recl. Trav. Chim. Pays-Bas* ***1947***, *66*, 201.

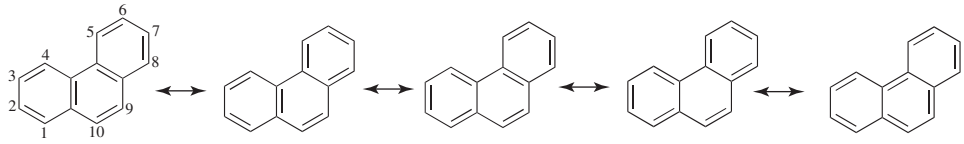
[147] For a review, see Efros, L.S. *Russ. Chem. Rev.* ***1960***, *29*, 66.

[148] Uto, T.; Nishinaga, T.; Matsuura, A.; Inoue, R.; Komatsu, K. *J. Am. Chem. Soc.* ***2005***, *127*, 10162.

[149] Rosokha, S.V.; Kochi, J.K. *J. Org. Chem.* ***2006***, *71*, 9357.

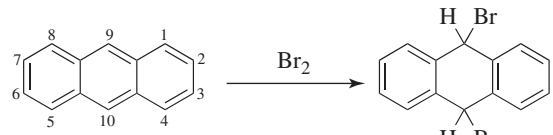
[150] See Belloli, R. *J. Chem. Educ.* ***1983***, *60*, 190.

In phenanthrene, where the 9,10 bond is a single bond in only one of five canonical forms, bond fixation is significant and this bond is readily attacked by many reagents:[151] It has been observed that increased steric crowding leads to an increase in Dewar-benzene type structures.[152] In general there is a good correlation between bond distances in fused aromatic compounds and bond orders. Another experimental quantity that correlates well with the bond order of a given bond in an aromatic system is the NMR coupling constant for coupling between the hydrogen atoms on the two carbons of the bond.[153]



Phenanthrene

The resonance energies of fused systems increase as the number of principal canonical forms increases, as predicted by rule 6 (Sec. 2.E).[154] Thus, for benzene, naphthalene, anthracene, and phenanthrene, for which can be drawn, respectively, two, three, four, and five canonical forms, the resonance energies are, respectively, 36, 61, 84, and 92 kcal mol^{-1} (152, 255, 351, and 385 kJ mol^{-1}), calculated from heat of combustion data.[155] Note that when phenanthrene, which has a total resonance energy of 92 kcal mol^{-1} (385 kJ mol^{-1}), loses the 9,10 bond by attack of a reagent such as ozone or bromine, two complete benzene rings remain, each with 36 kcal mol^{-1} (152 kJ mol^{-1}) that would be lost if those rings were similarly attacked. The fact that anthracene undergoes many reactions across the 9,10 positions can be explained in a similar manner. Resonance energies for fused systems can be estimated by counting canonical forms.[156] Calculations offer complementary evidence for the repulsive character of the H—H interactions in phenanthrene's bay region.[157]

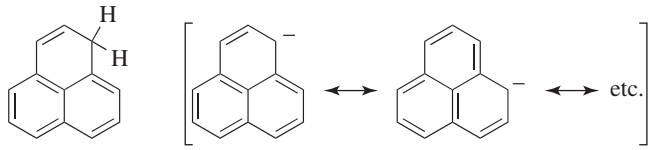


Anthracene

Not all fused systems can be fully aromatic. Thus for phenalene (**51**) there is no way to distribute double bonds so that each carbon has one single and one double bond.[158] However, phenalene is acidic and reacts with potassium methoxide to give the corresponding

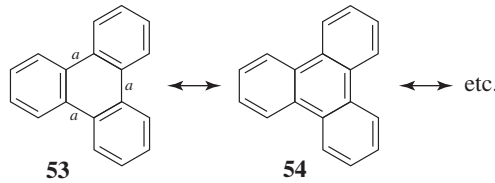
[151] See also, Lai, Y. *J. Am. Chem. Soc.* ***1985***, *107*, 6678.
[152] Zhang, J.; Ho, D.M.; Pascal Jr., R.A. *J. Am. Chem. Soc.* ***2001***, *123*, 10919.
[153] Cooper, M.A.; Manatt, S.L. *J. Am. Chem. Soc.* ***1969***, *91*, 6325.
[154] See Herndon, W.C.; Ellzey Jr., M.L. *J. Am. Chem. Soc.* ***1974***, *96*, 6631.
[155] Wheland, G.W. *Resonance in Organic Chemistry*, Wiley, NY, ***1955***, p. 98.
[156] Swinborne-Sheldrake, R.; Herndon, W.C. *Tetrahedron Lett.* ***1975***, 755.
[157] Poater, J.; Visser, R.; Solà, M.; Bickelhaupt, F.M. *J. Org. Chem.* ***2007***, *72*, 1134.
[158] For reviews of phenalenes, see Murata, I. *Top. Nonbenzenoid Aromat. Chem.* ***1973***, *1*, 159; Reid, D.H. *Q. Rev. Chem. Soc.* ***1965***, *19*, 274.

anion (**52**), which is completely aromatic. The corresponding radical and cation, in which the resonance energies are the same, are also completely aromatic (Sec. 2.I.iii).[159]



51 **52**

Molecules that contain fused rings, such as phenanthrene or anthracene, are generally referred to as linear or angular polyacenes. *Acenes* are a class of organic compounds and polycyclic aromatic hydrocarbons made up of linearly fused benzene rings. In a fused system, with a focus on each individual ring, there are not six electrons for each ring.[160] In naphthalene, for example, if one ring is to have six, the other must have only four. The greater reactivity of the ring system of naphthalene compared with benzene has been explained by regarding one of the naphthalene rings as aromatic and the other as a buta-1,3-diene system.[161] This effect can become extreme, as in the case of triphenylene, **53**.[162] For this compound, there are eight canonical forms like **53**, in which none of the three bonds marked *a* is a double bond and only one form (**54**) in which at least one of them is double. Thus the molecule behaves as if the 18 electrons were distributed so as to give each of the outer rings a sextet, while the middle ring is "empty." Since none of the outer rings need share any electrons with an adjacent ring, they are as stable as benzene; triphenylene, unlike most fused aromatic hydrocarbons, does not dissolve in concentrated sulfuric acid and has a low reactivity.[163] This phenomenon, whereby some rings in fused systems give up part of their aromaticity to adjacent rings, is called *annellation* and can be demonstrated by UV spectra[142] as well as chemical reactivity. In general, an increase of size of both linear and angular polyacenes is associated with a substantial decrease in their aromaticity, with a greater decrease for the linear polyacenes.[164] It is noted that molecular loops and belts can be made that involve acenes.[165] Heteroatoms can be incorporated into an acene, especially nitrogen.[166]



53 **54**

[159] Pettit, R. *J. Am. Chem. Soc.* ***1960***, *82*, 1972.
[160] See Glidewell, C.; Lloyd, D. *Tetrahedron* ***1984***, *40*, 4455, *J. Chem. Educ.* ***1986***, *63*, 306; Hosoya, H. *Top. Curr. Chem.* ***1990***, *153*, 255.
[161] Meredith, C.C.; Wright, G.F. *Can. J. Chem.* ***1960***, *38*, 1177.
[162] For a review of triphenylenes, see Buess, C.M.; Lawson, D.D. *Chem. Rev.* ***1960***, *60*, 313.
[163] Clar, E.; Zander, M. *J. Chem. Soc.* ***1958***, 1861.
[164] Cyrański, M.K.; Stępień, B.T.; Krygowski, T.M. *Tetrahedron* ***2000***, *56*, 9663.
[165] Tahara, K.; Tobe, Y. *Chem. Rev.* ***2006***, *106*, 5274
[166] Bunz, U.H.F. *Acc. Chem. Res.* ***2015***, *48*, 1676.

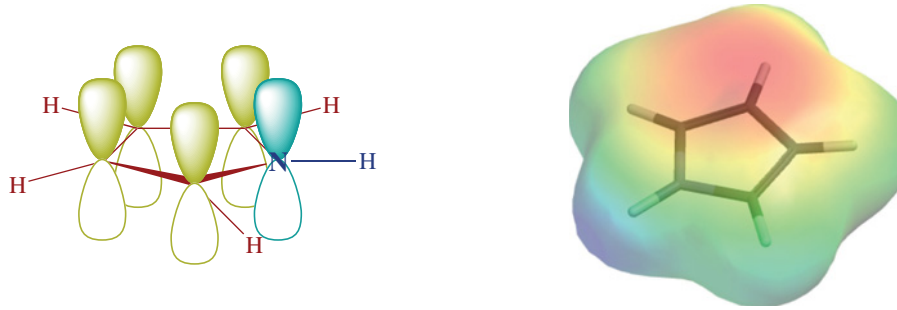


FIGURE 2.8. Overlap of five *p* orbitals in pyrrole and the electron potential map of pyrrole.

[*n*]Radialenes[167] are organic compounds that contain a ring, with cross-conjugated exocyclic double bonds. It has been shown that six-membered rings with large positive extracyclic resonance energies (ECREs) values are aromatic and "benzene-like," whereas those with negative or close to zero values are "[6]radialene-like" and not aromatic.[168]

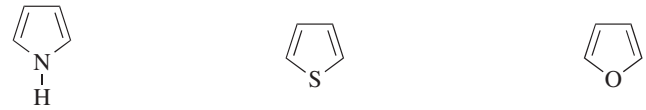
Quasi-aromatic compounds have been defined: "They contain an acyclic conjugated-electron system and show chemical properties typical of aromatic compounds, especially reaction by substitution with retention of type."[169] In general terms, "cyclic π electron systems in which three units as CH—CH—CH are replaced by —Y···M(+)···X—, where X and Y are electronegative atoms that are able to chelate atoms/ions as proton or cations of the first and second group of the periodic table behave as if they were aromatic."[170]

2.I.ii. Five-, Seven-, and Eight-Membered Rings

Aromatic sextets can also be present in five- and seven-membered rings. If a five-membered ring has two double bonds and the fifth atom possesses an unshared pair of electrons, as in pyrrole, the ring has five *p* orbitals that can overlap to create five new orbitals: three bonding and two antibonding. There are six electrons for these orbitals: the four *p* orbitals of the double bonds each contribute one and the filled orbital contributes the other two. The six electrons occupy the bonding orbitals and constitute an aromatic sextet, illustrated in Figure 2.8.

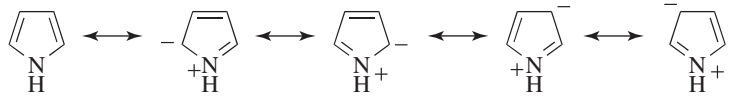
The electron potential map of pyrrole in Figure 2.8 shows the aromatic cloud (the dark area near the top of the model), indicative of significant electron density on nitrogen. The heterocyclic compounds pyrrole, thiophene, and furan are the most important examples of this kind of aromaticity, although furan has a lower degree of aromaticity when compared to the other two.[171]

[167] Hopf, H.; Maas, G. *Angew. Chem., Int. Ed. Engl.* ***1992***, *31*, 931.
[168] Berionni, G.; Wu, J.I-C.; Schleyer, P.v.R. *Org. Lett.* ***2014***, *16*, 6166.
[169] Mester, L. *J. Am. Chem. Soc.* ***1955***, *77*, 4301.
[170] Krygowski, T.M.; Bankiewicz, B.; Czarnocki, Z.; Palusiak, M. *Tetrahedron.* ***2015***, *71*, 4895.
[171] The order of aromaticity of these compounds is benzene > thiophene > pyrrole > furan, as calculated by an aromaticity index based on bond distance measurements. This index has been calculated for five- and six-membered monocyclic and bicyclic heterocycles: Bird, C.W. *Tetrahedron* ***1985***, *41*, 1409; ***1986***, *42*, 89; ***1987***, *43*, 4725. See Horner, K.E.; Karadakov, P.B. *J. Org. Chem.* ***2013***, *78*, 8037.

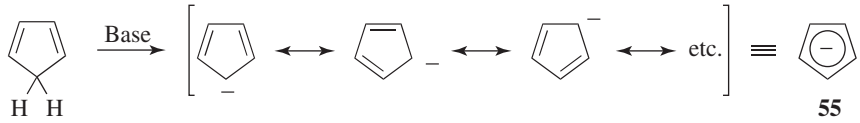


Pyrrole Thiophene Furan

Resonance energies for these three compounds are, respectively, 21, 29, and 16 kcal mol^{-1} (88, 121, and 67 kJ mol^{-1}).[172] The aromaticity can also be shown by canonical forms, e.g., for pyrrole:



In contrast to pyridine, the unshared pair in canonical structure **A** in pyrrole is needed for the aromatic sextet. Since the electron pair is not available for donation, pyrrole is a much weaker base than pyridine.

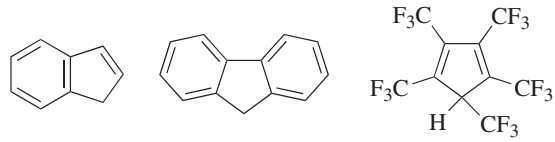


55

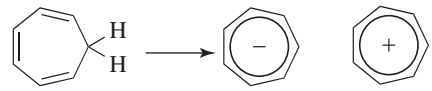
The fifth atom may be carbon rather than a heteroatom, if carbon has an unshared pair (as in an anion). Cyclopentadiene is known to react with a suitable base, and loss of a proton, to give a carbanion that is aromatic and therefore quite stable, although it is reactive to alkylating agents and electrophilic reagents. Due to formation of the stable cyclopentadienyl anion, cyclopentadiene (p$K_a \approx 16$) is approximately as strong an acid as water. The cyclopentadienide ion is sometimes represented as in **55**, although more commonly one of the canonical forms is used. All five carbons are equivalent, as demonstrated by labeling the starting compound with ^{14}C and finding all positions equally labeled when cyclopentadiene was regenerated.[173] Resonance in this ion is greater than in pyrrole, thiophene, and furan, since all five forms are equivalent, and the resonance energy for **55** has been estimated to be 24–27 kcal mol^{-1} (100–113 kJ mol^{-1}).[174] As expected for an aromatic system, **55** is diatropic[175] and aromatic substitutions (see Chapters 11 and 13) on it have been successfully carried out.[176] Average bond order has been proposed as a parameter to evaluate the aromaticity of such rings, but there is poor correlation with nonaromatic and antiaromatic systems.[177] A model that relies on calculating relative aromaticity from appropriate molecular fragments has also been developed.[178] Bird devised the aromatic index (I_A, or aromaticity index),[179] which is a statistical evaluation of the extent of ring bond order,

[172] Wheland, G.W. *Resonance in Organic Chemistry*, Wiley, NY, ***1955***, p 99. See also, Calderbank, K.E.; Calvert, R.L.; Lukins, P.B.; Ritchie, G.L.D. *Aust. J. Chem.* ***1981***, *34*, 1835.
[173] Tkachuk, R.; Lee, C.C. *Can. J. Chem.* ***1959***, *37*, 1644.
[174] Bordwell, F.G.; Drucker, G.E.; Fried, H.E. *J. Org. Chem.* ***1981***, *46*, 632.
[175] Bradamante, S.; Marchesini, A.; Pagani, G. *Tetrahedron Lett.* ***1971***, 4621.
[176] Webster, O.W. *J. Org. Chem.* ***1967***, *32*, 39; Rybinskaya, M.I.; Korneva, L.M. *Russ. Chem. Rev.* ***1971***, *40*, 247.
[177] Jursic, B.S. *J. Heterocyclic Chem.* ***1997***, *34*, 1387.
[178] Hosmane, R.S.; Liebman, J.F. *Tetrahedron Lett.* ***1992***, *33*, 2303.
[179] Bird, C.W. *Tetrahedron* ***1996***, *52*, 9945; Hosoya, H. *Monat. Chemie* ***2005***, *136*, 1037.

and has been used as a criterion of aromaticity. Another bond-order index was proposed by Pozharskii,[180] which builds on the work of Fringuelli and co-workers.[181] Absolute hardness (Sec. 8.E), calculated from molecular refractions for a range of aromatic and heteroaromatic compounds, shows good linear correlation with aromaticity.[182] Indene and fluorene are also acidic ($pK_a \approx 20$ and 23, respectively) but less so than cyclopentadiene, since annellation causes the electrons to be less available to the five-membered ring. On the other hand, the acidity of 1,2,3,4,5-pentakis(trifluoromethyl)cyclopentadiene (**56**) is greater than that of nitric acid,[183] because of the electron-withdrawing effects of the trifluoromethyl groups (Sec. 8.F). Modifications of the Bird and Pozharskii systems have been introduced that are particularly useful for five-membered ring heterocycles.[184] Recent work introduced a new local aromaticity measure, defined as the mean of Bader's electron delocalization index (DI)[185] of para-related carbon atoms in six-membered rings.[186] Bond resonance energy has been used as an indicator of local aromaticity.[187] The relative merits of several aromaticity indices has been discussed.[188]



Indene Fluorene **56**

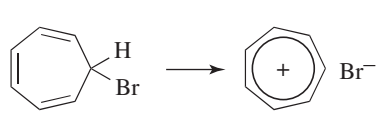


57 **58** **59**

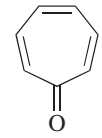
As seen above, relative acidity can be used to study the aromatic character of the resulting conjugate base of a given compound. In sharp contrast to cyclopentadiene (Sec. 2.I.ii) is cycloheptatriene (**57**), which has no unusual acidity. This would be hard to explain without the aromatic sextet theory, since, on the basis of resonance forms or a simple consideration of orbital overlaps, **58** should be as stable as the cyclopentadienyl anion (**55**). This eight-electron system is antiaromatic, however. While **58** has been prepared in solution,[189] it is less stable than **55** and far less stable than **59**, in which **57** has lost not a proton but the equivalent of a hydride ion. The six double-bond electrons of **59** overlap with the

[180] Pozharskii, A.F. *Khimiya Geterotsikl Soedin* ***1985***, 867.
[181] Fringuelli, F. Marino, G.; Taticchi, A.; Grandolini, G.J. Chem. Soc., *Perkin Trans. 2* ***1974***, 332.
[182] Bird, C.W. *Tetrahedron* ***1997***, *53*, 3319; *Tetrahedron* ***1998***, *54*, 4641.
[183] Laganis, E.D.; Lemal, D.M. *J. Am. Chem. Soc.* ***1980***, *102*, 6633.
[184] Kotelevskii, S.I.; Prezhdo, O.V. *Tetahedron* ***2001***, *57*, 5715.
[185] See Bader, R.F.W. *Atoms in Molecules: A Quantum Theory*, Clarendon, Oxford, ***1990***; Bader, R.F.W. *Acc. Chem. Res.* ***1985***, *18*, 9; Bader, R.F.W. *Chem. Rev.* ***1991***, *91*, 893.
[186] Poater, J.; Fradera, X.; Duran, M.; Solà, M. *Chem. Eur. J.* ***2003***, *9*, 400; 1113.
[187] Aihara, J.; Ishida, T.; Kanno, H. *Bull. Chem. Soc. Jpn.* ***2007***, *80*, 1518.
[188] Fallah-Bagher-Shaidaei, H.; Wannere, C.S.; Corminboeuf, C.; Puchta, R.; Schleyer, P.v.R. *Org. Lett.* ***2006***, *8*, 863.
[189] Dauben Jr., H.J.; Rifi, M.R. *J. Am. Chem. Soc.* ***1963***, *85*, 3041; also see, Breslow, R.; Chang, H.W. *J. Am Chem. Soc.* ***1965***, *87*, 2200.

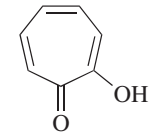
empty orbital on the seventh carbon and there is a sextet of electrons covering seven carbon atoms. The cycloheptatrienyl cation (known as the *tropylium ion*, **59**) is quite stable,[190] but such cations are generally formed from the corresponding halide rather than by loss of a hydride. Tropylium bromide (**60**), which could be completely covalent if the electrons of the bromine were sufficiently attracted to the ring, is actually better viewed as an ionic compound.[191] Many substituted tropylium ions have been prepared to probe the aromaticity, structure, and reactivity of such systems.[192] As with **55**, the equivalence of the carbon atoms in **59** has been demonstrated by isotopic labeling.[193] The aromatic cycloheptatrienyl cations $C_7Me_7^+$ and $C_7Ph_7^+$ are known,[194] although their coordination complexes with transition metals have been problematic, possibly because they assume a boat-like rather than a planar conformation[195] The planar homotropenylium cation has a transition state with reversed aromaticity.[196]



60



61



62

Tropone (**61**) is another seven-membered ring that shows some aromatic character. This molecule would have an aromatic sextet if the two C=O electrons stayed away from the ring and resided near the electronegative oxygen atom. In fact, tropones are stable compounds, and tropolones (**62**) are found in nature.[197] However, analyses of dipole moments, NMR spectra, and X-ray diffraction measurements show that tropones and tropolones display appreciable bond alternations.[198] These molecules must be regarded as essentially nonaromatic, although with some aromatic character. Tropolones readily undergo aromatic substitution, emphasizing that the old and the new definitions of aromaticity are not always parallel. It is known that **62** is acidic (pK_a about 6.7),[199] in large part because the resulting anion has aromatic character. Indeed, **62** is considered to be a vinylogous carboxylic acid. In sharp contrast to **61**, cyclopentadienone (**63**) has been isolated only in an argon matrix

[190] See Pietra, F. *Chem. Rev.* ***1973***, *73*, 293; Bertelli, D.J. *Top. Nonbenzenoid Aromat. Chem.* ***1973***, *1*, 29; Kolomnikova, G.D.; Parnes, Z.N. *Russ. Chem. Rev.* ***1967***, *36*, 735; Harmon, K.H., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4; Wiley, NY, ***1973***, pp. 1579–1641.

[191] Doering, W. von E.; Knox, L.H. *J. Am. Chem. Soc.* ***1954***, *76*, 3203.

[192] Pischel, U.; Abraham, W.; Schnabel, W.; Müller, U. *Chem. Commun.* ***1997***, 1383. See Komatsu, K.; Nishinaga, T.; Maekawa, N.; Kagayama, A.; Takeuchi, K. *J. Org. Chem.* ***1994***, *59*, 7316 for a tropylium dication.

[193] Vol'pin, M.E.; Kursanov, D.N.; Shemyakin, M.M.; Maimind, V.I.; Neiman, L.A. *J. Gen. Chem. USSR* ***1959***, *29*, 3667.

[194] Takeuchi, K.; Yokomichi, Y.; Okamoto, K. *Chem. Lett.* ***1977***, 1177; Battiste, M.A. *J. Am. Chem. Soc.* ***1961***, *83*, 4101.

[195] Tamm, M.; Dreßel, B.; Fröhlich, R. *J. Org. Chem.* ***2000***, *65*, 6795.

[196] Gibson, C.M.; Havenith, R.W.A.; Fowler, P.W.; Jenneskens, L.W. *J. Org. Chem.* ***2015***, *80*, 1395.

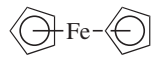
[197] Pietra, F. *Acc. Chem. Res.* ***1979***, *12*, 132; Nozoe, T. *Pure Appl. Chem.* ***1971***, *28*, 239.

[198] Schaefer, J.P.; Reed, L.L. *J. Am. Chem. Soc.* ***1971***, *93*, 3902; Watkin, D.J.; Hamor, T.A. *J. Chem. Soc. B* ***1971***, 2167; Barrow, M.J.; Mills, O.S.; Filippini, G. *J. Chem. Soc., Chem. Commun.* ***1973***, 66. For a discussion of the intramolecular proton transfer in thiotropolone, see Machiguchi, T.; Hasegawa, T.; Saitoh, H.; Yamabe, S.; Yamazaki, S. *J. Org. Chem.* ***2011***, *76*, 5457.

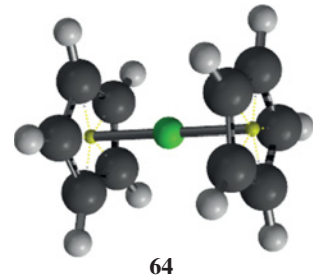
[199] von E. Doering, W.; Knox, L.H. *J. Am. Chem. Soc.* ***1951***, *73*, pp 828.

below 38 K.[200] Above this temperature it dimerizes. Many earlier attempts to prepare it were unsuccessful.[201] As in **61**, the electronegative oxygen atom draws electron density to itself, but in this case it leaves only four electrons and the molecule is unstable. Some derivatives of **63** have been prepared.[156]

63



Ferrocene



64

The *metallocenes* (also called *sandwich compounds*) constitute another type of five-membered aromatic compound in which two cyclopentadienide rings form a sandwich around a metal. The best known of these is ferrocene, where the η^5 coordination of the two cyclopentadienyl rings to iron is apparent in the 3D model **64**. Other metallocenes have been prepared with Co, Ni, Cr, Ti, V, and many other metals.[202] As a reminder (Sec. 2.C), the η terminology refers to π donation of electrons to the metal (η^3 for π-allyl systems, η^6 for coordination to a benzene ring, etc.), and η^5 refers to donation of five π electrons to the iron. Ferrocene is quite stable, subliming > 100 °C and unchanged at 400 °C. The two rings rotate freely.[203] Many aromatic substitutions (Chapter 11) have been carried out on metallocenes.[204] Metallocenes containing two metal atoms and three cyclopentadienyl rings have also been prepared and are known as *triple-decker sandwiches*.[205] Even tetradecker, pentadecker, and hexadecker sandwiches have been reported.[206]

The bonding in ferrocene may be looked upon in simplified molecular-orbital terms as follows.[207] Each of the cyclopentadienide rings has five molecular orbitals – three filled bonding orbitals and two empty antibonding orbitals (Sec. 2.I.ii). The outer shell of the Fe atom possesses nine atomic orbitals, that is, one 4*s*, three 4*p*, and five 3*d* orbitals. The six filled orbitals of the two cyclopentadienide rings overlap with the *s*, the three *p*, and two of the *d* orbitals of the Fe to form twelve new orbitals, six of which are bonding. These six orbitals make up two ring-to-metal triple bonds. In addition further bonding results from

[200] Maier, G.; Franz, L.H.; Hartan, H.; Lanz, K.; Reisenauer, H.P. *Chem. Ber.* ***1985***, *118*, 3196.

[201] See Ogliaruso, M.A.; Romanelli, M.G.; Becker, E.I. *Chem. Rev.* ***1965***, *65*, 261.

[202] See Rosenblum, M. *Chemistry of the Iron Group Metallocenes*, Wiley, NY, ***1965***; Lukehart, C.M. *Fundamental Transition Metal Organometallic Chemistry*, Brooks/Cole, Monterey, CA, ***1985***, pp. 85–118; Sikora, D.J.; Macomber, D.W.; Rausch, M.D. *Adv. Organomet. Chem.* ***1986***, *25*, 317; Pauson, P.L. *Pure Appl. Chem.* ***1977***, *49*, 839; Perevalova, E.G.; Nikitina, T.V. *Organomet. React.* ***1972***, *4*, 163; Bublitz, D.E.; Rinehart Jr., K.L. *Org. React.*, ***1969***, *17*, 1; Rausch, M.D. *Pure Appl. Chem.* ***1972***, *30*, 523; Bruce, M.I. *Adv. Organomet. Chem.* ***1972***, *10*, 273 (pp. 322–325).

[203] For a discussion of the molecular structure, see Haaland, A. *Acc. Chem. Res.* ***1979***, *12*, 415.

[204] See Plesske, K. *Angew. Chem. Int. Ed.* ***1962***, *1*, 312, 394.

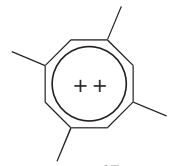
[205] For a review, see Werner, H. *Angew. Chem. Int. Ed.* ***1977***, *16*, 1.

[206] See, for example, Siebert, W. *Angew. Chem. Int. Ed.* ***1985***, *24*, 943.

[207] Rosenblum, M. *Chemistry of the Iron Group Metallocenes*, Wiley, NY, ***1965***, pp. 13–28; Coates, G.E.; Green, M.L.H.; Wade, K. *Organometallic Compounds*, 3rd ed., Vol. 2, Methuen, London, ***1968***, pp. 97–104; Grebenik, P.; Grinter, R.; Perutz, R.N. *Chem. Soc. Rev.* ***1988***, *17*, 453 (p. 460).

the overlap of the empty antibonding orbitals of the rings with additional filled *d* orbitals of the iron. All told, there are 18 electrons (10 of which may be considered to come from the rings and 8 from iron in the zero oxidation state) in nine orbitals; six of these are strongly bonding and three weakly bonding or nonbonding.

The tropylium ion has an aromatic sextet spread over seven carbon atoms. An analogous ion, with the sextet spread over eight carbon atoms, is 1,3,5,7-tetramethylcyclooctatetraene dictation (**65**). This ion, which is stable in solution at −50 °C, is diatropic and approximately planar. The dication **65** is not stable above about −30 °C.[208]



65

2.I.iii. Other Systems Containing Aromatic Sextets

Simple resonance theory predicts that pentalene (**66**), azulene (**67**), and heptalene (**68**) should be aromatic, although no nonionic canonical form can have a double bond at the ring junction. Molecular-orbital calculations show that azulene should be stable but not the other two, and this is borne out by experiment. Heptalene has been prepared[209] but reacts readily with oxygen, acids, and bromine, is easily hydrogenated, and polymerizes on standing. Analysis of its NMR spectrum shows that it is not planar.[210] The 3,8-dibromo and 3,8-dicarbomethoxy derivatives of **68** are stable in air at room temperature but are not diatropic.[211] A number of methylated heptalenes and dimethyl 1,2-heptalenedicarboxylates have also been prepared and are stable nonaromatic compounds.[212] Pentalene has not been prepared,[213] but the hexaphenyl[214] and 1,3,5-tri-*tert*-butyl derivatives[215] are known. The former is air sensitive in solution. The latter is stable, but X-ray diffraction and photoelectron spectral data show bond alternation.[216] Pentalene and its methyl and dimethyl

[208] Olah, G.A.; Staral, J.S.; Liang, G.; Paquette, L.A.; Melega, W.P.; Carmody, M.J. *J. Am. Chem. Soc.* ***1977***, *99*, 3349. See also, Radom, L.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1977***, *99*, 7522; Olah, G.A.; Liang, G. *J. Am. Chem. Soc.* ***1976***, *98*, 3033; Willner, I.; Rabinovitz, M. *Nouv. J. Chim.*, ***1982***, *6*, 129.

[209] Paquette, L.A.; Browne, A.R.; Chamot, E. *Angew. Chem. Int. Ed.* ***1979***, *18*, 546. For a review of heptalenes, see Paquette, L.A. *Isr. J. Chem.* ***1980***, *20*, 233.

[210] Bertelli, D.J., in Bergmann, E.D.; Pullman, B. *Aromaticity, Pseudo-Aromaticity, and Antiaromaticity*, Israel Academy of Sciences and Humanities, Jerusalem, ***1971***, p. 326. See also, Stegemann, J.; Lindner, H.J. *Tetrahedron Lett.* ***1977***, 2515.

[211] Vogel, E.; Ippen, J. *Angew. Chem. Int. Ed.* ***1974***, *13*, 734; Vogel, E.; Hogrefe, F. *Angew. Chem. Int. Ed.* ***1974***, *13*, 735.

[212] Hafner, K.; Knaup, G.L.; Lindner, H.J. *Bull. Soc. Chem. Jpn.* ***1988***, *61*, 155.

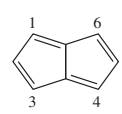
[213] See Knox, S.A.R.; Stone, F.G.A. *Acc. Chem. Res.* ***1974***, *7*, 321.

[214] LeGoff, E. *J. Am. Chem. Soc.* ***1962***, *84*, 3975. See also, Hartke, K.; Matusch, R. *Angew. Chem. Int. Ed.* ***1972***, *11*, 50.

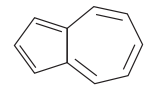
[215] Hafner, K.; Süss, H.U. *Angew. Chem. Int. Ed.* ***1973***, *12*, 575. See also, Hafner, K.; Suda, M. *Angew. Chem. Int. Ed.* ***1976***, *15*, 314.

[216] Bischof, P.; Gleiter, R.; Hafner, K.; Knauer, K.H.; Spanget-Larsen, J.; Süss, H.U. *Chem. Ber.* ***1978***, *111*, 932.

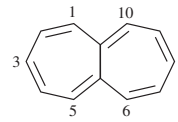
derivatives have been formed in solution, but they dimerize before they can be isolated.[217] Many other attempts to prepare these two systems have failed.



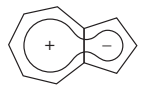
66



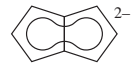
67



68

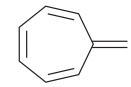


69

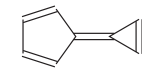


70

71



72



73

In sharp contrast to **66** and **68**, azulene (**67**) is a blue solid, is quite stable and many derivatives are known.[218] Azulene readily undergoes aromatic substitution. Azulene may be regarded as a combination of **55** and **59** and, indeed, possesses a dipole moment of 0.8 D (see **69**).[219] Interestingly, if two electrons are added to pentalene, a stable dianion (**70**) results.[220] It can be concluded that an aromatic system of electrons will be spread over two rings only if 10 electrons (not 8 or 12) are available for aromaticity. [*n*,*m*]Fulvalenes ($n \neq m$, where fulvalene is **71**) as well as azulene are known to shift their π electrons due to the influence of dipolar aromatic resonance structures.[221] Both the nucleus-independent chemical shift (NICS) and coulombic energy of fulvalenes are associated with the aromatic stabilization energy.[222] However, calculations showed that dipolar resonance structures contribute only 5% to the electronic structure of heptafulvalene (**72**), although they contribute 22–31% to calicene (**73**).[223] Based on Baird's theory,[224] these molecules are influenced by aromaticity in both the ground state and excited states, therefore acting as aromatic "chameleons." This premise was confirmed in work by Ottosson and co-workers.[221] Aromaticity indexes for various substituted fulvalene compounds has been reported.[225]

2.J. ALTERNANT AND NONALTERNANT HYDROCARBONS[226]

Aromatic hydrocarbons can be divided into alternant and nonalternant hydrocarbons. In alternant hydrocarbons, the conjugated carbon atoms can be divided into two sets such that no two atoms of the same set are directly linked. For convenience one set may be starred. Naphthalene is an alternant and azulene a nonalternant hydrocarbon.

[217] Hafner, K.; Dönges, R.; Goedecke, E.; Kaiser, R. *Angew. Chem. Int. Ed.* ***1973***, *12*, 337.
[218] For a review on azulene, see Mochalin, V.B.; Porshnev, Yu.N. *Russ. Chem. Rev.* ***1977***, *46*, 530.
[219] Tobler, H.J.; Bauder, A.; Günthard, H.H. *J. Mol. Spectrosc.* ***1965***, *18*, 239.
[220] Katz, T.J.; Rosenberger, M.; O'Hara, R.K. *J. Am. Chem. Soc.* ***1964***, *86*, 249. See also, Willner, I.; Becker, J.Y.; Rabinovitz, M. *J. Am. Chem. Soc.* ***1979***, *101*, 395.
[221] Möllerstedt, H.; Piqueras, M.C.; Crespo, R.; Ottosson, H. *J. Am. Chem. Soc.* ***2004***, *126*, 13938.
[222] Stanger, A. *J. Org. Chem.* ***2013***, *78*, 12374; Neuenschwander, M. *Helv. Chim. Acta* ***2015***, *98*, 763.
[223] Scott, A.P.; Agranat, A.; Biedermann, P.U.; Riggs, N.V.; Radom, L. *J. Org. Chem.* ***1997***, *62*, 2026.
[224] Baird, N.C. *J. Am. Chem. Soc.* ***1972***, *94*, 4941.
[225] Stepien, B.T.; Krygowski, T.M.; Cyrański, M.K. *J. Org. Chem.* ***2002***, *67*, 5987.
[226] See Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 122–129; Dewar, M.J.S. *Prog. Org. Chem.* ***1953***, *2*, 1.

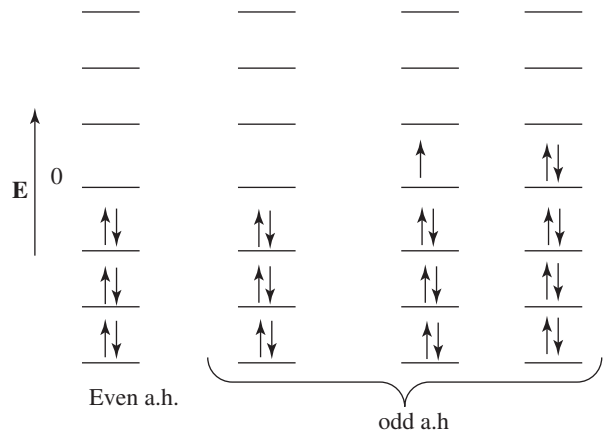
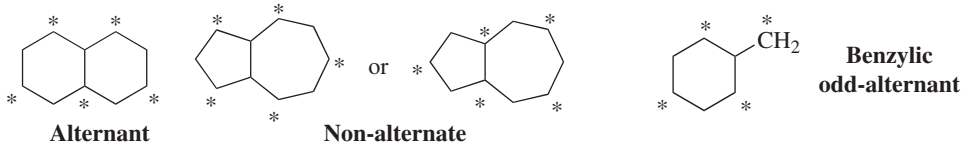


FIGURE 2.9. Energy levels in odd- and even-alternant hydrocarbons.[227] The arrows represent electrons. The orbitals are shown as having different energies, but some may be degenerate.



In alternant hydrocarbons, the bonding and antibonding orbitals occur in pairs; that is, for every bonding orbital with an energy $-E$ there is an antibonding one with energy $+E$ (Figure 2.9).[227] Even-alternant hydrocarbons are those with an even number of conjugated atoms, that is, an equal number of starred and unstarred atoms. For these hydrocarbons all the bonding orbitals are filled and the π electrons are uniformly spread over the unsaturated atoms.

As with the allylic system, odd-alternant hydrocarbons (which must be carbocations, carbanions, or radicals) in addition to equal and opposite bonding and antibonding orbitals also have a nonbonding orbital of zero energy. When an odd number of orbitals overlap, an odd number is created. Since orbitals of alternant hydrocarbons occur in $-E$ and $+E$ pairs, one orbital can have no partner and must therefore have zero bonding energy. For example, in the benzylic system the cation has an unoccupied nonbonding orbital, the free radical has one electron there, and the carbanion two (Figure 2.10). As with the allylic system, all three species have the same bonding energy. The charge distribution (or unpaired-electron distribution) over the entire molecule is also the same for the three species and can be calculated by a relatively simple process.[226]

For nonalternant hydrocarbons the energies of the bonding and antibonding orbitals are not equal and opposite and charge distributions are not the same in cations, anions, and radicals. Calculations are much more difficult but have been carried out.[228] Theoretical

[227] Taken from Dewar, M.J.S *Prog. Org. Chem.* ***1953***, *2*, 1, p. 8.

[228] Brown, R.D.; Burden, F.R.; Williams, G.R. *Aust. J. Chem.* ***1968***, *21*, 1939. For reviews, see Zahradnik, R., in Snyder, J.P. *Nonbenzenoid Aromatics* Vol. 2, Academic Press, NY, ***1971***, pp. 1–80; Zahradnik, R. *Angew. Chem. Int. Ed.* ***1965***, *4*, 1039.

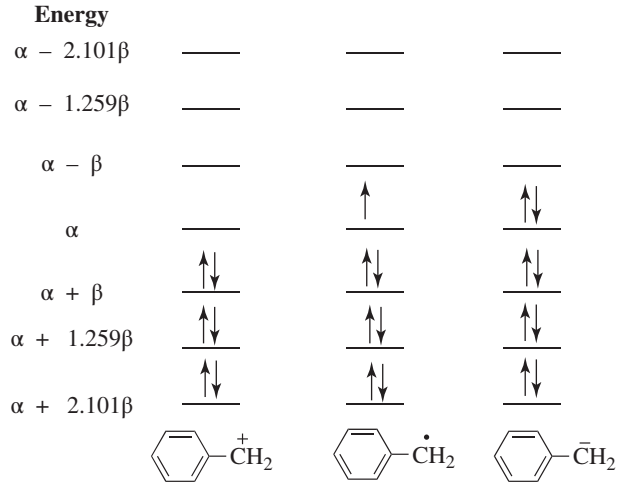
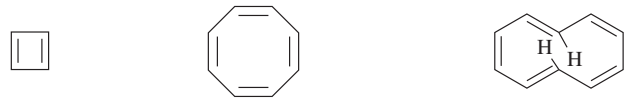


FIGURE 2.10. Energy levels for the benzyl cation, free radical, and carbanion. Since α is the energy of a *p* orbital (Sec. 2.B), the nonbonding orbital has no bonding energy.

approaches to calculate topological polarization and reactivity of these hydrocarbons have been reported.[229]

2.K. AROMATIC SYSTEMS WITH ELECTRON NUMBERS OTHER THAN SIX



74 **75** **76**

The special stability of benzene is well recognized, and this stability is also associated with rings that are similar but of different sizes, such as cyclobutadiene (**74**), cyclooctatetraene (**75**), cyclodecapentaene[230] (**76**), and so on. The general name *annulene* is given to these compounds,[231] benzene being [6]annulene, and **74** to **76** being called, respectively, [4], [8], and [10]annulene.[232] By a naïve consideration of resonance forms, these annulenes and higher ones should be as aromatic as benzene. Yet they proved remarkably elusive. The ubiquitous benzene ring is found in thousands of natural products, in coal and petroleum, and is formed by strong treatment of many noncyclic compounds. None of the other annulene ring systems has ever been found in nature and, except for cyclooctatetraene, their

[229] Langler, R.F. *Aust. J. Chem.* ***2000***, *53*, 471; Fredereiksen, M.U.; Langler, R.F.; Staples, M.A.; Verma, S.D. *Aust. J. Chem.* ***2000***, *53*, 481.

[230] For other stereoisomers, see Sec. **2.K.iv**.

[231] Spitler, E.L.; Johnson II, C.A.; Haley, M.M. *Chem. Rev.* ***2006***, *106*, 5344; For a discussion of annulenylenes, annulynes, and annulenes, see Stevenson, C.D. *Acc. Chem. Res.* ***2007***, *40*, 703.

[232] For a discussion of bond shifting and automerization in [10]annulene, see Castro, C.; Karney, W.L.; McShane, C.M.; Pemberton, R.P. *J. Org. Chem.* ***2006***, *71*, 3001.

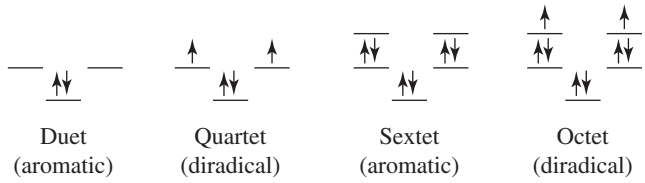


FIGURE 2.11. Adding electrons to an annulene.

synthesis is not simple. Obviously, there is something special about the number six in a cyclic system of electrons.

Hückel's rule, based on molecular-orbital calculations,[233] predicts that electron rings will constitute an aromatic system only if the number of electrons in the ring is of the form $4n + 2$, where n is zero or any positive integer. Systems that contain $4n$ electrons are predicted to be nonaromatic. The rule predicts that rings of 2, 6, 10, 14, and so on, electrons will be aromatic, while rings of 4, 8, 12, and so on, will not be. This observation is actually a consequence of *Hund's rule*. The first pair of electrons in an annulene goes into the π orbital of lowest energy. After that the bonding orbitals are degenerate and occur in pairs of equal energy, as shown in Figure 2.11. When there is a total of four electrons, Hund's rule predicts that two will be in the lowest orbital but the other two will be unpaired, so that the system will exist as a diradical rather than as two pairs. The degeneracy can be removed if the molecule is distorted from maximum molecular symmetry to a structure of lesser symmetry. For example, if **75** assumes a rectangular rather than a square shape, one of the previously degenerate orbitals has a lower energy than the other and will be occupied by two electrons. In this case, of course, the double bonds are essentially separate and the molecule is still not aromatic. Distortions of symmetry can also occur when one or more carbons are replaced by heteroatoms or in other ways.[234] The enthalpy of formation of cyclobutadiene was reported by Kass and co-workers.[235] There is a brief discussion of the importance of cyclobutadiene with respect to antiaromaticity.[236] A word of caution is in order for molecular-orbital calculations in these systems. It is known that *ab initio* computations on benzene at electron-correlated MP2, MP3, CISD, and CCSD levels using a number of popular basis sets[237] give anomalous, nonplanar equilibrium structures.[238] The origin of these anomalies has been addressed.[237] The isomerization stabilization energy method has been applied to evaluate the triplet aromaticity of triplet [n]annulenes with $4n$ π electrons, which are also aromatic.[239]

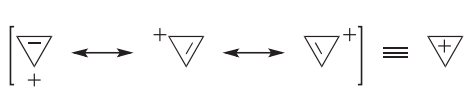
In the following sections, systems with various numbers of electrons are discussed. Any probe of aromaticity must include: (1) the presence of a diamagnetic ring current; (2) equal

[233] See Nakajima, T. *Pure Appl. Chem.* ***1971***, *28*, 219; *Fortschr. Chem. Forsch.* ***1972***, *32*, 1.
[234] See Hoffmann, R. *Chem. Commun.* ***1969***, 240.
[235] Fattahi, A.; Liz, L.; Tian, Z.; Kass, S.R. *Angew. Chem.* ***2006***, *118*, 5106.
[236] Bally, T. *Angew. Chem. Int. Ed.* ***2006***, *45*, 6616–6619.
[237] Hehre, W.J.; Radom, L.; Pople, J.A.; Schleyer, P.v.R. *Ab Initio Molecular Orbital Theory*, John Wiley & Sons: New York, ***1986***; Schleyer, P.v.R.; Allinger, N.L.; Clark, T.; Gasteiger, J.; Kollman, P.A.; Schaefer III, H.F.; Schreiner, P.R. (Eds.) *The Encyclopedia of Computational Chemistry*, John Wiley & Sons, Ltd., Chichester, ***1998***.
[238] Moran, D.; Simmonett, A.C.; Leach III, F.E.; Allen, W.D.; Schleyer, P.v.R.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***2006***, *128*, 9342.
[239] Zhu, J.; An, K.; Schleyer, R.V.R. *Org. Lett.* ***2013***, *15*, 2442.

or approximately equal bond distances, except when the symmetry of the system is disturbed by a heteroatom or in some other way; (3) planarity; (4) chemical stability; and (5) the ability to undergo aromatic substitution.

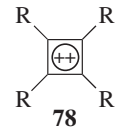
2.K.i. Systems of Two Electrons[240]

Obviously, there can be no ring of two carbon atoms (a double bond may be regarded as a degenerate case). However, by analogy to the tropylium ion, a three-membered ring with a double bond and a positive charge on the third atom (the *cyclopropenyl cation*) is a $4n+2$ system and expected to show aromaticity. Unsubstituted **77** has been prepared,[241] as well as several derivatives, e.g., the trichloro, diphenyl, and dipropyl derivatives, and they are stable despite bond angles of only 60°. Tripropylcyclopropenyl,[242] tricyclopropylcyclopropenyl,[243] chlorodipropylcyclopropenyl,[244] and chloro-*bis*-dialkylaminocyclopropenyl[245] cations are among the most stable carbocations known, being stable even in water solution. The tri-*tert*-butylcyclopropenyl cation is also very stable.[246] In addition, cyclopropenone and several of its derivatives are stable compounds,[247] in accord with the corresponding stability of the tropones.[248] The ring system **77** is nonalternant and the corresponding radical and anion (which do not have an aromatic duet) have electrons in antibonding orbitals, so that their energies are much higher. As with **55** and **59**, the equivalence of the three carbon atoms in the triphenylcyclopropenyl cation has been demonstrated by ^{14}C labeling experiments.[249] The interesting dications **78** (R = Me or Ph) have been prepared,[250] and they too should represent aromatic systems of two electrons.[251]



77

Cyclopropenone



78

[240] See Billups, W.E.; Moorehead, A.W., in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, ***1987***, pp. 1533–1574; Potts, K.T.; Baum, J.S. *Chem. Rev.* ***1974***, *74*, 189; Closs, G.L. *Adv. Alicyclic Chem.* ***1966***, *1*, 53 (pp. 102–126); Krebs, A.W. *Angew. Chem. Int. Ed.* ***1965***, *4*, 10.

[241] Breslow, R.; Groves, J.T. *J. Am. Chem. Soc.* ***1970***, *92*, 984.

[242] Breslow, R.; Höver, H.; Chang, H.W. *J. Am. Chem. Soc.* ***1962***, *84*, 3168.

[243] Moss, R.A.; Shen, S.; Krogh-Jespersen, K.; Potenza, J.A.; Schugar, H.J.; Munjal, R.C. *J. Am. Chem. Soc.* ***1986***, *108*, 134.

[244] Ito, S.; Morita, N.; Asao, T. *Tetrahedron Lett.* ***1992***, *33*, 3773.

[245] Taylor, M.J.; Surman, P.W.J.; Clark, G.R. *J. Chem. Soc., Chem. Commun.* ***1994***, 2517.

[246] Ciabattoni, J.; Nathan III, E.C. *J. Am. Chem. Soc.* ***1968***, *90*, 4495.

[247] See Breslow, R.; Oda, M. *J. Am. Chem. Soc.* ***1972***, *94*, 4787; Yoshida, Z.; Konishi, H.; Tawara, Y.; Ogoshi, H. *J. Am. Chem. Soc.* ***1973***, *95*, 3043.

[248] See Eicher, T.; Weber, J.L. *Top. Curr. Chem. Soc.* ***1975***, *57*, 1; Tobey, S.W., in Bergmann, E.D.; Pullman, B. *Aromaticity, Pseudo-Aromaticity, and Antiaromaticity*, Israel Academy of Sciences and Humanities, Jerusalem, ***1971***, pp. 351–362; Greenberg, A.; Tomkins, R.P.T.; Dobrovolny, M.; Liebman, J.F. *J. Am. Chem. Soc.* ***1983***, *105*, 6855.

[249] D'yakonov, I.A.; Kostikov, R.R.; Molchanov, A.P. *J. Org. Chem. USSR* ***1969***, *5*, 171; ***1970***, *6*, 304.

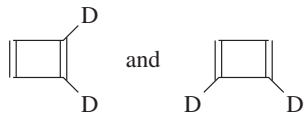
[250] Olah, G.A.; Staral, J.S. *J. Am. Chem. Soc.* ***1976***, *98*, 6290. See also, Lambert, J.B.; Holcomb, A.G. *J. Am. Chem. Soc.* ***1971***, *93*, 2994; Seitz, G.; Schmiedel, R.; Mann, K. *Synthesis*, ***1974***, 578.

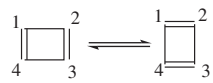
[251] See Pittman Jr., C.U.; Kress, A.; Kispert, L.D. *J. Org. Chem.* ***1974***, *39*, 378. Matsuo, Y.; Maruyama, M. *Chem. Commun.* ***2012***, *48*, 9334. See, however, Krogh-Jespersen, K.; Schleyer, P.v.R.; Pople, J.A.; Cremer, D. *J. Am. Chem. Soc.* ***1978***, *100*, 4301.

2.K.ii. Systems of Four Electrons: Antiaromaticity

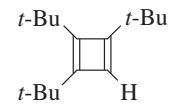
The most obvious compound in which to look for a closed loop of four electrons is cyclobutadiene (**74**).[252] Hückel's rule predicts no aromatic character since 4 is not a number generated from $4n+2$. There is a long history of attempts to prepare this compound and its simple derivatives, and those experiments fully bear out Hückel's prediction. Cyclobutadienes display none of the characteristics that would lead us to call them aromatic, and there is evidence that a closed loop of four electrons is actually *antiaromatic*.[253] If such compounds simply lacked aromaticity, we would expect them to be about as stable as similar nonaromatic compounds, but both theory and experiment show that they are *much less stable*.[254] An antiaromatic compound may be defined as a compound that is destabilized by a closed loop of electrons.

Cyclobutadiene was first prepared by Pettit and co-workers.[255] It is now clear that **74** and its simple derivatives are extremely unstable compounds with very short lifetimes (they dimerize by a *Diels-Alder reaction*; see **15-56**) unless they are stabilized in some fashion, either at ordinary temperatures embedded in the cavity of a hemicarcerand[256] (see the structure of a carcerand in Sec. 3.C.iii), or in matrices at very low temperatures (generally under 35 K). In either of these cases, the cyclobutadiene molecules are forced to remain apart from each other, and other molecules cannot get in. The structures of **74** and some of its derivatives have been studied a number of times using the low-temperature matrix technique.[257] The ground-state structure of **74** is a rectangular diene (not a diradical), as shown by the infrared (IR) spectra of **74** and deuterated **74** trapped in matrices[258] as well as by a photoelectron spectrum.[259] Molecular-orbital calculations agree.[260] The same conclusion was also reached in an elegant experiment in which 1,2-dideuterocyclobutadiene was generated. If **74** is a rectangular diene, the dideutero compound should exist as two isomers as shown.





74a **74b**



79

[252] For a monograph, see Cava, M.P.; Mitchell, M.J. *Cyclobutadiene and Related Compounds*, Academic Press, NY, ***1967***. For reviews, see Maier, G. *Angew. Chem. Int. Ed.* ***1988***, *27*, 309; ***1974***, *13*, 425–438; Bally, T.; Masamune, S. *Tetrahedron* ***1980***, *36*, 343; Vollhardt, K.P.C. *Top. Curr. Chem.* ***1975***, *59*, 113.

[253] See Glukhovtsev, M.N.; Simkin, B.Ya.; Minkin, V.I. *Russ. Chem. Rev.* ***1985***, *54*, 54; Breslow, R. *Pure Appl. Chem.* ***1971***, *28*, 111; *Acc. Chem. Res.* ***1973***, *6*, 393.

[254] See Bauld, N.L.; Welsher, T.L.; Cessac, J.; Holloway, R.L. *J. Am. Chem. Soc.* ***1978***, *100*, 6920.

[255] Watts, L.; Fitzpatrick, J.D.; Pettit, R. *J. Am. Chem. Soc.* ***1965***, *87*, 3253, ***1966***, *88*, 623. See also, Cookson, R.C.; Jones, D.W. *J. Chem. Soc.* ***1965***, 1881.

[256] Cram, D.J.; Tanner, M.E.; Thomas, R. *Angew. Chem. Int. Ed.* ***1991***, *30*, 1024.

[257] See Chapman, O.L.; McIntosh, C.L.; Pacansky, J. *J. Am. Chem. Soc.* ***1973***, *95*, 614; Maier, G.; Mende, U. *Tetrahedron Lett.* ***1969***, 3155. For a review, see Sheridan, R.S. *Org. Photochem.* ***1987***, *8*, 159 (pp. 167–181).

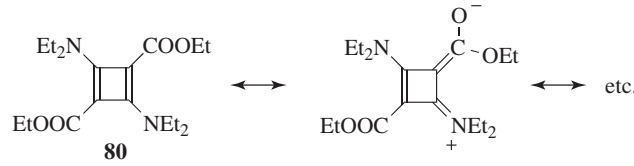
[258] Masamune, S.; Souto-Bachiller, F.A.; Machiguchi, T.; Bertie, J.E. *J. Am. Chem. Soc.* ***1978***, *100*, 4889.

[259] Kreile, J.; Münzel, N.; Schweig, A.; Specht, H. *Chem. Phys. Lett.* ***1986***, *124*, 140.

[260] See Ermer, O.; Heilbronner, E. *Angew. Chem. Int. Ed.* ***1983***, *22*, 402; Voter, A.F.; Goddard III, W.A. *J. Am. Chem. Soc.* ***1986***, *108*, 2830.

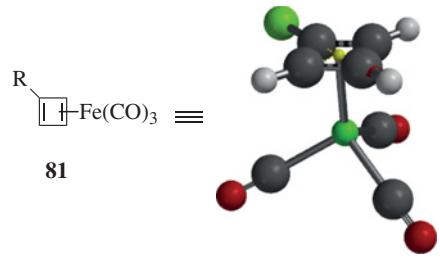
The compound was generated (as an intermediate that was not isolated) and two isomers were indeed found.[261] The cyclobutadiene molecule is not static, even in the matrices. There are two forms (**74a** and **74b**) that rapidly interconvert.[262] Note that there is experimental evidence that the aromatic and antiaromatic characters of neutral and dianionic systems are measurably increased via deuteration.[263]

There are some simple cyclobutadienes that are stable at room temperature for varying periods of time. These either have bulky substituents or carry certain other stabilizing substituents such as seen in tri-*tert*-butylcyclobutadiene (**79**),[264] the first well established example of a delocalized [4]annulene. Such compounds are relatively stable because dimerization is hindered by steric interactions. Examination of the NMR spectrum of **79** showed that the ring proton ($\delta = 5.38$) was shifted *upfield*, compared with the position expected for a nonaromatic proton, for example, cyclopentadiene. As will be seen in Section 2.K.vi, this indicates that the compound is antiaromatic.



80

The other type of stable cyclobutadiene has two electron-donating and two electron-withdrawing groups,[265] and is stable in the absence of water.[266] An example is **80**. The stability of these compounds is generally attributed to the resonance shown, a type of resonance stabilization called the *push-pull effect* or *captodative effect*,[267] although it has been concluded from a photoelectron spectroscopy study that second-order bond fixation is more important.[268] An X-ray crystallographic study of **80** has shown[269] the ring to be a distorted square with bond lengths of 1.46 Å and angles of 87° and 93°.



81

[261] Whitman, D.W.; Carpenter, B.K. *J. Am. Chem. Soc.* ***1980***, *102*, 4272. See also, Whitman, D.W.; Carpenter, B.K. *J. Am. Chem. Soc.* ***1982***, *104*, 6473.

[262] Orendt, A.M.; Arnold, B.R.; Radziszewski, J.G.; Facelli, J.C.; Malsch, K.D.; Strub, H.; Grant, D.M.; Michl, J. *J. Am. Chem. Soc.* ***1988***, *110*, 2648. See, however, Arnold, B.R.; Radziszewski, J.G.; Campion, A.; Perry, S.S.; Michl, J. *J. Am. Chem. Soc.* ***1991***, *113*, 692.

[263] For experiments with [16]annulene (Sec. 2.K.v), see Stevenson, C.D.; Kurth, T.L. *J. Am. Chem. Soc.* ***1999***, *121*, 1623

[264] Masamune, S.; Nakamura, N.; Suda, M.; Ona, H. *J. Am. Chem. Soc.* ***1973***, *95*, 8481; Maier, G.; Alzérreca, A. *Angew. Chem. Int. Ed.* ***1973***, *12*, 1015; Masamune, S. *Pure Appl. Chem.* ***1975***, *44*, 861. See Gompper, R.; Kroner, J.; Seybold, G.; Wagner, H.-U. *Tetrahedron* ***1976***, *32*, 629.

[265] See Gompper, R.; Wagner, H. *Angew. Chem. Int. Ed.* ***1988***, *27*, 1437.

[266] Gompper, R.; Kroner, J.; Seybold, G.; Wagner, H. *Tetrahedron* ***1976***, *32*, 629.

[267] Hess Jr., B.A.; Schaad, L.J. *J. Org. Chem.* ***1976***, *41*, 3058.

[268] Gompper, R.; Holsboer, F.; Schmidt, W.; Seybold, G. *J. Am. Chem. Soc.* ***1973***, *95*, 8479.

[269] Lindner, H.J.; von Ross, B. *Chem. Ber.* ***1974***, *107*, 598.

It is clear that simple cyclobutadienes, which could easily adopt a square planar shape if that would result in aromatic stabilization, do not in fact do so and are not aromatic. The high reactivity of these compounds is not caused merely by steric strain, since the strain should be no greater than that of simple cyclopropenes, which are known compounds. It is probably caused by antiaromaticity.[270]

The cyclobutadiene system can be stabilized as a η^4 complex with metals,[271] as with the iron complex **81** (see Chapter 3), but in these cases electron density is withdrawn from the ring by the metal and there is no aromatic quartet. In fact, these cyclobutadiene–metal complexes can be looked upon as systems containing an aromatic duet. The ring is square planar,[272] the compounds undergo aromatic substitution,[273] and NMR spectra of monosubstituted derivatives show that the C-2 and C-4 protons are equivalent.[248]

82 **83** **84**

Other systems that have been studied as possible aromatic or antiaromatic four-electron systems include the cyclopropenyl anion (**83**) and the cyclopentadienyl cation (**84**).[274] With respect to **83**, HMO theory predicts that an unconjugated **82** (i.e., a single canonical form) is more stable than a conjugated **83**,[275] so that **82** would actually lose stability by forming a closed loop of four electrons. The HMO theory is supported by experiment. Among other evidence, it has been shown that **85** (R═COPh) loses its proton in hydrogen-exchange reactions ~6000 times more slowly than **86** (R═COPh).[276] Where R═CN, the ratio is ~10 000.[277] This indicates that **85** are much more reluctant to form carbanions (which would have to be cyclopropenyl carbanions) than **86**, which form ordinary carbanions. Thus the carbanions of **85** are less stable than corresponding ordinary carbanions. Although derivatives of cyclopropenyl anion have been prepared as fleeting intermediates (as in the exchange reactions mentioned above), all attempts to prepare the ion or any of its derivatives as relatively stable species have so far met with failure.[278]

85 **86**

[270] For evidence, see Breslow, R.; Murayama, D.R.; Murahashi, S.; Grubbs, R. *J. Am. Chem. Soc.* ***1973***, *95*, 6688; Herr, M.L. *Tetrahedron* ***1976***, *32*, 2835.

[271] Efraty, A. *Chem. Rev.* ***1977***, *77*, 691; Pettit, R. *Pure Appl. Chem.* ***1968***, *17*, 253; Maitlis, P.M. *Adv. Organomet. Chem.* ***1966***, *4*, 95; Maitlis, P.M.; Eberius, K.W., in Snyder, J.P. *Nonbenzenoid Aromatics*, Vol. 2, Academic Press, NY, ***1971***, pp. 359–409.

[272] SeeYannoni, C.S.; Ceasar, G.P.; Dailey, B.P. *J. Am. Chem. Soc.* ***1967***, *89*, 2833.

[273] Fitzpatrick, J.D.; Watts, L.; Emerson, G.F.; Pettit, R. *J. Am. Chem. Soc.* ***1965***, *87*, 3255. For a discussion, see Pettit, R. *J. Organomet. Chem.* ***1975***, *100*, 205.

[274] See Breslow, R. *Top. Nonbenzenoid Aromat. Chem.* ***1973***, *1*, 81.

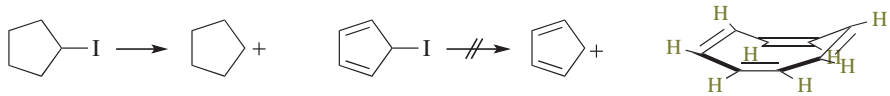
[275] Breslow, R. *Pure Appl. Chem.* ***1971***, *28*, 111; *Acc. Chem. Res.* ***1973***, *6*, 393.

[276] Breslow, R.; Brown, J.; Gajewski, J.J. *J. Am. Chem. Soc.* ***1967***, *89*, 4383.

[277] Breslow, R.; Douek, M. *J. Am. Chem. Soc.* ***1968***, *90*, 2698.

[278] See Breslow, R.; Cortés, D.A.; Juan, B.; Mitchell, R.D. *Tetrahedron Lett.* ***1982***, *23*, 795. See Bartmess, J.E.; Kester, J.; Borden, W.T.; Köser, H.G. *Tetrahedron Lett.* ***1986***, *27*, 5931.

In the case of **84**, the ion has been prepared and shown to be a diradical in the ground state,[279] as predicted by the discussion elsewhere in this section.[280] Evidence that **84** is not only nonaromatic, but is antiaromatic comes from studies on **87** and **89**.[281] When **87** is treated with silver perchlorate in propionic acid, the molecule is rapidly solvolyzed (a reaction in which the intermediate **88** is formed; see Chapters 5 and 10). Under the same conditions, **89** undergoes no solvolysis at all; that is, **84** does not form. If **84** were merely nonaromatic, it should be about as stable as **88** (which of course has no resonance stabilization at all). The fact that it is so much more reluctant to form indicates that **84** is much less stable than **88**. It is noted that under certain conditions, **88** can be generated solvolytically.[282]



87 **88** **89** **84** **75a**

The fact that **83** and **84** are not aromatic while the cyclopropenyl cation (**77**) and the cyclopentadienyl anion (**55**) are aromatic is strong evidence for *Hückel's rule* since simple resonance theory predicts no difference between **83** and **77** or **84** and **55** (the same number of equivalent canonical forms can be drawn for **83** as for **77** and for **84** as for **55**). In recent work, the antiaromaticity of dehydro[12], dehydro[16], and dehydro[20]annulenes has been quantified by ^{1}H NMR.[283]

2.K.iii. Systems of Eight Electrons

Cyclooctatetraene[284] ([8]annulene, **75a**) is not planar, but tub-shaped[285] so it is neither aromatic nor antiaromatic, since both these conditions require overlap of parallel *p* orbitals. The reason for the lack of planarity is that a regular octagon has angles of 135°, while sp^2 angles are most stable at 120°. To avoid the strain, the molecule assumes a nonplanar shape, in which orbital overlap is greatly diminished.[286] Single- and double-bond distances in **75** are, respectively, 1.46 and 1.33 Å, which is expected for a compound made up of four individual double bonds.[285] The *Jahn-Teller effect* has been invoked to explain the instability of

[279] Saunders, M.; Berger, R.; Jaffe, A.; McBride, J.M.; O'Neill, J.; Breslow, R.; Hoffman Jr., J.M.; Perchonock, C.; Wasserman, E.; Hutton, R.S.; Kuck, V.J. *J. Am. Chem. Soc.* ***1973***, *95*, 3017.

[280] See Breslow, R.; Chang, H.W.; Hill, R.; Wasserman, E. *J. Am. Chem. Soc.* ***1967***, *89*, 1112; Gompper, R.; Glöckner, H. *Angew. Chem. Int. Ed.* ***1984***, *23*, 53.

[281] Breslow, R.; Mazur, S. *J. Am. Chem. Soc.* ***1973***, *95*, 584. See Lossing, F.P.; Treager, J.C. *J. Am. Chem. Soc.* ***1975***, *97*, 1579. See also, Breslow, R.; Canary, J.W. *J. Am. Chem. Soc.* ***1991***, *113*, 3950.

[282] Allen, A.D.; Sumonja, M.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1997***, *119*, 2371.

[283] Kleinpeter, E.; Koch, A. *Tetrahedron.* ***2013***, *69*, 1481.

[284] See Fray, G.I.; Saxton, R.G. *The Chemistry of Cyclooctatetraene and its Derivatives*, Cambridge University Press, Cambridge, ***1978***; Paquette, L.A. *Tetrahedron* ***1975***, *31*, 2855. For reviews of heterocyclic 8π systems, see Kaim, W. *Rev. Chem. Intermed.* ***1987***, *8*, 247; Schmidt, R.R. *Angew. Chem. Int. Ed.* ***1975***, *14*, 581.

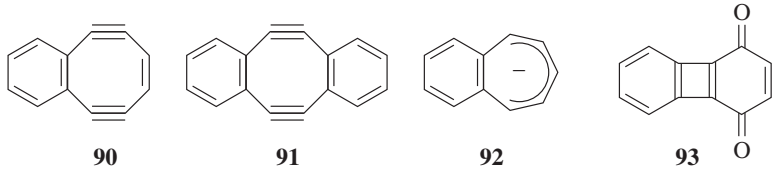
[285] Bastiansen, O.; Hedberg, K.; Hedberg, L. *J. Chem. Phys.* ***1957***, *27*, 1311. See Havenith, R.W.A.; Fowler, P.W.; Jenneskens, L.W. *Org. Lett.* ***2006***, *8*, 1255.

[286] See Einstein, F.W.B.; Willis, A.C.; Cullen, W.R.; Soulen, R.L. *J. Chem. Soc., Chem. Commun.* ***1981***, 526. See also, Paquette, L.A.; Wang, T.; Cottrell, C.E. *J. Am. Chem. Soc.* ***1987***, *109*, 3730.

such antiaromatic compounds.[287] The Jahn-Teller effect arises from molecular distortions due to an electronically degenerate *ground* state.[288]

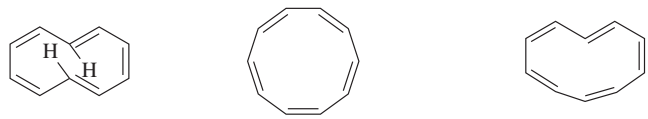
The reactivity is also what would be expected for a linear polyene. Reactive intermediates can be formed in solution. Dehydrohalogenation of bromocyclooctatetraene at −100 °C has been reported, for example, and trapping by immediate electron transfer gave a stable solution of the [8]annulyne anion radical.[289]

The cyclooctadiendiynes **90** and **91** are planar conjugated eight-electron systems (the four extra triple-bond electrons do not participate), which NMR evidence show to be antiaromatic.[290] There is evidence that part of the reason for the lack of planarity in **75** itself is that a planar molecular would have to be antiaromatic.[291] There is a loss of aromaticity in such systems in singlet states but the aromaticity is recovered when triplet states are taken into account.[292] The cycloheptatrienyl anion (**58**) also has eight electrons, but does not behave like an aromatic system.[183] The bond lengths for a series of molecules containing the cycloheptatrienide anion have recently been published.[293] The NMR spectrum of the benzocycloheptatrienyl anion (**92**) shows that, like **79**, **90**, and **91**, this compound is antiaromatic.[294] A new antiaromatic compound 1,4-biphenylene quinone (**93**) was prepared, but it rapidly dimerizes due to instability.[295]



90 **91** **92** **93**

2.K.iv. Systems of Ten Electrons[296]



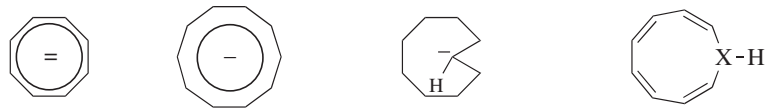
76 **94** **95**

There are three possible geometrical isomers of [10]annulene: the all-*cis* (**94**), the mono-*trans* (**95**), and the *cis-trans-cis-cis-trans* (**76**). If Hückel's rule applies, they should be

[287] Klärner, F.-G. *Angew. Chem. Int. Ed.* ***2001***, *40*, 3977.
[288] *The Jahn–Teller Effect* Bersuker, I.B. Cambridge University Press, ***2006***; Ceulemans, A.; Lijnen, E. *Bull. Chem. Soc. Jpn.* ***2007***, *80*, 1229.
[289] Peters, S.J.; Turk, M.R.; Kiesewetter, M.K.; Stevenson, C.D. *J. Am. Chem. Soc.* ***2003***, *125*, 11264.
[290] Huang, N.Z.; Sondheimer, F. *Acc. Chem. Res.* ***1982***, *15*, 96. See also, Chan, T.; Mak, T.C.W.; Poon, C.; Wong, H.N.C.; Jia, J.H.; Wang, L.L. *Tetrahedron* ***1986***, *42*, 655.
[291] Figeys, H.P.; Dralants, A. *Tetrahedron Lett.* ***1971***, 3901; Buchanan, G.W. *Tetrahedron Lett.* ***1972***, 665.
[292] Sánchez-Sanz, G.; Trujillo, C.; Rozas, I.; Elguero, J. *Tetrahedron.* ***2013***, *69*, 7333.
[293] Dietz, F.; Rabinowitz, M.; Tadjer, A.; Tyutyulkov, N. *J. Chem. Soc., Perkin Trans. 2* ***1995***, 735.
[294] Staley, S.W.; Orvedal, A.W. *J. Am. Chem. Soc.* ***1973***, *95*, 3382.
[295] Kiliç, H.; Balci, M. *J. Org. Chem.* ***1997***, *62*, 3434.
[296] See Kemp-Jones, A.V.; Masamune, S. *Top. Nonbenzenoid Aromat. Chem.* ***1973***, *1*, 121; Masamune, S.; Darby, N. *Acc. Chem. Res.* ***1972***, *5*, 272; Burkoth, T.L.; van Tamelen, E.E. in Snyder, J.P. *Nonbenzenoid Aromaticty*, Vol. 1, Academic Press, NY, ***1969***, pp. 63–116; Vogel, E., in Garratt, P.J. Aromaticity, Wiley, NY, ***1986***, pp. 113–147.

planar. But it is far from obvious that the molecules would adopt a planar shape, since they must overcome considerable strain to do so. For a regular decagon (**94**) the angles would have to be 144°, considerably larger than the 120° required for sp^2 angles. Some of this strain would also be present in **95** but this kind of strain is eliminated in **76** since all the angles are 120°. However, it was pointed out by Mislow[297] that the hydrogen atoms in the 1 and 6 positions should interfere with each other and force the molecule out of planarity. Such configurational changes are not necessarily without cost energetically. It has been determined that configurational changes in [14]annulene, for example. requires Möbius antiaromatic bond shifting.[298]

Compounds **94** and **95** have been prepared[299] as crystalline solids at −80 °C. The NMR spectra show that all the hydrogen atoms lie in the alkene region, and it was concluded that neither compound is aromatic. Calculations on **95** suggest that it may indeed be aromatic, although the other isomers are not.[300] It is known that the Hartree-Fock (HF) method incorrectly favors bond-length-alternating structures for [10]annulene, and aromatic structures are incorrectly favored by density functional theory. Improved calculations predict that the twist conformation is lowest in energy, and the naphthalene-like and heart-shaped conformations lie higher than the twist by 1.40 and 4.24 kcal mol^{-1} (5.96 and 17.75 kJ mol^{-1}), respectively.[301] Analysis of ^{13}C and ^{1}H NMR spectra suggest that neither is planar. However, the preparation of several compounds that have large angles, but that are definitely planar 10-electron aromatic systems,[302] clearly demonstrate that the angle strain is not insurmountable. Among these are the dianion **96**, the anions **97** and **98**, and the azonine **99**.[303]



96 **97** **98** **99**

Compound **96**[304] has angles of about 135°, while **97**[305] and **98**[306] have angles of about 140°, which are not very far from 144°. The inner proton in **98**[307] (which is the mono-*trans* isomer of the all-*cis* **97**) is found far upfield in the NMR (−3.5 δ). For **94** and **95**, the cost in

[297] Mislow, K. *J. Chem. Phys.* ***1952***, *20*, 1489.

[298] Moll, J.F.; Pemberton, R.P.; Gertrude Gutierrez, M.; Castro, C.; Karney, W.L. *J. Am. Chem. Soc.* ***2007***, *129*, 274.

[299] Masamune, S.; Hojo, K.; Bigam, G.; Rabenstein, D.L. *J. Am. Chem. Soc.* ***1971***, *93*, 4966; van Tamelen, E.E.; Burkoth, T.L.; Greeley, R.H. *J. Am. Chem. Soc.* ***1971***, *93*, 6120.

[300] Sulzbach, H.M.; Schleyer, P.v.R.; Jiao, H.; Xie, Y.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1995***, *117*, 1369; Sulzbach, H.M.; Schaefer III, H.F.; Klopper, W.; Lüthi, H.P. *J. Am. Chem. Soc.* ***1996***, *118*, 3519.

[301] King, R.A.; Crawford, T.D.; Stanton, J.F.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1999***, *121*, 10788.

[302] See Kurbatov, S.; Lakhdar, S.; Goumont, R.; Terrier, F *Org. Prep. Proceed. Int.* ***2012***, *44*, 289.

[303] See Anastassiou, A.G. *Acc. Chem. Res.* ***1972***, *5*, 281, *Top. Nonbenzenoid Aromat. Chem.* ***1973***, *1*, 1, *Pure Appl. Chem.* ***1975***, *44*, 691. For a review of heteroannulenes in general, see Anastassiou, A.G.; Kasmai, H.S. *Adv. Heterocycl. Chem.* ***1978***, *23*, 55.

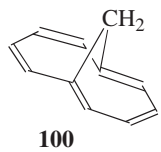
[304] Evans, W.J.; Wink, D.J.; Wayda, A.L.; Little, D.A. *J. Org. Chem.* ***1981***, *46*, 3925; Heinz, W.; Langensee, P.; Müllen, K. *J. Chem. Soc., Chem. Commun.* ***1986***, 947.

[305] Paquette, L.A.; Ley, S.V.; Meisinger, R.H.; Russell, R.K.; Oku, M. *J. Am. Chem. Soc.* ***1974***, *96*, 5806; Radlick, P.; Rosen, W. *J. Am. Chem. Soc.* ***1966***, *88*, 3461.

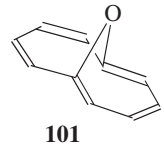
[306] Anastassiou, A.G.; Gebrian, J.H. *Tetrahedron Lett.* ***1970***, 825.

[307] Boche, G.; Weber, H.; Martens, D.; Bieberbach, A. *Chem. Ber.* ***1978***, *111*, 2480. See also, Anastassiou, A.G.; Reichmanis, E. *Angew. Chem. Int. Ed.* ***1974***, *13*, 728.

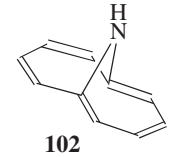
strain energy to achieve planarity apparently outweighs the extra stability that would come from an aromatic ring. Further emphasizing the delicate balance between these factors, it is known that the oxygen analog of **99** (X = O, oxonin) and the *N*-carbethoxy derivative of **98** (X = CH) are nonaromatic and nonplanar, while **99** (X = N) is aromatic and planar.[308] Other azaannulenes are known, including Vogel's 2,7-methanoazaannulene,[309] as well as 3,8-methanoaza[10]annulene,[310] and the alkoxy derivative of both.[311] Calculations for aza[10]annulene concluded that the best olefinic twist isomer is 2.1 kcal mol^{-1} (8.8 kJ mol^{-1}) more stable than the aromatic form,[312] and is probably the more stable form.



100



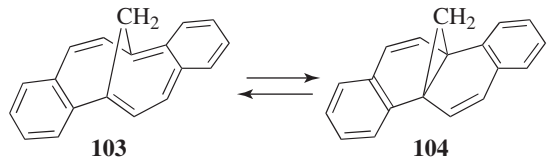
101



102

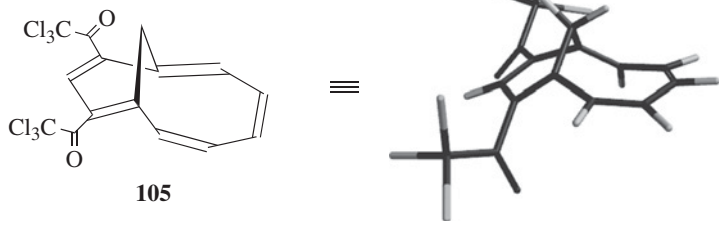
So far, **76** from above has not been prepared despite many attempts. However, there are various ways of avoiding the interference between the two inner protons. The approach that has been most successful involves bridging the 1 and 6 positions.[313] Thus, 1,6-methano[10]annulene (**100**)[314] and its oxygen and nitrogen analogs **101**[315] and **102**[316] have been prepared and they are stable compounds, are diatropic, and undergo aromatic substitution.[317] For example, the perimeter protons of **100** are found at 6.9–7.3 δ, while the bridge protons are at −0.5 δ. The crystal structure of **100** shows that the perimeter is nonplanar, but the bond distances are in the range 1.37–1.42 Å.[318] It has therefore been amply demonstrated that a closed loop of 10 electrons is an aromatic system, although some molecules that could conceivably have such a system are too distorted from planarity to be aromatic. A small distortion from planarity (as in **100**) does not prevent aromaticity, at least in part because the σ orbitals so distort themselves as to maximize the favorable (parallel) overlap of *p* orbitals to form the aromatic 10-electron loop.[319]

[308] Chiang, C.C.; Paul, I.C.; Anastassiou, A.G.; Eachus, S.W. *J. Am. Chem. Soc.* ***1974***, *96*, 1636.
[309] Shani, A.; Sondheimer, F. *J. Am. Chem. Soc.* ***1967***, *89*, 6310; Bailey, N.A.; Mason, R. *J. Chem. Soc., Chem. Commun.* ***1967***,1039.
[310] Destro, R.; Simonetta, M.; Vogel, E. *J. Am. Chem. Soc.* ***1981***, *103*, 2863.
[311] Schleyer, P.v.R.; Jiao, H.; Sulzbach, H.M.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1996***, *118*, 2093.
[312] Bettinger, H.F.; Sulzbach, H.M.; Schleyer, P.v.R.; Schaefer III, H.F. *J. Org. Chem.* ***1999***, *64*, 3278.
[313] See Vogel, E. *Pure Appl. Chem.* ***1982***, *54*, 1015; *Isr. J. Chem.* ***1980***, *20*, 215; *Chimia*, ***1968***, *22*, 21; Vogel, E.; Günther, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 385.
[314] Vogel, E.; Roth, H.D. *Angew. Chem. Int. Ed.* ***1964***, *3*, 228; Vogel, E.; Böll, W.A. *Angew. Chem. Int. Ed.* ***1964***, *3*, 642; Vogel, E.; Böll, W.A.; Biskup, M. *Tetrahedron Lett.* ***1966***, 1569.
[315] Vogel, E.; Biskup, M.; Pretzer, W.; Böll, W.A. *Angew. Chem. Int. Ed.* ***1964***, *3*, 642; Shani, A.; Sondheimer, F. *J. Am. Chem. Soc.* ***1967***, *89*, 6310; Bailey, N.A.; Mason, R. *Chem. Commun.* ***1967***, 1039.
[316] Vogel, E.; Pretzer, W.; Böll, W.A. *Tetrahedron Lett.* ***1965***, 3613. See also, Vogel, E.; Biskup, M.; Pretzer, W.; Böll, W.A. *Angew. Chem. Int. Ed.* ***1964***, *3*, 642.
[317] Also see McCague, R.; Moody, C.J.; Rees, C.W. *J. Chem. Soc., Perkin Trans. 1* ***1984***, 165, 175; Gibbard, H.C.; Moody, C.J.; Rees, C.W. *J. Chem. Soc., Perkin Trans. 1* ***1985***, 731, 735.
[318] Bianchi, R.; Pilati, T.; Simonetta, M. *Acta Crystallogr. Sect. B* ***1980***, *36*, 3146. See also, Dobler, M.; Dunitz, J.D. *Helv. Chim Acta* ***1965***, *48*, 1429.
[319] For a discussion, see Haddon, R.C. *Acc. Chem. Res.* ***1988***, *21*, 243.



103 **104**

In **103**, where **100** is fused to two benzene rings in such a way that no canonical form can be written in which both benzene rings have six electrons, the aromaticity is diminished by annellation, as shown by the fact that the molecule rapidly converts to the more stable **104**, in which both benzene rings can be fully aromatic[320] (this is similar to the cycloheptatriene–norcaradiene conversions discussed in **18-32**).



105

Molecules can sustain significant distortion from planarity and retain their aromatic character. 1,3-Bis(trichloroacetyl)homoazulene (**105**) qualifies as aromatic using the geometric criterion that there is only a small average deviation from the C—C bond length in the [10]annulene perimeter.[321] The X-ray crystal structure shows that the 1,5 bridge distorts the [10]annulene π system away from planarity (see the 3D model) with torsion angles as large as 42.2° at the bridgehead position, but **105** does not lose its aromaticity.

2.K.v. Systems of More than Ten Electrons: $4n + 2$ Electrons[322]

Extrapolating from the discussion of [10]annulene, larger $4n + 2$ systems are expected to be aromatic if they are planar. Mislow[297] predicted that [14]annulene (**106**) would possess the same type of interference as **76**, although to a lesser degree. This is borne out by experiment. Compound **106** is aromatic (it is diatropic; inner protons at 0.00 δ, outer protons at 7.6 δ),[323] but is highly reactive and is completely destroyed by light and air in 1 day. X-ray analysis shows that although there are no alternating single and double bonds, the molecule is not

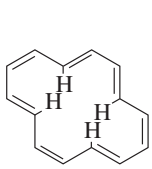
[320] Hill, R.K.; Giberson, C.B.; Silverton, J.V. *J. Am. Chem. Soc.* ***1988***, *110*, 497. See also, McCague, R.; Moody, C.J.; Rees, C.W.; Williams, D.J. *J. Chem. Soc., Perkin Trans. 1* ***1984***, 909.

[321] Scott, L.T.; Sumpter, C.A.; Gantzel, P.K.; Maverick, E.; Trueblood, K.N. *Tetrahedron* ***2001***, *57*, 3795.

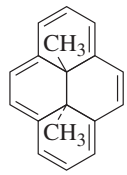
[322] See Sondheimer, F. *Acc. Chem. Res.* ***1972***, *5*, 81–91, *Pure Appl. Chem.* ***1971***, *28*, 331, *Proc. R. Soc. London. Ser. A*, ***1967***, *297*, 173; Sondheimer, F.; Calder, I.C.; Elix, J.A.; Gaoni, Y; Garratt, P.J.; Grohmann, K.; di Maio, G.; Mayer, J.; Sargent, M.V.; Wolovsky, R. in Garratt, P.J. *Aromaticity*, Wiley, NY, ***1986***, pp. 75–107; Nakagawa, M. *Angew. Chem. Int. Ed.* ***1979***, *18*, 202; Müllen, K. *Chem. Rev.* ***1984***, *84*, 603; Rabinovitz, M. *Top. Curr. Chem.* ***1988***, *146*, 99. Also see, Cyvin, S.J.; Brunvoll, J.; Chen, R.S.; Cyvin, B.N.; Zhang, F.J. *Theory of Coronoid Hydrocarbons II*, Springer-Verlag, Berlin, ***1994***.

[323] Gaoni, Y.; Melera, A.; Sondheimer, F.; Wolovsky, R. *Proc. Chem. Soc.* ***1964***, 397.

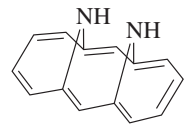
planar.[324] A number of stable bridged [14]annulenes have been prepared,[325] for example, *trans*-15,16-dimethyldihydropyrene (**107**),[326] *syn*-1,6:8,13-diimino[14]annulene (**108**),[327] and *syn*- and *anti*-1,6:8,13-bismethano[14]annulene (**109** and **110**).[328] The dihydropyrene **107** (and its diethyl and dipropyl homologs) is undoubtedly aromatic: the π perimeter is approximately planar,[329] the bond distances are all 1.39–1.40 Å, and the molecule undergoes aromatic substitution[326] and is diatropic.[330] The outer protons are found at 8.14–8.67 δ, while the CH_3 protons are at −4.25 δ. Other nonplanar aromatic dihydropyrenes are known.[331] Annulenes **108** and **109** are also diatropic,[332] although X-ray crystallography indicates that the π periphery in **108** is not quite planar.[333] In **110** the geometry of the molecule greatly reduces the overlap of the *p* orbitals at the bridgehead positions with adjacent *p* orbitals, and it is definitely not aromatic,[334] as shown by NMR spectra[328] and X-ray crystallography, from which bond distances of 1.33 to 1.36 Å for the double bonds and 1.44 to 1.49 Å for the single bonds have been obtained.[335] In contrast, all the bond distances in **108** are ∼1.38 to 1.40 Å.[333]



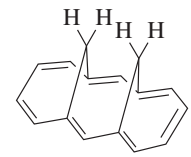
106



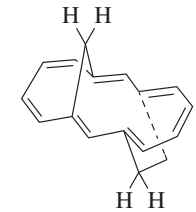
107



108



109



110

Another way of eliminating the hydrogen interferences of [14]annulene is to introduce one or more triple bonds into the system, as in dehydro[14]annulene (**111**).[336] All

[324] Chiang, C.C.; Paul, I.C. *J. Am. Chem. Soc.* ***1972***, *94*, 4741; Oth, J.F.M.; Schröder, G. *J. Chem. Soc. B*, ***1971***, 904. See also Willner, I.; Gutman, A.L.; Rabinovitz, M. *J. Am. Chem. Soc.* ***1977***, *99*, 4167; Röttele, H.; Schröder, G. *Chem. Ber.* ***1982***, *115*, 248.

[325] For a review, see Vogel, E. *Pure Appl. Chem.* ***1971***, *28*, 355.

[326] Boekelheide, V.; Phillips, J.B. *J. Am. Chem. Soc.* ***1967***, *89*, 1695; Boekelheide, V.; Miyasaka, T. *J. Am. Chem. Soc.* ***1967***, *89*, 1709. For reviews of dihydropyrenes, see Mitchell, R.H. *Adv. Theor. Interesting Mol.* ***1989***, *1*, 135; Boekelheide, V. *Top. Nonbenzoid Arom. Chem.* ***1973***, *1*, 47; *Pure Appl. Chem.* ***1975***, *44*, 807.

[327] Destro, R.; Pilati, T.; Simonetta, M.; Vogel, E. *J. Am. Chem. Soc.* ***1985***, *107*, 3185, 3192. For the di -*O*- analog of **99**, see Vogel, A.; Biskup, M.; Vogel, E.; Günther, H. *Angew. Chem. Int. Ed.* ***1966***, *5*, 734.

[328] Vogel, E.; Sombroek, J.; Wagemann, W. *Angew. Chem. Int. Ed.* ***1975***, *14*, 564.

[329] Hanson, A.W. *Acta Crystallogr.* ***1965***, *18*, 599, 1967, 23, 476.

[330] See Mitchell, R.H.; Williams, R.V.; Mahadevan, R.; Lai, Y.H.; Dingle, T.W. *J. Am. Chem. Soc.* ***1982***, *104*, 2571 and other papers in this series.

[331] Bodwell, G.J.; Bridson, J.N.; Chen, S.-L.; Poirier, R.A. *J. Am. Chem. Soc.* ***2001***, *123*, 4704; Bodwell, G.J.; Fleming, J.J.; Miller, D.O. *Tetrahedron* ***2001***, *57*, 3577.

[332] See Vogel, E.; Wieland, H.; Schmalstieg, L.; Lex, J. *Angew. Chem. Int. Ed.* ***1984***, *23*, 717; Neumann, G.; Müllen, K. *J. Am. Chem. Soc.* ***1986***, *108*, 4105.

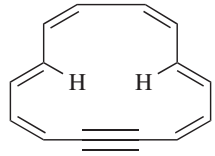
[333] Ganis, P.; Dunitz, J.D. *Helv. Chim. Acta*, ***1967***, *50*, 2369.

[334] See Vogel, E.; Nitsche, R.; Krieg, H. *Angew. Chem. Int. Ed.* ***1981***, *20*, 811. See also, Vogel, E.; Schieb, T.; Schulz, W.H.; Schmidt, K.; Schmickler, H.; Lex, J. *Angew. Chem. Int. Ed.* ***1986***, *25*, 723.

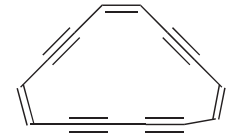
[335] Gramaccioli, C.M.; Mimun, A.; Mugnoli, A.; Simonetta, M. *Chem. Commun.* ***1971***, 796. See also, Destro, R.; Simonetta, M. *Tetrahedron* ***1982***, *38*, 1443.

[336] For a review of dehydroannulenes, see, Nakagawa, M. *Top. Nonbenzenoid Aromat. Chem.* ***1973***, *1*, 191.

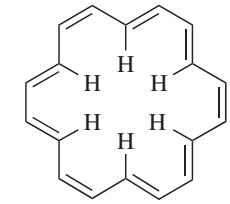
five known dehydro[14]annulenes are diatropic, and **111** can be nitrated or sulfonated.[337] The extra electrons of the triple bond do not form part of the aromatic system, but it simply exists as a localized bond. There has been a debate concerning the extent of delocalization in dehydrobenzoannulenes,[338] but there is evidence for a weak, but discernible, ring current.[339] 3,4,7,8,9,10,13,14-Octahydro[14]annulene (**112**) has been prepared, for example, and the evidence supported its aromaticity.[340] This study suggested that increasing benzoannelation of the parent **112** led to a stepdown in aromaticity, a result of competing ring currents in the annulenic system. It is noted that [12]annulyne has been prepared.[341]



111



112



113

[18]Annulene (**113**) is diatropic:[342] the 12 outer protons are found at about $\delta = 9$ and the 6 inner protons at $\sim\delta = -3$.[343] X-ray crystallography[344] shows that it is nearly planar, so that interference of the inner hydrogen atoms is not important in annulenes this large. Compound **113** is reasonably stable, being distillable at reduced pressures, and undergoes aromatic substitutions[345] (Chapter 11). The C—C bond distances are not equal, but they do not alternate. There are 12 inner bonds of ~1.38 Å and 6 outer bonds of ~1.42 Å.[344] Compound **113** has been estimated to have a resonance energy of ~37 kcal mol^{-1} (155 kJ mol^{-1}), similar to that of benzene.[346]

[337] Gaoni, Y.; Sondheimer, F. *J. Am. Chem. Soc.* ***1964***, *86*, 521.

[338] Balaban, A.T.; Banciu, M.; Ciorba, V. *Annulenes, Benzo-, Hetero-, Homo- Derivatives and their Valence Isomers,* Vol. 1–3, CRC Press, Boca Raton, FL, ***1987***; Garratt, P.J. *Aromaticity*, Wiley, NY, ***1986***; Minkin, V.I.; Glukhovtsev, M.N.; Simkin, B.Ya. *Aromaticity and Antiaromaticity*, Wiley, NY, ***1994***.

[339] Bell, M.L.; Chiechi, R.C.; Johnson, C.A.; Kimball, D.B.; Matzger, A.J.; Wan, W.B.; Weakley, T.J.R.; Haley, M.M. *Tetrahedron* ***2001***, *57*, 3507; Wan, W.B.; Chiechi, R.C.; Weakley, T.J.R.; Haley, M.M. *Eur. J. Org. Chem.* ***2001***, 3485.

[340] Boydston, A.J.; Haley, M.M.; Williams, R.V.; Armantrout, J.R. *J. Org. Chem.* ***2002***, *67*, 8812.

[341] Gard, M.N.; Kiesewetter, M.K.; Reiter, R.C.; Stevenson, C.D. *J. Am. Chem. Soc.* ***2005***, *127*, 16143.

[342] Gilles, J.; Oth, J.F.M.; Sondheimer, F.; Woo, E.P. *J. Chem. Soc. B* ***1971***, 2177. For a thorough discussion, see Baumann, H.; Oth, J.F.M. *Helv. Chim. Acta* ***1982***, *65*, 1885.

[343] See Tanimura, H.; Honda, Y.; Sugiura, K.; Hada, M. *Bull. Chem. Soc. Jpn.* ***2011***, *84*, 845; ***2012***, *85*,1244.

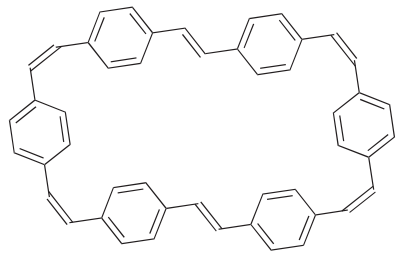
[344] Bregman, J.; Hirshfeld, F.L.; Rabinovich, D.; Schmidt, G.M.J. *Acta Crystallogr.* ***1965***, *19*, 227; Hirshfeld, F.L.; Rabinovich, D. *Acta Crystallogr.* ***1965***, *19*, 235.

[345] Sondheimer, F. *Tetrahedron* ***1970***, *26*, 3933.

[346] Oth, J.F.M.; Bünzli, J.; de Julien de Zélicourt, Y. *Helv. Chim. Acta*, ***1974***, *57*, 2276.

The known bridged [18]annulenes are also diatropic[347] as are most of the known dehydro[18]annulenes.[348] The dianions of open and bridged [16]annulenes[349] are also 18-electron aromatic systems,[350] and there are dibenzo[18]annulenes.[351]

[22]Annulene[352] and dehydro[22]annulene[353] are also diatropic. A dehydrobenzo[22]annulene has been prepared that has eight C≡C units, is planar and possesses a weak induced ring current.[354] In the latter compound there are 13 outer protons at 6.25–8.45 δ and 7 inner protons at 0.70–3.45 δ. Some aromatic bridged [22]annulenes are known.[355] [26]Annulene has not yet been prepared, but several dehydro[26]annulenes are aromatic.[356] Furthermore, the dianion of 1,3,7,9,13,15,19,21-octadehydro[24]annulene is another 26-electron system that is aromatic.[357] Ojima and co-workers have prepared bridged dehydro derivatives of [26], [30], and [34]annulenes.[358] All are diatropic. The same workers prepared a bridged tetradehydro[38]annulene,[356] which showed no ring current. On the other hand, the dianion of the cyclophane, **114**, also has 38 perimeter electrons, and this species is diatropic.[359]



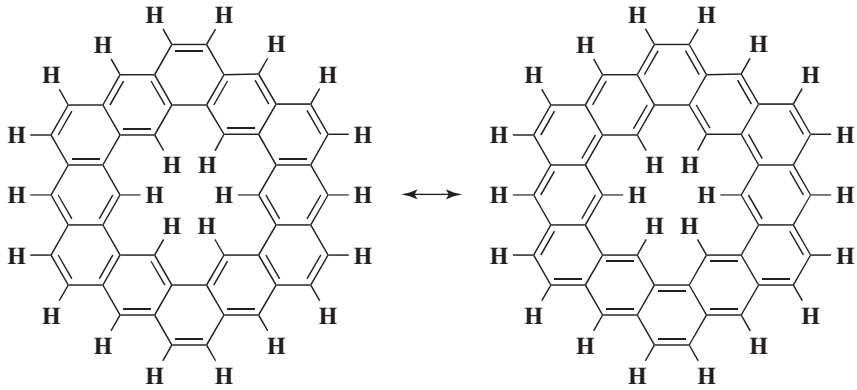
114

There is now no doubt that $4n + 2$ systems are aromatic if they can be planar, although **94** and **110**, among others, demonstrate that not all such systems are in fact planar enough for

[347] Vogel, E.; Sicken, M.; Röhrig, P.; Schmickler, H.; Lex, J.; Ermer, O. *Angew. Chem. Int. Ed.* ***1988***, *27*, 411.
[348] Sondheimer, F. *Acc. Chem. Res.* ***1972***, *5*, 81. For two that are not, see Endo, K.; Sakata, Y.; Misumi, S. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 2465.
[349] See Rabinovitz, M.; Willner, I.; Minsky, A. *Acc. Chem. Res.* ***1983***, *16*, 298.
[350] Oth, J.F.M.; Baumann, H.; Gilles, J.; Schröder, G. *J. Am. Chem. Soc.* ***1972***, *94*, 3948. See also, Brown, J.M.; Sondheimer, F. *Angew. Chem. Int. Ed.* ***1974***, *13*, 337; Rabinovitz, M.; Minsky, A. *Pure Appl. Chem.* ***1982***, *54*, 1005.
[351] Michels, H.P.; Nieger, M.; Vögtle, F. *Chem. Ber.* ***1994***, *127*, 1167.
[352] McQuilkin, R.M.; Metcalf, B.W.; Sondheimer, F. *Chem. Commun.* ***1971***, 338.
[353] Iyoda, M.; Nakagawa, M. *J. Chem. Soc., Chem. Commun.* ***1972***, 1003. See also, Akiyama, S.; Nomoto, T.; Iyoda, M.; Nakagawa, M. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 2579.
[354] Wan, W.B.; Kimball, D.B.; Haley, M.M. *Tetrahedron Lett.* ***1998***, *39*, 6795.
[355] See Yamamoto, K.; Kuroda, S.; Shibutani, M.; Yoneyama, Y.; Ojima, J.; Fujita, S.; Ejiri, E.; Yanagihara, K. *J. Chem. Soc., Perkin Trans. 1* ***1988***, 395.
[356] Ojima, J.; Fujita, S.; Matsumoto, M.; Ejiri, E.; Kato, T.; Kuroda, S.; Nozawa, Y.; Hirooka, S.; Yoneyama, Y.; Tatemitsu, H. *J. Chem. Soc., Perkin Trans. 1* ***1988***, 385.
[357] McQuilkin, R.M.; Garratt, P.J.; Sondheimer, F. *J. Am. Chem. Soc.* ***1970***, *92*, 6682. See also, Huber, W.; Müllen, K.; Wennerström, O. *Angew. Chem. Int. Ed.* ***1980***, *19*, 624.
[358] Ojima, J.; Fujita, S.; Matsumoto, M.; Ejiri, E.; Kato, T.; Kuroda, S.; Nozawa, Y.; Hirooka, S.; Yoneyama, Y.; Tatemitsu, H. *J. Chem. Soc., Perkin Trans. 1* ***1988***, 385.
[359] Müllen, K.; Unterberg, H.; Huber, W.; Wennerström, O.; Norinder, U.; Tanner, D.; Thulin, B. *J. Am. Chem. Soc.* ***1984***, *106*, 7514.

aromaticity. Both **106** and **108** prove that absolute planarity is not required for aromaticity, but that aromaticity decreases with decreasing planarity.

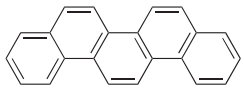
The ^{1}H NMR spectrum of **115** (called kekulene) showed that in a case where electrons can form either aromatic sextets or larger systems, the sextets are preferred.[360] There was initial speculation that kekulene might be *superaromatic*, that is, it would show enhanced aromatic stabilization. Calculations suggest that there is no enhanced stabilization.[361] The 48 π electrons of **115** might, in theory, prefer structure **115a**, where each ring is a fused benzene ring, or **115b**, which has a [30]annulene on the outside and an [18]annulene on the inside. The ^{1}H NMR spectrum of this compound shows three peaks at δ = 7.94, 8.37, and 10.45 in a ratio of 2:1:1. Examination of the structure shows that **115** contains three groups of protons. The peak at 7.94 δ is attributed to the 12 ortho protons and the peak at 8.37 δ to the six external para protons. The remaining peak comes from the six inner protons. If the molecule preferred **115b**, this peak should be upfield, probably with a negative δ, as in the case of **112**. The fact that this peak is far downfield indicates that the electrons prefer to be in benzenoid rings. Note that in the case of the dianion of **114**, the opposite situation prevails. In this ion, the 38-electron system is preferred even though 24 of these must come from the six benzene rings, which therefore cannot have aromatic sextets.



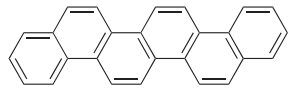
115a **115b**

Phenacenes are a family of "graphite ribbons," where benzene rings are fused together in an alternating pattern. Phenanthrene is the simplest member of this family and other members include the 22-electron system picene (**116**), the 26-electron system fulminene (**117**), and the larger member of this family, the 30-electron [7]phenancene, with seven rings (**118**).[362] In the series benzene to heptacene, reactivity increases although acene resonance energies per π electron are nearly constant. The inner rings of the "acenes" are more reactive, and calculations shown that those rings are more aromatic than the outer rings, and even more aromatic than benzene itself.[363] *N*-Heteroacenes are also known.[364]

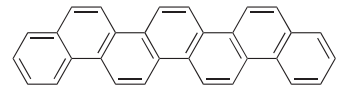
[360] Funhoff, D.J.H.; Staab, H.A. *Angew. Chem. Int. Ed.* ***1986***, *25*, 742.
[361] Jiao, H.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.* ***1996***, *35*, 2383.
[362] Mallory, F.B.; Butler, K.E.; Evans, A.C.; Mallory, C.W. *Tetrahedron Lett.* ***1996***, *37*, 7173.
[363] Schleyer, P.v.R.; Manoharan, M.; Jiao, H.; Stahl, F. *Org. Lett.* ***2001***, *3*, 3643. For a discussion of local aromaticity, see Portella, G.; Poater, J.; Bofill, J.M.; Alemany, P.; Solà, M. *J. Org. Chem.* ***2005***, *70*, 2509.
[364] Bunz, U.H.F. *Chemistry: Eur. J.* ***2009***, *15*, 6780.



116

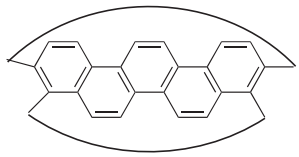


117

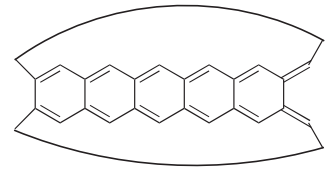


118

A super-ring molecule is formed by rolling a polyacene molecule into one ring with one edge benzene ring folding into the other. These are called cyclopolyacenes or cyclacenes.[365] Although the *zigzag* cyclohexacenes (**119**) are highly aromatic (this example is a 22-electron system), the linear cyclohexacenes (e.g., the 24-electron **120**) are much less aromatic.[366] It is possible to deform an acene by attaching bulky substituents to its periphery by single covalent bonds. The presence of these substituents, which often leads to twisting of torsion angles, is usually easier than distortion of bond angles or C–C bond lengths. Such compounds are called twisted acenes.[367]



119



120

2.K.vi. Systems of More Than Ten Electrons: 4*n* Electrons[372]

121 **122**

As seen in Section 2.K.ii, these systems are expected to be not only nonaromatic, but also antiaromatic. The [12]annulene **121** has been prepared.[368] In solution **121** exhibits rapid conformational mobility (as do many other annulenes),[369] and above −150 °C in this particular case, all protons are magnetically equivalent. However, at −170 °C the mobility is greatly slowed and the three inner protons are found at ∼8 δ while the nine outer protons

[365] Ashton, P.R.; Girreser, U.; Giuffrida, D.; Kohnke, F.H.; Mathias, J.P.; Raymo, F.M.; Slawin, A.M.Z.; Stoddart, J.F.; Williams, D.J. *J. Am. Chem. Soc.* ***1993***, *115*, 5422.

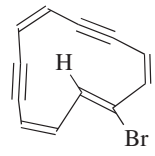
[366] Aihara, J-i. *J. Chem. Soc., Perkin Trans. 2* ***1994***, 971. For a discussion of hexacene stability, see Mondal, R.; Adhikari, R.M.; Shah, B.K.; Neckers, D.C. *Org. Lett.* ***2007***, *9*, 2505.

[367] Pascal, Jr., R.A. *Chem. Rev.* ***2006***, *106*, 4809. See also Chauvin, R.; Lepetit, C.; Maraval, V.; Leroyer, L. *Pure Appl. Chem.* ***2010***, *82*, 769.

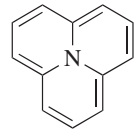
[368] Oth, J.F.M.; Röttele, H.; Schröder, G. *Tetrahedron Lett.* ***1970***, 61; Oth, J.F.M.; Gilles, J.; Schröder, G. *Tetrahedron Lett.* ***1970***, 67. See Braten, M.N.; Castro, C.; Herges, R.; Köhler, F.; Karney, W.L. *J. Org. Chem.* ***2008***, *73*, 1532.

[369] For a review of conformational mobility in annulenes, see Oth, J.F.M. *Pure Appl. Chem.* ***1971***, *25*, 573.

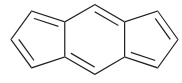
are at ~6 δ. Interaction of the "internal" hydrogen atoms in annulene **121** leads to nonplanarity. **121** is unstable above −50 °C and rearranges to **122**. Several bridged and dehydro[12]annulenes are known, for example, 5-bromo-1,9-didehydro[12]annulene (**123**),[370] cycl[3.3.3]azine (**124**),[371] *s*-indacene (**125**),[372] and 1,7-methano[12]annulene (**126**).[373] *s*-Indacene is a planar, conjugated system perturbed by two cross links, and studies showed that the low-energy structure has *localized* double bonds. In these compounds, both hydrogen interference and conformational mobility are prevented. In **124**–**126**, the bridge prevents conformational changes, while in **123** the bromine atom is too large to be found inside the ring. The NMR spectra show that all four compounds are paratropic, the inner proton of **123** being found at 16.4 δ. The dication of **109**[374] and the dianion of **100**[375] are also 12-electron paratropic species. An interesting 12-electron [13]annulenone has recently been reported, 5,10-dimethyl[13]annulenone (**127**), which is the first monocyclic annulene larger than tropane,[376] and a linearly fused benzodehydro[12]annulene system has been reported.[377]



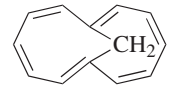
123



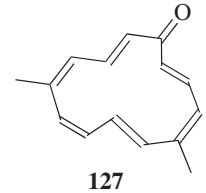
124



125



126



127

The results for [16]annulene are similar. The compound was synthesized in two different ways,[378] both of which gave **128**, which in solution is in equilibrium with **129**. Above −50 °C there is conformational mobility, resulting in the magnetic equivalence of all protons, but at −130 °C the compound is clearly paratropic: there are 4 protons at 10.56 δ and 12 at 5.35 δ. In the solid state, where the compound exists entirely as **128**, X-ray crystallography[379] shows that the molecules are nonplanar with almost complete bond alternation: the single bonds are 1.44–1.47 Å and the double bonds 1.31–1.35 Å. A number of dehydro and bridged [16]annulenes are also paratropic,[380] as are

[370] Untch, K.G.; Wysocki, D.C. *J. Am. Chem. Soc.* ***1967***, *89*, 6386.

[371] Farquhar, D.; Leaver, D. *Chem. Commun.* ***1969***, 24. For a review, see Matsuda, Y.; Gotou, H. *Heterocycles* ***1987***, *26*, 2757.

[372] Hertwig, R.H.; Holthausen, M.C.; Koch, W.; Maksić, Z.B. *Angew. Chem. Int. Ed.* ***1994***, *33*, 1192.

[373] Scott, L.T.; Kirms, M.A.; Günther, H.; von Puttkamer, H. *J. Am. Chem. Soc.* ***1983***, *105*, 1372; Destro, R.; Ortoleva, E.; Simonetta, M.; Todeschini, R. *J. Chem. Soc., Perkin Trans. 2* ***1983***, 1227.

[374] Müllen, K.; Meul, T.; Schade, P.; Schmickler, H.; Vogel, E. *J. Am. Chem. Soc.* ***1987***, *109*, 4992. See also, Hafner, K.; Thiele, G.F. *Tetrahedron Lett.* ***1984***, *25*, 1445.

[375] Schmalz, D.; Günther, H. *Angew. Chem. Int. Ed.* ***1988***, *27*, 1692.

[376] Higuchi, H.; Hiraiwa, N.; Kondo, S.; Ojima, J.; Yamamoto, G. *Tetrahedron Lett.* ***1996***, *37*, 2601.

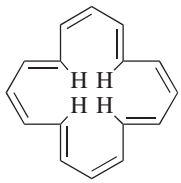
[377] Gallagher, M.E.; Anthony, J.E. *Tetrahedron Lett.* ***2001***, *42*, 7533.

[378] Gilles, J. *Tetrahedron Lett.* ***1968***, 6259; Calder, I.C.; Gaoni, Y.; Sondheimer, F. *J. Am. Chem. Soc.* ***1968***, *90*, 4946. See Schröder, G.; Kirsch, G.; Oth, J.F.M. *Chem. Ber.* ***1974***, *107*, 460.

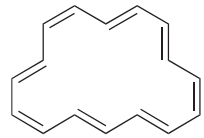
[379] Johnson, S.M.; Paul, I.C.; King, G.S.D. *J. Chem. Soc. B* ***1970***, 643.

[380] See Nakatsuji, S.; Morigaki, M.; Akiyama, S.; Nakagawa, M. *Tetrahedron Lett.* ***1975***, 1233; Vogel, E.; Kürshner, U.; Schmickler, H.; Lex, J.; Wennerström, O.; Tanner, D.; Norinder, U.; Krüger, C. *Tetrahedron Lett.* ***1985***, *26*, 3087.

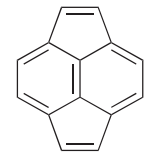
[20]annulene[381] and [24]annulene.[382] However, a bridged tetradehydro[32]annulene was atropic.[356]



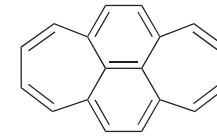
128



129



130



131

Both pyracyclene (**130**)[383] (which because of strain is stable only in solution) and dipleiadiene (**131**)[384] are paratropic, as shown by NMR spectra. These molecules might have been expected to behave like naphthalenes with outer bridges, but the outer π frameworks (12 and 16 electrons, respectively) constitute antiaromatic systems with an extra central double bond. With respect to **130**, the $4n+2$ rule predicts pyracylene to be "aromatic" if it is regarded as a 10-π-electron naphthalene unit connected to two 2-π-electron etheno systems, but "antiaromatic" if it is viewed as a 12-π-electron cyclododecahexaene periphery perturbed by an internal cross-linked etheno unit.[385] Recent studies have concluded on energetic grounds that **130** is a "borderline" case, in terms of aromaticity–antiaromaticity character.[383] Dipleiadiene appears to be antiaromatic.[384]

The fact that many $4n$ systems are paratropic even though they may be nonplanar and have unequal bond distances indicates that if planarity were enforced, the ring currents might be even greater. The NMR spectrum of the dianion of **107**[386] (and its diethyl and dipropyl homologs)[387] effectively illustrate this point. Recall that in **107**, the outer protons were found at 8.14–8.67 δ with the methyl protons at −4.25 δ. For the dianion, however, which is forced to have approximately the same planar geometry but now has 16 electrons, the outer protons are shifted to about −3 δ while the methyl protons are found at about 21 δ, a shift of ∼25 δ. A converse shift was made when [16]annulenes that were antiaromatic were converted to 18-electron dianions that were aromatic.[304] In these cases, the changes in NMR chemical shifts were almost as dramatic. Heat of combustion measures also show that [16]annulene is much less stable than its dianion.[388] It has also been reported that the fluorenyl cation shows substantial destabilization, suggesting that it is an antiaromatic species.[389]

It seems clear that $4n$ systems will be at a maximum where a molecule is constrained to be planar (as in **83** or the dianion of **107**) but, where possible, the molecule will distort

[381] Metcalf, B.W.; Sondheimer, F. *J. Am. Chem. Soc.* ***1971***, *93*, 6675. See also, Wilcox, Jr., C.F.; Farley, E.N. *J. Am. Chem. Soc.* ***1984***, *106*, 7195.

[382] Calder, I.C.; Sondheimer, F. *Chem. Commun.* ***1966***, 904. See also, Yamamoto, K.; Kuroda, S.; Shibutani, M.; Yoneyama, Y.; Ojima, J.; Fujita, S.; Ejiri, E.; Yanagihara, K. *J. Chem. Soc., Perkin Trans. 1* ***1988***, 395.

[383] Trost, B.M.; Herdle, W.B. *J. Am. Chem. Soc.* ***1976***, *98*, 4080.

[384] Vogel, E.; Neumann, B.; Klug, W.; Schmickler, H.; Lex, J. *Angew. Chem. Int. Ed.* ***1985***, *24*, 1046.

[385] Diogo, H.P.; Kiyobayashi, T.; Minas da Piedade, M.E.; Burlak, N.; Rogers, D.W.; McMasters, D.; Persy, G.; Wirz, J.; Liebman, J.F. *J. Am. Chem. Soc.* ***2002***, *124*, 2065.

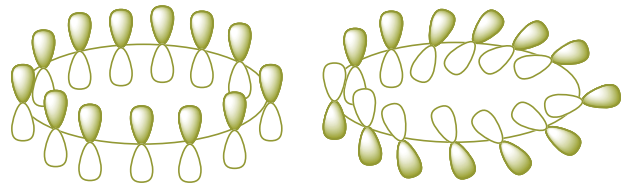
[386] For a review of polycyclic dianions, see Rabinovitz, M.; Cohen, Y. *Tetrahedron* ***1988***, *44*, 6957.

[387] Mitchell, R.H.; Klopfenstein, C.E.; Boekelheide, V. *J. Am. Chem. Soc.* ***1969***, *91*, 4931. For another example, see Deger, H.M.; Müllen, K.; Vogel, E. *Angew. Chem. Int. Ed.* ***1978***, *17*, 957.

[388] Stevenson, G.R.; Forch, B.E. *J. Am. Chem. Soc.* ***1980***, *102*, 5985.

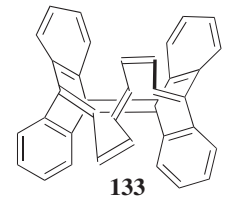
[389] Herndon, W.C.; Mills, N.S. *J. Org. Chem.* ***2005***, *70*, 8492.

itself from planarity and avoid equal bond distances in order to reduce distortion and bond alternation. In some cases, such as cyclooctatraene, the distortion and bond alternation are great enough to be completely avoided. In other cases, for example, **121** or **128**, it is apparently not possible for the molecules to avoid at least some *p* orbital overlap. Such molecules show evidence of paramagnetic ring currents, although the degree of of paramagnetic ring current is not is not as great as in molecules such as **83** or the dianion of **107**.



Hückel **Möbius**

132

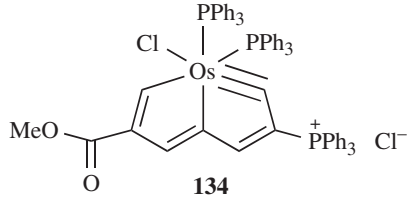


133

The concept of "Möbius aromaticity" was conceived by Helbronner in 1964[390] when he suggested that large cyclic [4*n*]annulenes might be stabilized if the π orbitals were twisted gradually around a Möbius strip. This concept is illustrated by the diagrams labeled Hückel, which is a destabilized [4*n*] system, in contrast to the Möbius model, which is a stabilized [4*n*] system.[391] Zimmerman generalized this idea and applied the "Hückel-Möbius concept" to the analysis of ground-state systems such as barrelene (**132**).[392] In 1998, a computational reinterpretation of existing experimental evidence for $(CH)_9^+$ as a Möbius aromatic cyclic annulene with 4*n* π electrons was reported.[393] This reversal of [4*n*]annulene antiaromaticity has been demonstrated by stacking cyclooctatetraene rings into a superphane.[394] A superphane is a 6-fold bridged cyclophane with all arene positions in the corresponding dimer taken up by ethene spacers.[395] The cyclooctatetraene dianion is about as aromatic as benzene, and greater than that of the cyclopentadienyl anion.[396] A recent computational study predicted several Möbius local minima for [12], [16], and [20]annulenes.[397] Charged [4*n*]annulenes can also exhibit Möbius aromaticity.[398] A twisted [16]annulene has been prepared and calculations suggested it should show Möbius aromaticity.[399] High performance

[390] Heilbronner, E. *Tetrahedron Lett.* ***1964***, 1923.
[391] Kawase, T; Oda, M. *Angew. Chem. Int. Ed.*, ***2004***, *43*, 4396.
[392] Zimmerman, H.E. *J. Am. Chem. Soc.* ***1966***, *88*, 1564.; Zimmerman, H.E. *Acc. Chem. Res.* ***1972***, *4*, 272.
[393] Mauksch, M.; Gogonea, V.; Jiao, H.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.*, ***1998***, *37*, 2395.
[394] Bean, D.E.; Fowler, P.W. *Org. Lett.* ***2008***, *10*, 5573.
[395] For a discussion of superphanes and beltenes, see Gleiter, R.; Hellbach, B.; Gath, S.; Schaller, R.J. *Pure Appl. Chem.* ***2006***, *78*, 699.
[396] Mitchell, R.H.; Zhang, P.; Berg, D.J.; Williams, R.V. *Chem. Commun.* ***2012***, *48*, 8144.
[397] Castro, C.; Isborn, C.M.; Karney, W.L.; Mauksch, M.; Schleyer, P.v.R. *Org. Lett.* ***2002***, *4*, 3431.
[398] Mucke, E.K.; Schönborn, B.; Köhler, F.; Herges, R. *J. Org. Chem.* ***2011***, *76*, 35.
[399] Ajami, D.; Oeckler, O.; Simon, A.; Herges, R. *Nature* ***2003***, *426*, 819; Rappaport, S.M.; Rzepa, H.S. *J. Am. Chem. Soc.* ***2008***, *130*, 7613.

liquid chromatography (HPLC) separation of isomers gave **133**, and the authors concluded it is Möbius aromatic. The synthesis and study of molecules that demonstrate Möbius aromaticity continues to be an area of interest.[400] For example, [28]hexaphyrin phosphonium adducts that are formed from the reaction with phosphines are Möbius aromatic entities.[401]



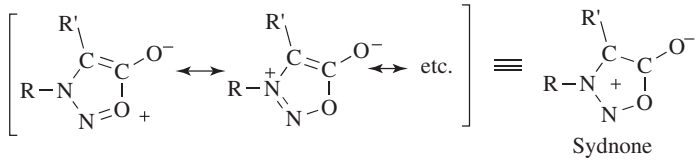
134

Metallacycles chelated with polydentate conjugated-carbon chain ligands are called *carbolong complexes,*[402] and some are *Craig-type Möbius metallaaromatics*.[403] Conjugated carbon–ligated carbon chains such as triynes are polydentate chelating ligands and are called "carbolong ligands," ranging from 7 to 12 carbon atoms. An example of a carbolong complex was osmapentalyne[404] (**134**) and the aromaticity of this complex has been confirmed. In these carbolong complexes, all coordinated carbon atoms lie in one plane, and the metal atoms are located in the bridgehead of the polycyclic framework.

2.L. OTHER AROMATIC COMPOUNDS

Three additional types of aromatic compounds must be noted.

1. *Mesoionic compounds*:[405] These compounds cannot be satisfactorily represented by Lewis structures not involving charge separation. Most of them contain five-membered rings. The most common are the *sydnones*, stable aromatic compounds that undergo aromatic substitution when R' is hydrogen.



[400] Rzepa, H.S. *Chem. Rev.* ***2005***, *105*, 3697; Herges, R. *Chem. Rev.* ***2006***, *106*, 4820. Castro, C.; Karney, W.L. *J. Phys. Org. Chem.* ***2012***, *25*, 612. For monocyclic [11]annulenium cations see Warner, P.M. *J. Org. Chem.* ***2006***, *71*, 9271. For lemniscular hexaphyrins see Rzepa, H.S. *Org. Lett.* ***2008***, *10*, 949.

[401] Inoue, M.; Yoneda, T.; Youfu, K.; Aratani, N.; Osuka, A. *Chem. Eur. J.* ***2011***, *17*, 9028.

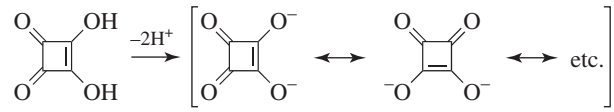
[402] Zhuo, Q.; Lin, J.; Hua, Y.; Zhou, X.; Shao, Y.; Chen, S.; Chen, Z.; Zhu, J.; Zhang, H.; Xia, H. *Nat. Commun.* ***2017***, *8*, 1912; Li, R.; Lu, Z.; Cai, Y.; Jiang, F.; Tang, C.; Chen, Z.; Zheng, J.; Pi, J.; Zhang, R.; Liu, J.; Chen, Z.; Yang, Y.; Shi, J.; Hong, W.; Xia, H. *J. Am. Chem. Soc.* ***2017***, *139*, 14344; Zhou, X.; Wu, J.; Hao, Y.; Zhu, C.; Zhuo, Q.; Xia, H., Zhu, J. *Chem. Eur. J.* ***2018***, *24*, 2389; Zhu, C.; Wu, J.; Li, S.; Yang, Y.; Zhu, J.; Lu, X.; Xia, H. *Angew. Chem. Int. Ed.* ***2017***, 56, 9067; *Angew. Chem.* ***2017***, *129*, 9195.

[403] See Craig, D.P.; Paddock, N.L. *Nature* ***1958***, *181*, 1052; Mason, S.F. *Nature* ***1965***, *205*, 495.

[404] Wang, T.; Zhang, H.; Han, F.; Lin, R.; Lin, Z.; Xia, H. *Angew. Chem. Int. Ed.* ***2012***, *51*, 9838.

[405] For reviews, see Newton, C.G.; Ramsden, C.A. *Tetrahedron* ***1982***, *38*, 2965; Ollis, W.D.; Ramsden, C.A. *Adv. Heterocycl. Chem.* ***1976***, *19*, 1; Yashunskii, V.G.; Kholodov, L.E. *Russ. Chem. Rev.* ***1980***, *49*, 28; Ohta, M.; Kato, H., in Snyder, J.P. *Nonbenzenoid Aromaticity*, Vol. 1, Academic Press, NY, ***1969***, pp. 117–248.

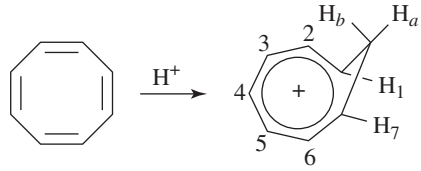
2. *The dianion of squaric acid*.[406] The stability of this system is illustrated by the fact that the pK_1 of squaric acid[407] is ∼1.5 and the pK_2 is ∼3.5,[408] which means that even the second proton is given up much more readily than the proton of acetic acid.[409] The analogous three-,[410] five-, and six-membered ring compounds are also known.[411]



3. *Homoaromatic compounds*. When cyclooctatetraene is dissolved in concentrated H_2SO_4, a proton adds to one of the double bonds to form the homotropylium ion **135**.[412] In this species an aromatic sextet is spread over seven carbons, as in the tropylium ion. The eighth carbon is an sp^3 carbon and so cannot take part in the aromaticity. The NMR spectra show the presence of a diatropic ring current: H_b is found at $\delta = -0.3$; H_a at 5.1 δ; H_1 and H_7 at 6.4 δ; H_2–H_6 at 8.5 δ. This ion is an example of a *homoaromatic* compound, generally defined as a compound that contains one or more[413] sp^3-hybridized carbon atoms in an otherwise conjugated cycle.[414] In order for the orbitals to overlap most effectively so as to close a loop, the sp^3 atoms are forced to lie almost vertically above the plane of the aromatic atoms.[415] In **135**, H_b is directly above the aromatic sextet, and so is shifted far upfield in the NMR. Virtually all homoaromatic compounds so far discovered are ions, and the existence of homoaromatic character in uncharged systems[416] has been questioned.[417] However, neutral homoaromaticity in some heterocyclic compounds has been observed

[406] West, R.; Powell, D.L. *J. Am. Chem. Soc.* ***1963***, *85*, 2577; Ito, M.; West, R. *J. Am. Chem. Soc.* ***1963***, *85*, 2580.
[407] See Wong, H.N.C.; Chan, T.; Luh, T. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 2, Wiley, NY, ***1988***, pp. 1501–1563.
[408] MacDonald, D.J. *J. Org. Chem.* ***1968***, *33*, 4559.
[409] There has been a controversy as to whether this dianion is in fact aromatic. See Aihara, J. *J. Am. Chem. Soc.* ***1981***, *103*, 1633.
[410] Eggerding, D.; West, R. *J. Am. Chem. Soc.* ***1976***, *98*, 3641; Pericás, M.A.; Serratosa, F. *Tetrahedron Lett.* ***1977***, 4437; Semmingsen, D.; Groth, P. *J. Am. Chem. Soc.* ***1987***, *109*, 7238.
[411] See West, R. *Oxocarbons*, Academic Press, NY, ***1980***; Serratosa, F. *Acc. Chem. Res.* ***1983***, *16*, 170; Schmidt, A.H. *Synthesis* ***1980***, 961; West, R. *Isr. J. Chem.* ***1980***, *20*, 300; West, R.; Niu, J., in Snyder, J.P. *Nonbenzenoid Aromaticity*, Vol. 1, Academic Press, NY, ***1969***, pp. 311–345; Maahs, G.; Hegenberg, P. *Angew. Chem. Int. Ed.* ***1966***, *5*, 888.
[412] Haddon, R.C. *J. Am. Chem. Soc.* ***1988***, *110*, 1108. See also, Alkorta, I.; Elguero, J.; Eckert-Maksić, M.; Maksić, Z.B. *Tetrahedron* ***2004***, *60*, 2259.
[413] If a compound contains two such atoms it is bishomoaromatic; if three, trishomoaromatic, and so on. For examples see Paquette, L.A. *Angew. Chem. Int. Ed.* ***1978***, *17*, 106.
[414] See Childs, R.F. *Acc. Chem. Res.* ***1984***, *17*, 347; Paquette, L.A. *Angew. Chem. Int. Ed.* ***1978***, *17*, 106; Garratt, P.J. *Aromaticity*, Wiley, NY, ***1986***, pp. 5–45; and in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Wiley, NY, Vol. 3, ***1972***, the reviews by Story, P.R.; Clark Jr., B.C. 1007–1098, pp. 1073–1093.
[415] Calculations show that only ∼60% of the chemical shift difference between H_a and H_b is the result of the aromatic ring current, and that even H_a is shielded; it would appear at $\delta \sim 5.5$ without the ring current: Childs, R.F.; McGlinchey, M.J.; Varadarajan, A. *J. Am. Chem. Soc.* ***1984***, *106*, 5974.
[416] Examples of uncharged homoantiaromatic compounds have been claimed: See Scott, L.T.; Cooney, M.J.; Rogers, D.W.; Dejroongruang, K. *J. Am. Chem. Soc.* ***1988***, *110*, 7244.
[417] Houk, K.N.; Gandour, R.W.; Strozier, R.W.; Rondan, N.G.; Paquette, L.A. *J. Am. Chem. Soc.* ***1979***, *101*, 6797; Paquette, L.A.; Snow, R.A.; Muthard, J.L.; Cynkowski, T. *J. Am. Chem. Soc.* ***1979***, *101*, 6991. See however, Liebman, J.F.; Paquette, L.A.; Peterson, J.R.; Rogers, D.W. *J. Am. Chem. Soc.* ***1986***, *108*, 8267.

by replacing the CH_2 at C2 in bicyclo[3.2.1]octa-3,6-diene with X = BH, AlH, Be, Mg, O, S, PH, NH (antihomoaromatic for X = BH, AlH, and Be; nonhomoaromatic for X = O, S, NH, PH); replacement of the CH at C3 in bicyclo[3.2.1]octa-3,6-dien-2-yl anion with PH, S, NH, O (homoaromatic for X = S, PH, NH, O); and replacement at C2 and C3 with N and O (homoaromatic).[418] Homoaromatic ions of 2 and 10 electrons are also known and 1,3,5-cycloheptatriene has been shown to be homoaromatic.[419]



135

New conceptual applications to 3D homoaromatic systems with cubane, dodecahedrane, and adamantane frameworks have been presented.[420] This concept includes families of spherical homoaromatics with both 2 and 8 mobile electrons. Each set has complete *spherical homoaromaticity*, that is, all the sp^2 carbon atoms in a highly symmetrical framework are separated by one or two sp^3-hybridized atoms.

4. *Fullerenes.* Fullerenes are a family of aromatic hydrocarbons[421] based on the parent buckminsterfullerene (**136**; C_{60})[422] that have a variety of very interesting properties.[423] Derivatives of **137** are sometimes called buckyballs. Molecular-orbital calculations show that "fullerene aromaticity lies within 2 kcal mol^{-1} (8.4 kJ mol^{-1}) per carbon of a hypothetical ball of rolled up graphite."[424] Fullerenes may exhibit what is known as spherical aromaticity (3D aromaticity),[425] and the *Hückel rule* cannot be used for spherical systems such as fullerenes. The $2(n+1)^2$ rule was proposed by Hirsch[426] as the 3D analog of the $4n+2$ rule for planar systems proposed by Hückel.[427] Heterofullerenes are also known.[428]

[418] Freeman, P.K. *J. Org. Chem.* ***2005***, *70*, 1998. See the discussion for methano[10]annulenes, Caramori, G.F.; de Oliveira,K.T.; Galembeck, S.E.; Bultinck, P.; Constantino, M.G. *J. Org. Chem.* ***2007***, *72*, 76.

[419] Williams, R.V.; Edwards, W.D.; Zhang, P.; Berg, D.J.; Mitchel, R.H. *J. Am. Chem. Soc.* ***2012***, *134*, 16742.

[420] Chen, Z.; Jiao, H.; Hirsch, A.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.*, ***2002***, *41*, 4309

[421] Thilgen, C.; François Diederich, F. *Chem. Rev.* ***2006***, *106*, 5049.

[422] Billups, W.E.; Ciufolini, M.A. *Buckminsterfullerenes*, VCH, NY, ***1993***; Taylor, R. *The Chemistry of Fullerenes*, World Scientific, River Edge, NJ, Singapore, ***1995***; Aldersey-Williams, H. *The Most Beautiful Molecule: The Discovery of the Buckyball*, Wiley, NY, ***1995***; Baggott, J.E. *Perfect Symmetry: the Accidental Discovery of Buckminsterfullerene*, Oxford University Press, Oxford, NY, ***1994***. Also see, Kroto, H.W.; Heath, J.R.; O'Brien, S.C.; Curl, R.F.; Smalley, R.E. *Nature (London)* ***1985***, *318*, 162.

[423] Smalley, R.E. *Acc. Chem. Res.* ***1992***, *25*, 98; Diederich, F.; Whetten, R.L. *Acc. Chem. Res.* ***1992***, *25*, 119; Hawkins, J.M. *Acc. Chem. Res.* ***1992***, *25*, 150; Wudl, F. *Acc. Chem. Res.* ***1992***, *25*, 157; McElvany, S.W.; Ross, M.M.; Callahan, J.H. *Acc. Chem. Res.* ***1992***, *25*, 162; Johnson, R.D.; Bethune, D.S.; Yannoni, C.S. *Acc. Chem. Res.* ***1992***, *25*, 169. And, see Matsuo, Y. *Pure Appl. Chem.* ***2012***, *84*, 945.

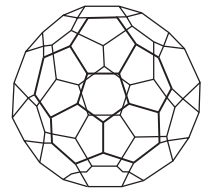
[424] Warner, P.M. *Tetrahedron Lett.* ***1994***, *35*, 7173. Also see Kerim, A. *J. Phys. Org. Chem.* ***2012***, *25*, 379.

[425] Chen, Z.; King, R.B. *Chem. Rev.* ***2005***, *105*, 3613; Bühl, M.; Hirsch, A. *Chem. Rev*. ***2001***, *101*, 1153.

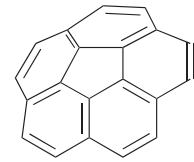
[426] Hirsch, A.; Chen, Z.; Jiao, H. *Angew. Chem., Int. Ed.* ***2000***, *39*, 3915.

[427] Hückel, E. *Z. Phys.* ***1931***, *70*, 204; Hückel, E. *Z. Phys.* ***1931***, *72*, 310; Hückel, E. *Z. Phys.* ***1932***, *76*, 628.

[428] Vostrowsky, O.; Hirsch, A. *Chem. Rev.* ***2006***, *106*, 5191



136



137

5. *Other aromatic compounds. Buckybowls* constitute another class of polynuclear aromatic hydrocarbons, and they are essentially fragments of **136**. Corannulene (**137**)[429] (also called 5-circulene), for example, is the simplest curved-surface hydrocarbon possessing a carbon framework that can be identified with the buckminsterfullerene surface. It has been synthesized by Scott *et al*.[429] and several other groups.[430] Corannulene is a flexible molecule, with a bowl-to-bowl inversion barrier of about 10–11 kcal mol^{-1} (41.8–46.0 kJ mol^{-1}).[431] Benzocorannulenes are known,[432] and other bowl-shaped hydrocarbons include acenaphtho[3,2,1,8-*ijklm*]diindeno[4,3,2,1-*cdef*-1',2',3',4'-*pqra*]triphenylene.[433] The inversion barrier to buckybowl inversion has been lowered by such benzannelation of the rim.[434] Other semi-buckminsterfullerenes include C_{2v}-$C_{30}H_{12}$ and C_3-$C_{30}H_{12}$.[429] Larger fullerenes include C_{60},C_{80}, and C_{84} and fullerenes are known that contain an endohedral metal such as scandium or even Sc_3N.[435] Synthetic methods often generate mixtures of fullerenes that must be separated, as in the report of new methods for separating C_{84} fullerenes.[436] A homofullerene has been prepared,[437] and the azaacepentalenide anion, which is a bowl-shaped heterocycle, has been prepared.[438] It is possible to replace carbon in aromatic compounds such as benzene or naphthalene with heteroatoms, and the resulting compound is aromatic. The Z-pnictogen derivatives (Z = N, P, and As) are examples.[439]

2.M. HYPERCONJUGATION

Conjugation in molecules such as buta-1,3-diene and benzene was well known to organic chemists in the 19th century. For example, it became understood that one could view

[429] Scott, L.T.; Hashemi, M.M.; Meyer, D.T.; Warren, H.B. *J. Am. Chem. Soc.* ***1991***, *113*, 7082.
[430] Liu, C.Z.; Rabideau, P.W. *Tetrahedron Lett.* ***1996***, *37*, 3437.
[431] Biedermann, P.U.; Pogodin, S.; Agranat, I. *J. Org. Chem.* ***1999***, *64*, 3655; Rabideau, P.W.; Sygula, A. *Acc. Chem. Res.* ***1996***, *29*, 235; Hagan, S.; Bratcher, M.S.; Erickson, M.S.; Zimmermann, G.; Scott, L.T. *Angew. Chem. Int. Ed.* ***1997***, *36*, 406. See also, Dinadayalane, T.C.; Sastry, G.N. *Tetrahedron* ***2003***, *59*, 8347.
[432] Dinadayalane, T.C.; Sastry, G.N. *J. Org. Chem.* ***2002***, *67*, 4605.
[433] Marcinow, Z.; Grove, D.I.; Rabideau, P.W. *J. Org. Chem.* ***2002***, *67*, 3537. Multiethynyl corannulenes have been prepared: Wu, Y.-T.; Bandera, D.; Maag, R.; Linden, A.; Baldridge, K.K.; Siegel, J.S. *J. Am. Chem. Soc.* ***2008***, *130*, 10729.
[434] Marcinow, Z.; Sygula, A.; Ellern, D.A.; Rabideau, P.W. *Org. Lett.* ***2001***, *3*, 3527.
[435] Stevenson, S.; Rice, G.; Glass, T.; Harich, K.; Cromer, F.; Jordan, M.R.; Craft, J.; Hadju, E.; Bible, R.; Olmstead, M.M.; Maitra, K.; Fisher, A.J.; Balch, A.L.; Dorn, H.C. *Nature (London)* ***1999***, *401*, 55.
[436] Wang, G.-W.; Saunders, M.; Khong, A.; Cross, R.J. *J. Am. Chem. Soc.* ***2000***, *122*, 3216.
[437] Kiely, A.F.; Haddon, R.C.; Meier, M.S.; Selegue, J.P.; Brock, C.P.; Patrick, B.O.; Wang, G.-W.; Chen, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 7971.
[438] Mascal, M.; Bertran, J.C. *J. Am. Chem. Soc.* ***2005***, *127*, 1352.
[439] Sánchez-Sanz, G. *Tetrahedron.* ***2015***, *71*, 826.

buta-1,3-diene as two ethene units. The overlap of the end *p* orbitals of the two ethenes that are to be attached leads to conjugation, which in turn leads to a lowering of the energy of the system, a change in geometry in several respects, and most obviously, to changes in chemical and physical properties of the molecule. In this case, two *p* orbitals overlap. Mulliken suggested that overlap of a σ orbital and a *p* orbital constitutes "hyperconjugation." Qualitatively, hyperconjugation is similar to conjugation, but smaller. When a methyl group is attached to ethene, for example, there is a shift of the ultraviolet absorption spectrum to longer wavelength, an increase in the reactivity of the molecule, and a lowering of energy, similar to the changes that occur in the ethene to butadiene case, but to a lesser extent. Hyperconjugation shows the same effects but to a lesser amount because the σ orbital lies at a lower energy than the π orbital, and hence the electrons delocalize out of the σ orbital in hyperconjugation to a lesser extent than from a π orbital in conjugation. The term "hyperconjugation" therefore arises from the hyperconjugative forms that make small but definite contributions to the ground state of a molecule.[440]

Another delocalization phenomenon has been discussed that involves σ electrons.[441] Baker and Nathan observed[442] that the rates of reaction of *p*-substituted benzyl bromides with pyridine (see reaction **10-30**) were opposite from the results expected from electron release. That is, the methyl-substituted compound reacted fastest and the *tert*-butyl-substituted compounded reacted slowest. This appeared to be an anomalous electron-release pattern for alkyl groups because the field effect predicted the order of electron release for simple alkyl groups connected to an unsaturated system should be *tert*-butyl > isopropyl > ethyl > methyl. At least one hydrogen atom should be attached to the α carbon that is connected to the sp^2 carbon for the Baker-Nathan effect. The Baker-Nathan effect has clouded the issue because some interpreted that it indicates hyperconjugation occurs with hydrogen and a double bond, but either did not occur or occurred to a very small amount with carbon. In the 1930s, Baker and Nathan did not have the tools to experimentally or theoretically understand hyperconjugation to any great extent. Those chemists looked for lowering of energy that could be detected, but these experiments do not necessarily help to explain hyperconjugation.[443] Indeed, it is now known that the Baker-Nathan effect is a result of changes in solvation energy[444] and has very little to do with hyperconjugation. It has recently been reported that hyperconjugation is an important factor determining alkane C—H bond dissociation energies.[445] In certain instances where the Baker-Nathan effect was found to apply in solution, the order was completely reversed in the gas phase.[446] Since the molecular structures are unchanged in going from the gas phase into solution, it appears that each alkyl group is solvated to a different extent.[447] However, this only demonstrates that

[440] Pauling, L.; Springall, H. D.; Palmer, K. J. *J. Am. Chem. Soc.* ***1939***, *61*, 927; Wheland, G.W. *J. Chem. Phys.* ***1934***, *2*, 474.

[441] For monographs, see Baker, J.W. *Hyperconjugation*, Oxford University Press, Oxford, ***1952***; Dewar, M.J.S. *Hyperconjugation*, Ronald Press, NY, ***1962***. For a review, see de la Mare, P.B.D. *Pure Appl. Chem.* ***1984***, *56*, 1755.

[442] Baker, J.W.; Nathan, W.S. *J. Chem. Soc.* ***1935***, 1840, 1844.

[443] Hyperconjugation has been probed using the conformational deuterium isotope effect. See Greenway, K.T.; Bischoff, A.G.; Pinto, B.M. *J. Org. Chem.* ***2012***, *77*, 9221.

[444] This idea was first suggested by Schubert, W.M.; Sweeney, W.A. *J. Org. Chem.* ***1956***, *21*, 119.

[445] Ingold, K.U.; DiLabio, G.A. *Org. Lett.* ***2006***, *8*, 5923.

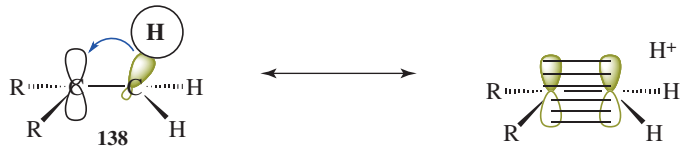
[446] Hehre, W.J.; McIver Jr., R.T.; Pople, J.A.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1974***, *96*, 7162; Arnett, E.M.; Abboud, J.M. *J. Am. Chem. Soc.* ***1975***, *97*, 3865; Glyde, E.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* ***1977***, 678. See also, Taylor, R. *J. Chem. Res. (S)* ***1985***, 318.

[447] For an opposing view, see Cooney, B.T.; Happer, D.A.R. *Aust. J. Chem.* ***1987***, *40*, 1537.

the Baker-Nathan effect is not the same as hyperconjugation. The structural changes that occur upon hyperconjugation can be determined from quantum mechanics and from experiment. Such changes can be qualitatively predicted by looking at the resonance structures involved.

Hyperconjugation is probably important for carbocations, and also for free radicals[448] and for excited states of molecules.[449] In free radicals and carbocations, the canonical forms display no more charge separation than the main form. Muller and Mulliken call this *isovalent hyperconjugation*.

Apart from contributions to aromaticity, hyperconjugation has been used to explain the stability of intermediates such as carbocations[450] (see Chapter 5 for an introduction to carbocations). It has been stated that C—C hyperconjugation is most important in stabilizing carbocations when the C—C bond(s) involved have more than *75% p* character.[451] This effect can be illustrated by a typical case such as carbocation **138**, where hyperconjugation is invoked to explain the relative stability of the ion as attached groups are varied. If the orbitals of an adjacent C—H bond align with the empty orbital of the positive center; a canonical form can be drawn by electron donation to C^+ to form a canonical form that is formally an alkene and H^+. Note that the H in **138** could be any atom and C could be any sp^2-hybridized atom and hyperconjugation would still occur. The key part is that a σ bond overlaps a π bond. For **138**, an alkene and a closely bound proton constitute a canonical form that helps stabilize the carbocation. Each of the three methyl hydrogen atoms in **138** can contribute to the hyperconjugative stabilization. In other words, resonance contributors involving the C—H bonds represent the bond elongation due to hyperconjugation, and provide stabilization of a carbocation.[452] To determine whether hyperconjugation is important in a given situation using molecular modeling, one must ask if the localized model is adequate for that situation at the particular level of precision, or whether the model must be corrected by including some delocalization.[453] To a first approximation, delocalization can be neglected, but it is needed for better approximations. The effect of the alkene canonical form on **138** is that the electrons in the C—H bond are closer to the carbon than if hyperconjugation did not contribute at all.

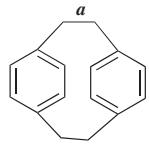


138

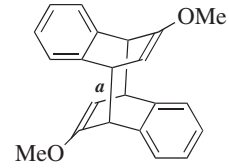
In neutral molecules, the structural elements noted above should be present for hyperconjugation. There is usually least one sp^2-hybridized atom, usually carbon, but for hyperconjugation in general, all that is needed is a σ bond.[454] Resonating structures due

[448] Symons, M.C.R. *Tetrahedron* ***1962***, *18*, 333.
[449] Rao, C.N.R.; Goldman, G.K.; Balasubramanian, A. *Can. J. Chem.* ***1960***, *38*, 2508.
[450] See Reed, C.A.; Stoyanov, E.S.; Tham, F.S. *Org. Biomol. Chem.* ***2013***, *11*, 3797.
[451] Jensen, F.R.; Smart, B.E. *J. Am. Chem. Soc.* ***1969***, *91*, 5686.
[452] See Radom, L.; Poppinger, D.; Haddon, R.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, *Vol. 5*., Wiley: NY, ***1976***, pp. 2303–2426.
[453] Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry*, 3rd ed., HarperCollins, NY, ***1987***, p. 68.
[454] See Wu, J.I.-C.; Schleyer, P.v.R. *Pure Appl. Chem.* ***2013***, *85*, 921.

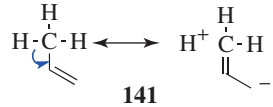
to hyperconjugation may be written involving "no bonds" between the alpha carbon and hydrogen atoms, as shown for propene (**141**).



139



140



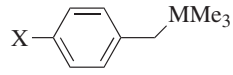
141

Contributions of this type are seen by a comparison of the X-ray data for **139** and **140** with the calculated data (MM40). The bond length for bond *a* in **139** is 1.571 Å by analysis of the X-ray data, but analysis by MM40 calculations gave a value of 1.565 A.[455] Similar analysis of bond *a* in **140** gave an experimental value of 1.627 Å but MM40 calculations gave a value of 1.589 Å. The calculated values are shorter than the actual values. When hyperconjugation was included in the MM40 calculations, the calculated values were 1.574 Å for **139** and 1.623 Å for **140**.[455] The hyperconjugative stretching effect was calculated to be 0.009 Å for **139** and 0.034 Å for **140**. This work suggests that hyperconjugation is actually a bond stretching effect,[452] and it has been represented as resonance contributors several times in this chapter. If the bond elongation found in propene, due to hyperconjugation, is represented as the canonical forms shown for **141**, the charge separation illustrates bond elongation. In a different example, using toluene, there is evidence that the main interaction between methyl groups and the ring system in the positive ions of aromatic hydrocarbons is due to hyperconjugation rather than an inductive effect.[456]

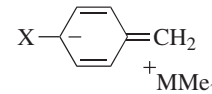
There is evidence that bond length effects were the result of the *s* character of the saturated carbon rather than of neutral hyperconjugation.[457] These experimental results seem to follow from hyperconjugation in the ground states of neutral molecules, and there is evidence in favor of hyperconjugation.[458] Indeed, hyperconjugation appears to operate for both carbon and hydrogen in various systems (supported by quantum mechanics).[459] These works tie together experimental and computational results into a unified picture that supports hyperconjugation.[458,459] A study of the one-bond coupling constants for the aromatic system **142** appears to provide structural evidence for hyperconjugation in a neutral ground

[455] Allinger, N.L. *J. Comput. Aided Mol. Des.* ***2011***, *25*, 295.
[456] Bolton, J.R.; Carrington, A.; McLachlan, A.D. *Mol. Physics* ***1962***, *5*, 31
[457] Dewar, M.J.S.; Schmeising, H.N. Tetrahedron ***1959***, 5, 166; Dewar, M.J.S. *Hyperconjugation*, Ronald Press: NY, ***1962***; Alden, R.A.; Kraut, J.; Traylor, T.G. *J. Am. Chem. Soc.* ***1968***, *90*, 74. Also see Lambert, J.B.; Shawl, C.E.; Basso, E. *Can. J. Chem.* ***2000***, 78, 1441.
[458] See Laube, T.; Ha, T. *J. Am. Chem. Soc.* ***1988***, *110*, 5511.
[459] Allinger, N.L. *Molecular Structure: Understanding Steric and Electronic Effect from Molecular Mechanics* Wiley, Hoboken, NJ, ***2010***.

state.[460] Hyperconjugation in the ground state of neutral molecules has been called *sacrificial hyperconjugation* by Muller and Mulliken.[461]



142



M = C, Si, Ge, Sn
X = NO_2, CN, H, Me, OMe

Another way to view this phenomenon is to say that electron release is permitted by a mechanism that is essentially a type of tautomeric effect (Sec. 2.N). Dewar suggested that the delocalization of electrons of single bonds (hyperconjugation) and of *p* or π electrons (conjugation) should be included as part of the electronic description only if the localized bond picture fails.[462] This a good first approximation, but modern molecular mechanics allows a much better analysis.

Hyperconjugation has been invoked to explain various aspects of aromaticity, as utilized early in this chapter. It is known that 5,5-disubstituted cyclopentadienes, where the substituents are electropositive groups, show enhanced cyclic conjugation in comparison with cyclopentadiene itself.[463] 5,5-Distannylcyclopentadiene, for example, was found to be nearly as aromatic as furan. This is explained by hyperconjugative electron donation by the substituents, resulting in a partially anionic ring.[458] Another effect is the so-called C*-aromaticity, which is a hyperconjugative effect found in small disubstituted rings that leads to lowering of ring strain energies for the unsaturated rings, particularly when electronegative substituents are attached.[464]

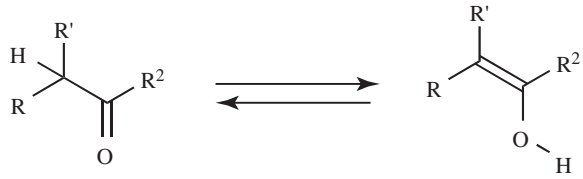
There is evidence that the trityl group contributes negative hyperconjugation.[465]

2.N. TAUTOMERISM[466]

There is another topic that is important for an understanding of chemical bonding in organic compounds. For most compounds, all the molecules are represented by a single structure. But for many compounds there is a mixture of two or more structurally distinct compounds that are in rapid equilibrium. When this phenomenon, called *tautomerism*,[467] exists, there is a rapid shift back and forth among the molecules. In most cases, it is a proton that shifts from one atom of a molecule to another. Mass spectrometry has been used to study tautomerism,[468] which takes several forms.

[460] Lambert, J.B.; Singer, R.A. *J. Am. Chem. Soc.* ***1992***, *114*, 10246.
[461] Muller, N.; Mulliken, R.S. *J. Am. Chem. Soc.* ***1958***, *80*, 3489.
[462] *Hyperconjugation* Dewar, M.J.S. Ronald Press Co., NY, ***1962***.
[463] Nyulászi, L.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1999***, *121*, 6872.
[464] Goller, A.; Clark, T.J. *J. Mol. Model.* ***2000***, *6*, 133. Also see Fernández, I.; Wu, J.I.; Schleyer, P.v.R. *Org. Lett.* ***2013***, *15*, 2990.
[465] Erdmann, H.; An, F.; Mayer, P.; Ofial, A.R.; Lakhdar, S.; Mayr, H. *J. Am. Chem. Soc.* ***2014***, *136*, 14263.
[466] Baker, J.W. *Tautomerism*, D. Van Nostrand Company, Inc., NY, ***1934***; Minkin, V.I.; Olekhnovich, L.P.; Zhdanov, Y.A. *Molecular Design of Tautomeric Compounds*, D. Reidel Publishing Co.: Dordrecht, Holland, ***1988***.
[467] Toullec, J. *Adv. Phys. Org. Chem.* ***1982***, *18*, 1; Kolsov, A.I.; Kheifets, G.M. *Russ. Chem. Rev.* ***1971***, *40*, 773; ***1972***, *41*, 452–467; Forsén, S.; Nilsson, M., in Zabicky, J. *The Chemistry of the Carbonyl Group*, Vol. 2, Wiley, NY, ***1970***, pp. 157–240.
[468] Furlong, J.J.P.; Schiavoni, M.M.; Castro, E.A.; Allegretti, P.E. *Russ. J. Org. Chem.* ***2008***, *44*, 1725.

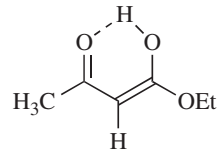
2.N.i. Keto–Enol Tautomerism[469]



Keto form **Enol form**

A very common form of tautomerism is that between a carbonyl compound containing an α hydrogen and its enol form:[470] Such an equilibrium is pH dependent, as in the case of 2-acetylcyclohexanone.[471] In simple cases ($R^2 = H$, alkyl, OR, etc.) the equilibrium lies well to the left (Table 2.1). Examining the bond energies in Table 1.7 leads to an explanation for this fact. The keto form differs from the enol form by the presence of a C—H, a C—C, and a C=O bond whereas the enol has a C=C, a C—O, and an O—H bond. The approximate sum of the first three is 359 kcal mol^{-1} (1500 kJ mol^{-1}) and of the second three is 347 kcal mol^{-1} (1452 kJ mol^{-1}). The keto form is thermodynamically more stable by about 12 kcal mol^{-1} (48 kJ mol^{-1}), and in most cases the enol forms cannot normally be isolated.[472] In certain cases, however, a larger amount of the enol form is present, and it can even be the predominant form.[473] There are three main types of the more stable enols:[474]

1. *Molecules in which the enolic double bond is in conjugation with another double bond.* Some of these are shown in Table 2.1. Carboxylic esters have a much smaller enol content than ketones, for example. In molecules like acetoacetic ester (**143**), the enol is also stabilized by internal hydrogen bonding, which is unavailable to the keto form:



143

[469] The mechanism for conversion of one tautomer to another is discussed in Chapter 12 (reaction **12-3**). For a theoretical study by quantum mechanical calculations, see Emamian, S.R.; Zahedi, E. *J. Phys. Org. Chem.* ***2012***, *25*, 748.

[470] Capponi, M.; Gut, I.G.; Hellrung, B.; Persy, G.; Wirz, J. *Can. J. Chem.* ***1999***, *77*, 605. For a treatise, see Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***.

[471] Iglesias, E. *J. Org. Chem.* ***2003***, *68*, 2680.

[472] For reviews on the generation of unstable enols, see Kresge, A.J. *Pure Appl. Chem.* ***1991***, *63*, 213; Capon, B. in Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***, pp. 307–322.

[473] For reviews of stable enols, see Kresge, A.J. *Acc. Chem. Res.* ***1990***, *23*, 43; Hart, H.; Rappoport, Z.; Biali, S.E. in Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***, pp. 481–589; Hart, H. *Chem. Rev.* ***1979***, *79*, 515; Hart, H.; Sasaoka, M. *J. Chem. Educ.* ***1980***, *57*, 685.

[474] For some examples of other types, see Pratt, D.V.; Hopkins, P.B. *J. Am. Chem. Soc.* ***1987***, *109*, 5553; Nadler, E.B.; Rappoport, Z.; Arad, D.; Apeloig, Y. *J. Am. Chem. Soc.* ***1987***, *109*, 7873.

TABLE 2.1 The enol content of some carbonyl compounds

Compound	Enol content, %	Ref.
Acetone	6×10^{-7}	475
Acetophenone	1.1×10^{-6}	476
Cyclopentanone	1×10^{-6}	477
CH_3CHO	6×10^{-5}	478
Cyclohexanone	4×10^{-5}	479
Butanal	5.5×10^{-4}	479
$(CH_3)_2CHCHO$	1.4×10^{-2}	480, 481
Ph_2CHCHO	9.1	481
CH_3COOEt	No enol founda	479
CH_3COCH_2COOEt	8.4	482
$CH_3COCH_2COCH_3$	80	376
$PhCOCH_2COCH_3$	89.2	479
$EtOOCCH_2COOEt$	7.7×10^{-3}	479
$N{\equiv}CCH_2COOEt$	2.5×10^{-1}	479
Indane-1-one	3.3×10^{-8}	483
Malonamide	No enol found	484

[a]Less than 1 part in 10 million.

Analysis of acetoacetamide by gas electron diffraction shows that it exists as a mixture of 63% enol tautomer and 37% diketo form at 74 °C.[485] There is a discussion of electron delocalization with respect to amides.[486] Gas-phase experiments of acetylacetone show that 81% of the pure liquid is the enol form[487] and 95% in CCl_4 solution.[488] In DMSO there is only 63% of the enol[488] and only 17% in water.[489] The enol content has also been studied by quantum mechanical calculations and by gas-phase electron diffraction.

[475] Chiang, Y.; Kresge, A.J.; Tang, Y.S.; Wirz, J. *J. Am. Chem. Soc.* ***1984***, *106*, 460. See also, Dubois, J.E.; El-Alaoui, M.; Toullec, J. *J. Am. Chem. Soc.* ***1981***, *103*, 5393; Toullec, J. *Tetrahedron Lett.* ***1984***, *25*, 4401; Chiang, Y.; Kresge, A.J.; Schepp, N.P. *J. Am. Chem. Soc.* ***1989***, *111*, 3977.

[476] Keeffe, J.R.; Kresge, A.R.; Toullec, J. *Can. J. Chem.* ***1986***, *64*, 1224.

[477] Keeffe, J.R.; Kresge, A.J.; Schepp, N.P. *J. Am. Chem. Soc.* ***1990***, *112*, 4862; Iglesias, E. *J. Chem. Soc., Perkin Trans. 2* ***1997***, 431. See these papers for values for other simple compounds.

[478] Chiang, Y.; Hojatti, M.; Keeffe, J.R.; Kresge, A.J.; Schepp, N.P.; Wirz, J. *J. Am. Chem. Soc.* ***1987***, *109*, 4000.

[479] Bohne, C.; MacDonald, I.D.; Dunford, H.B. *J. Am. Chem. Soc.* ***1986***, *108*, 7867.

[480] Chiang, Y.; Kresge, A.J.; Walsh, P.A. *J. Am. Chem. Soc.* ***1986***, *108*, 6314.

[481] Chiang, Y.; Kresge, A.J.; Krogh, E.T. *J. Am. Chem. Soc.* ***1988***, *110*, 2600.

[482] Moriyasu, M.; Kato, A.; Hashimoto, Y. *J. Chem. Soc., Perkin Trans. 2* ***1986***, 515. For enolization of β-ketoamides, see Hynes, M.J.; Clarke, E.M. *J. Chem. Soc., Perkin Trans. 2* ***1994***, 901.

[483] Jefferson, E.A.; Keeffe, J.R.; Kresge, A.J. *J. Chem. Soc., Perkin Trans. 2* ***1995***, 2041.

[484] Williams, D.L.H.; Xia, L. *J. Chem. Soc., Chem. Commun.* ***1992***, 985.

[485] Belova, N.V.; Girichev, G.V.; Shlykov, S.A.; Oberhammer, H. *J. Org. Chem.* ***2006***, *71*, 5298.

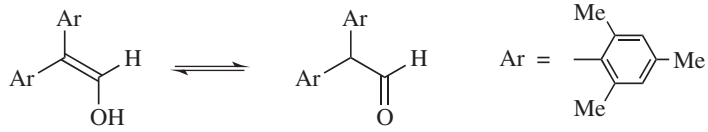
[486] Mujika, J.I.; Matxain, J.M.; Eriksson, L.A.; Lopez, X. *Chemistry: European J.* ***2006***, *12*, 7215; Kemnitz, C.R.; Loewen, M.J. *J. Am. Chem. Soc.* ***2007***, *129*, 2521.

[487] Burdett, J.L.; Rogers, M.T. *J. Am. Chem. Soc.* ***1964***, *86*, 2105.

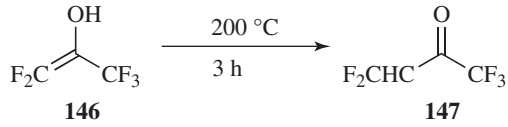
[488] Grushow, A.; Zielinski, T.J. *J. Chem. Educ.* ***2002***, *79*, 707.

[489] Bunting, J.W.; Kanter, J.P.; Nelander, R.; Wu, Z. *Can. J. Chem.* ***1995***, *73*, 1305.

2. *Molecules that contain two or three bulky aryl groups*.[490] An example is 2,2-dimesitylethenol (**144**), where the keto content at equilibrium is only 5%.[491] In cases such as this, steric hindrance (Sec. 4.Q.iv) destabilizes the keto form. In **144** the two aryl groups are about 120° apart, but in **145** they must move closer together (~109.5°). Such compounds are often called *Fuson-type enols*.[492] There is one example of an amide with a bulky aryl group [*N*-methyl *bis*-(2,4,6-triisopropylphenyl)acetamide] that has a measurable enol content, in sharp contrast to most amides.[493]



3. *Highly fluorinated enols such as* **146**.[494] In this case the enol form is not more stable than the keto form (**147**). The enol form is less stable, and converts to the keto form upon prolonged heating. It can, however, be kept at room temperature for long periods of time because the tautomerization reaction (**12-3**) is very slow, owing to the electron-withdrawing power of the fluorines.



Frequently, when the enol content is high, both forms can be isolated. The pure keto form of acetoacetic ester melts at −39 °C, while the enol is a liquid even at −78 °C. Each can be kept at room temperature for days if catalysts, such as acids or bases, are rigorously excluded.[495] Even the simplest enol, vinyl alcohol CH_2=CHOH, has been prepared in the gas phase at room temperature, where it has a half-life of ~30 min.[496] The enol Me_2C=CCHOH is indefinitely stable in the solid state at −78 °C and has a half-life of about 24 hours in the liquid state at 25 °C.[497] When both forms cannot be isolated, the extent of enolization is often measured by NMR.[498]

[490] For a review, see Rappoport, Z.; Biali, S.E. *Acc. Chem. Res.* ***1988***, *21*, 442. For a discussion of their structures, see Kaftory, M.; Nugiel, D.A.; Biali, D.A.; Rappoport, Z. *J. Am. Chem. Soc.* ***1989***, *111*, 8181.

[491] Nugiel, D.A.; Nadler, E.B.; Rappoport, Z. *J. Am. Chem. Soc.* ***1987***, *109*, 2112; O'Neill, P.; Hegarty, A.F. *J. Chem. Soc., Chem. Commun.* ***1987***, 744; Becker, H.; Andersson, K. *Tetrahedron Lett.* ***1987***, *28*, 1323.

[492] See Fuson, R.C.; Southwick, P.L.; Rowland, S.P. *J. Am. Chem. Soc.* ***1944***, *66*, 1109.

[493] Frey, J.; Rappoport, Z. *J. Am. Chem. Soc.* ***1996***, *118*, 3994.

[494] For a review, see Bekker, R.A.; Knunyants, I.L. *Sov. Sci. Rev. Sect. B* ***1984***, *5*, 145.

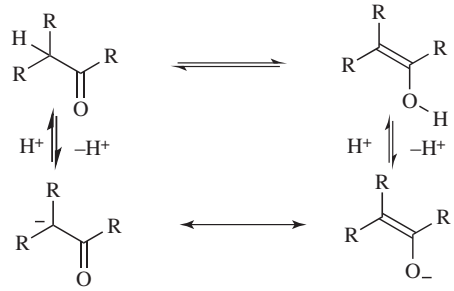
[495] For an example of particularly stable enol and keto forms, which could be kept in the solid state for more than a year without significant interconversion, see Schulenberg, J.W. *J. Am. Chem. Soc.* ***1968***, *90*, 7008.

[496] Saito, S. *Chem. Phys. Lett.* ***1976***, *42*, 399. See also, Rodler, M.; Blom, C.E.; Bauder, A. *J. Am. Chem. Soc.* ***1984***, *106*, 4029; Capon, B.; Guo, B.; Kwok, F.C.; Siddhanta, A.K.; Zucco, C. *Acc. Chem. Res.* ***1988***, *21*, 135.

[497] Chin, C.S.; Lee, S.Y.; Park, J.; Kim, S. *J. Am. Chem. Soc.* ***1988***, *110*, 8244.

[498] Cravero, R.M.; González-Sierra, M.; Olivieri, A.C. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 1067.

The extent of enolization[499] is greatly affected by solvent,[500] concentration, and temperature. Lactone enols, for example, have been shown to be stable in the gas phase, but are unstable in solution.[501] Another example is acetoacetic ester, which has an enol content of 0.4% in water and 19.8% in toluene.[502] In this case, water reduces the enol concentration by hydrogen bonding with the carbonyl, making this group less available for internal hydrogen bonding. The effect of temperature is clear from the enol content of pentan-2,4-dione, $CH_3COCH_2COCH_3$, which was found to be 95, 68, and 44%, respectively, at 22, 180, and 275 °C.[503] When a strong base is present, both the enol form and the keto form can lose a proton. The resulting anion (the *enolate ion*) is the same in both cases. Since **148** and **149** differ only in placement of electrons, *they are not tautomers, but canonical forms*. The true structure of the enolate ion is a hybrid of **148** and **149** although **149** contributes more, since in this form the negative charge is on the more electronegative atom.



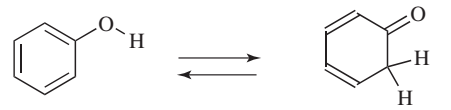
148 **149**

2.N.ii. Other Proton-Shift Tautomerism

Valence tautomerism is discussed in reaction 18-32.

Proton-shift tautomerism results because removal of a proton from either tautomer is the same due to resonance. Some examples are given in the next sub-sections.[504]

1. Phenol–Keto Tautomerism[505]



Phenol **Cyclohexadienone**

[499] See Toullec, J. in Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***, pp. 323–398.

[500] For an extensive study, see Mills, S.G.; Beak, P. *J. Org. Chem.* ***1985***, *50*, 1216. For keto-enol tautomerism in aqueous alcohol solutions, see Blokzijl, W.; Engberts, J.B.F.N.; Blandamer, M.J. *J. Chem. Soc., Perkin Trans. 2* ***1994***, 455; For theoretical calculations of keto–enol tautomerism in aqueous solutions, see Karelson, M.; Maran, U.; Katritzky, A.R. *Tetrahedron* ***1996***, *52*, 11325.

[501] Tureček, F.; Vivekananda, S.; Sadílek, M.; Polášek, M. *J. Am. Chem. Soc.* ***2002***, *124*, 13282.

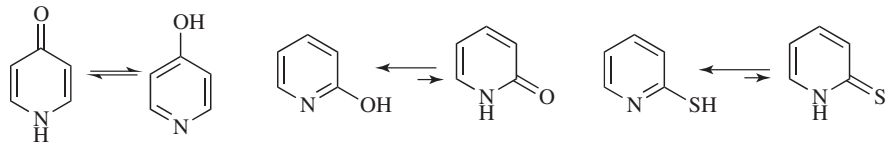
[502] Meyer, K.H. *Leibigs Ann. Chem.* ***1911***, *380*, 212. See also, Moriyasu, M.; Kato, A.; Hashimoto, Y. *J. Chem. Soc., Perkin Trans. 2* ***1986***, 515.

[503] Hush, N.S.; Livett, M.K.; Peel, J.B.; Willett, G.D. *Aust. J. Chem.* ***1987***, *40*, 599.

[504] For a review of the use of X-ray crystallography to determine tautomeric forms, see Furmanova, N.G. *Russ. Chem. Rev.* ***1981***, *50*, 775.

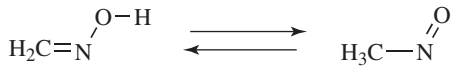
[505] For reviews, see Ershov, V.V.; Nikiforov, G.A. *Russ. Chem. Rev.* ***1966***, *35*, 817; Forsén, S.; Nilsson, M., in Zabicky, J. *The Chemistry of the Carbonyl Group*, Vol. 2, Wiley, NY, ***1970***, pp. 168–198.

For most simple phenols, this equilibrium lies well to the side of the phenol, which is aromatic. For phenol itself, there is no evidence for the existence of the keto form.[506] However, the keto form becomes important and may predominate: (i) where certain groups, such as a second OH group or an N=O group, are present;[507] (ii) in systems of fused aromatic rings;[508] and (iii) in heterocyclic systems. In many heterocyclic compounds in the liquid phase or in solution, the keto form is more stable,[509] although in the vapor phase the positions of many of these equilibria are reversed.[510] For example, **150** is the only form detectable in ethanolic solution in the equilibrium between 4-pyridone (**150**) and 4-hydroxypyridine (**151**), while **151** predominates in the vapor phase.[510] In other heterocycles, the hydroxy form predominates. 2-Hydroxypyridone (**152**) and pyridone-2-thiol (**154**)[511] are in equilibrium with their tautomers, 2-pyridone **153** and pyridine-2-thione **155**, respectively. In both cases, the most stable form is the hydroxy or thiol tautomer, **152** and **154**.[512] 5-Alkylidene-2-oxazolidinone tautomerizes to 2-oxazalone, catalyzed by a *N*-heterocyclic carbene (Sec. 6.J).[513]



150 **151** **152** **153** **154** **155**

2. Nitroso–Oxime Tautomerism



The equilibrium shown for formaldehyde oxime and nitrosomethane illustrates this process.[514] In molecules where the products are stable, the equilibrium lies far to the right, and as a rule nitroso compounds are stable only when there is not a hydrogen on the adjacent carbon atom.

Amides exist as an amide–iminol equilibrium,[515] an amide–iminol tautomerism, but the amide form is adopted almost exclusively.[516] However, the position of this equilibrium

[506] See Lasne, M.; Ripoll, J.; Denis, J. *Tetrahedron Lett.* ***1980***, *21*, 463. See also, Capponi, M.; Gut, I.; Wirz, J. *Angew. Chem. Int. Ed.* ***1986***, *25*, 344.

[507] Ershov, V.V.; Nikiforov, G.A. *Russ. Chem. Rev.* ***1966***, *35*, 817. See also, Highet, R.J.; Chou, F.E. *J. Am. Chem. Soc.* ***1977***, *99*, 3538.

[508] See, for example, Majerski, Z.; Trinajstic, N. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 2648.

[509] See Elguero, J.; Marzin, C.; Katritzky, A.R.; Linda, P. *The Tautomerism of Heterocycles*, Academic Press, NY, ***1976***. For reviews, see Katritzky, A.R.; Karelson, M.; Harris, P.A. *Heterocycles* ***1991***, *32*, 329; Beak, P. *Acc. Chem. Res.* ***1977***, *10*, 186; Katritzky, A.R. *Chimia* ***1970***, *24*, 134.

[510] Beak, P.; Fry Jr., F.S.; Lee, J.; Steele, F. *J. Am. Chem. Soc.* ***1976***, *98*, 171.

[511] Moran, D.; Sukcharoenphon, K.; Puchta, R.; Schaefer III, H.F.; Schleyer, P.v.R.; Hoff, C.D. *J. Org. Chem.* ***2002***, *67*, 9061.

[512] Parchment, O.G.; Burton, N.A.; Hillier, I.H.; Vincent, M.A. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 861.

[513] Fujita, K.; Sato, J.; Yasuda, H.: *Synlett* ***2015***, *26*, 1106.

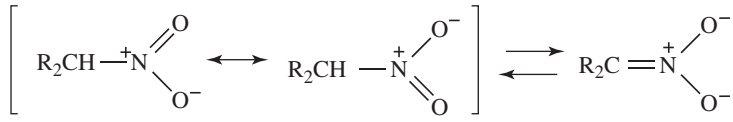
[514] Long, J.A.; Harris, N.J.; Lammertsma, K. *J. Org. Chem.* ***2001***, *66*, 6762.

[515] Skulski, L.; Palmer, G.C.; Calvin, M. *Tetrahedron Lett.* ***1963***, 1773.

[516] Sigel, H.; Martin, R.B. *Chem. Rev.* ***1982***, *82*, 385.

is solvent dependent.[517] Amide–iminol tautomerism was studied for oxamic acid in the gas phase.[518] The amide resonance stabilization and amidicities relative to *N*,*N*-dimethylacetamide for acyclic amides and lactams has been determined using computational methods.[519]

3. Aliphatic Nitro Compounds Are in Equilibrium with Aci Forms



Nitro form Aci form

The nitro form is much more stable than the aci form, in sharp contrast to the parallel case of nitroso–oxime tautomerism, undoubtedly because the nitro form has resonance not found in the nitroso case. Aci forms of nitro compounds are also called nitronic acids and azinic acids.

4. Imine–Enamine Tautomerism[520]

Imine Enamine

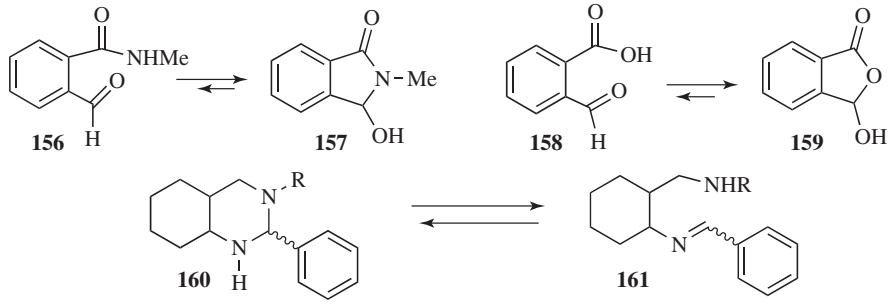
Enamines are normally stable only when no hydrogen is attached to the nitrogen ($R_2C{=}CR{-}NR_2$). Otherwise, the imine form predominates.[521] The energy of various imine–enamine tautomers has been calculated.[522] In the case of 6-aminofulvene-1-aldimines, tautomerism was observed in the solid state as well as in solution.[523] Porphyrins and porphycenes also undergo this type of tautomerism, and the two tautomers may be imaged using single-molecule spectroscopy.[524]

5. Ring–Chain Tautomerism

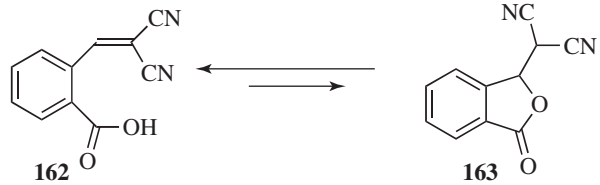
Ring–chain tautomerism[525] occurs in sugars (aldehyde versus the pyranose or furanose structures) and in γ-oxocarboxylic acids.[526] In benzamide carbaldehyde (**156**), whose

[517] See Allegretti, P.E.; Schiavoni, M.d.l.M.; Castro, E.A.; Furlong, J.J.P. *World J. Chem.* ***2007***, *2*, 25.
[518] Raczyńska E.D., Makowski M.; Duczmal, K. *Comput. Theor. Chem.* ***2011***, *964*, 310.
[519] Glover, S.A.; Rosser, A.A. *J. Org. Chem.* ***2012***, *77*, 5492.
[520] See Shainyan, B.A.; Mirskova, A.N. *Russ. Chem. Rev.* ***1979***, *48*, 107; Mamaev, V.P.; Lapachev, V.V. *Sov. Sci. Rev. Sect. B.* ***1985***, *7*, 1.
[521] For examples of the isolation of primary and secondary enamines, see Shin, C.; Masaki, M.; Ohta, M. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 1657; de Jeso, B.; Pommier, J. *J. Chem. Soc., Chem. Commun.* ***1977***, 565.
[522] Lammertsma, K.; Prasad, B.V. *J. Am. Chem. Soc.* ***1994***, *116*, 642.
[523] Sanz, D.; Perez-Torralba, M.; Alarcon, S.H.; Claramunt, R.M.; Foces-Foces, C.; Elguero, J. *J. Org. Chem.* ***2002***, *67*, 1462.
[524] Piwoński, H.; Stupperich, C.; Hartschuh, A.; Sepioł, J.; Meixner, A.; Waluk, J. *J. Am. Chem. Soc.* ***2005***, *127*, 5302.
[525] Valters, R.E.; Flitsch, W. *Ring-Chain Tautomerism*, Plenum, NY, ***1985***. For reviews, see Valters, R.E. *Russ. Chem. Rev.* ***1973***, *42*, 464; ***1974***, *43*, 665; Escale, R.; Verducci, J. *Bull. Soc. Chim. Fr.*, ***1974***, 1203.
[526] Fabian, W.M.F.; Bowden, K. *Eur. J. Org. Chem.* ***2001***, 303.

ring–chain tautomer is **157**, the equilibrium favors the cyclic form (**157**).[527] Similarly, benzoic acid 2-carbaldehyde (**158**) exists largely as the cyclic form (**159**).[528] In these latter cases, and in many others, this tautomerism influences chemical reactivity. Conversion of **158** to an ester, for example, is difficult since most standard methods lead to the OR derivative of **159** rather than the ester of **158**. Ring–chain tautomerism also occurs in spriooxathianes,[529] in decahydroquinazolines, such as **160** and **161**,[530] in other 1,3-heterocycles,[531] and in 2-ferrocenyl-2,4-dihydro-1*H*-3,1-benzoxazine derivatives.[532]



There are many other highly specialized cases of proton-shift tautomerism, including an internal *Michael reaction* (see **15-24**) in which 2-(2,2-dicyano-1-methylethenyl)benzoic acid (**162**) exists largely in the open-chain form rather as its tautomer (**16**) in the solid state, but in solution there is an increasing amount of **163** as the solvent becomes more polar.[533]



[527] Bowden, K.; Hiscocks, S.P.; Perjéssy, A. *J. Chem. Soc., Perkin Trans. 2* ***1998***, 291.
[528] Ring chain tautomer of benzoic acid 2-carboxaldehdye.
[529] Terec, A.; Grosu, I.; Muntean, L.; Toupet, L.; Plé, G.; Socaci, C.; Mager, S. *Tetrahedron* ***2001***, *57*, 8751; Muntean, L.; Grosu, I.; Mager, S.; Plé, G.; Balog, M. *Tetrahedron Lett.* ***2000***, *41*, 1967.
[530] Lazar, L.; Goblyos, A.; Martinek, T. A.; Fulop, F. *J. Org. Chem.* ***2002***, *67*, 4734.
[531] Lázár, L.; Fülöp, F. *Eur. J. Org. Chem.* ***2003***, 3025.
[532] Pérez, S.; López, C.; Caubet, A.; Roig, A.; Molins, E. *J. Org. Chem.* ***2005***, *70*, 4857.
[533] Kolsaker, P.; Arukwe, J.; Barcóczy, J.; Wiberg, A.; Fagerli, A.K. *Acta Chem. Scand. B* ***1998***, *52*, 490.

CHAPTER 3

Bonding Weaker Than Covalent

The discussions in the first two chapters focused on the structure of molecules as an aggregate of atoms in a distinct three-dimensional (3D) arrangement, held together by bonds with energies on the order of 50–100 kcal mol^{-1} (200–400 kJ mol^{-1}). There are also very weak attractive forces *between* molecules, on the order of a few tenths of a kilocalorie per mole. These forces, called *van der Waals forces*,[1] are caused by electrostatic attractions such as those between dipole and dipole, or induced dipole and induced dipole, and are responsible for liquefaction of gases at sufficiently low temperatures. The bonding discussed in this chapter has energies of the order of 2–10 kcal mol^{-1} (9–40 kJ mol^{-1}), intermediate between the bond orders given above, and produces clusters of molecules. Compounds will also be discussed in which portions of molecules are held together without any attractive forces.

3.A. HYDROGEN BONDING[2]

A *hydrogen bond* is less than a covalent bond, but it is an attractive force between a functional group A—H and an atom or group of atoms B in the same or a different molecule.[3] The covalency of a hydrogen bond has been discussed.[4] Hydrogen bonds are *assumed to form only when A is oxygen, nitrogen, or fluorine and when B is oxygen, nitrogen, or fluorine*,[5] although a few exceptions will be noted later. The ability of functional groups to act as hydrogen bond acids and bases can be obtained from either equilibrium constants for

[1] For a theoretical treatment, see Becker, A.A.A.; Kannemann, F.O. *Can. J. Chem.* ***2010***, *88*, 1057. See Hermann, J.; DiStasio Jr., R.A.; Tkatchenko, A. *Chem. Rev.* ***2017***, *117*, 4714.

[2] For a discussion of hydrogen bonding in organic synthesis, see *Hydrogen Bonding in Organic Synthesis*, Pihko, P.M. (ed.), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. ***2009***.

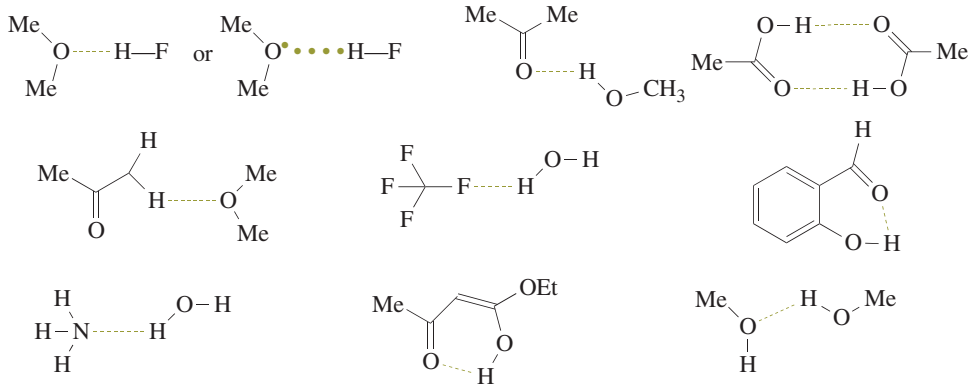
[3] See Schuster, P.; Zundel, G.; Sandorfy, C. *The Hydrogen Bond*, 3 Vols., North Holland Publishing Co., Amsterdam, ***1976***. For a monograph, see Joesten, M.D.; Schaad, L.J. *Hydrogen Bonding*, Marcel Dekker, NY, ***1974***. For reviews, see Meot-Ner, M. *Mol. Struct. Energ.* ***1987***, *4*, 71; Joesten, M.D. *J. Chem. Educ.* ***1982***, *59*, 362; Gur'yanova, E.N.; Gol'dshtein, I.P.; Perepelkova, T.I. *Russ. Chem. Rev.* ***1976***, *45*, 792; Kollman, P.A.; Allen, L.C. *Chem. Rev.* ***1972***, *72*, 283; Huggins, M.L. *Angew. Chem. Int. Ed.* ***1971***, *10*, 147; Rochester, C.H. in Patai, S. *The Chemistry of the Hydroxyl Group, pt. 1*, Wiley, NY, ***1971***, pp. 327–392 (pp. 328–369). See also, Hamilton, W.C.; Ibers, J.A. *Hydrogen Bonding in Solids*, W.A. Benjamin, NY, ***1968***; Desiraju, G.R. *Angew. Chem. Int. Ed.* ***2011***, *50*, 52. Also see, Chen, J.; McAllister, M.A.; Lee, J.K.; Houk, K.N. *J. Org. Chem.* ***1998***, *63*, 4611.

[4] Grabowski, S.J. *Chem. Rev.* ***2011***, *111*, 2597. Also see Dubecký, M.; Mitas, L.; Jurečka, P. *Chem. Rev.* ***2016***, *116*, 5188.

[5] Abraham, M.H.; Platts, J.A. *J. Org. Chem.* ***2001***, *66*, 3484.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

1:1 hydrogen bonding or overall hydrogen bond constants.[5] There are so-called unconventional hydrogen bonds, particularly with organometallic complexes and alteration metal or main-group hydrides.[6] This chapter will largely ignore such compounds. In normal hydrogen bonds, to oxygen or nitrogen, oxygen may be singly or doubly bonded and the nitrogen singly, doubly, or triply bonded. In structures, hydrogen bonds are usually represented by dotted or dashed lines, as shown in the following examples:



Hydrogen bonds can exist in solid[7] and liquid phases, and in solution.[8] The efficacy of many organic reactions that will be discussed in later chapters is due to the use of aqueous media,[9] which is due, in part, to the hydrogen bonding nature of such media.[10] Even in the gas phase, compounds that form particularly strong hydrogen bonds may remain associated.[11] Acetic acid, for example, exists in the gas phase as a dimer, except at very low pressures.[12] In the liquid phase and in solution, hydrogen bonds rapidly form and break. The mean lifetime of the NH_3••••H_2O bond is 2×10^{-12} s, for example.[13] Except for a few very strong hydrogen bonds,[14] such as the FH••••F^- bond (which has an energy of ~50 kcal mol^{-1} or 210 kJ mol^{-1}), the strongest hydrogen bonds are those connecting one carboxylic acid with another. The energies of these bonds are in the range of 6 to 8 kcal mol^{-1} or 25–30 kJ mol^{-1} (for carboxylic acids, this refers to the energy of each bond). In general, short-contact hydrogen bonds between fluorine and H—O or N—H are rare.[15] Other O—H••••O and N—H••••N bonds[16] have energies of 3–6 kcal mol^{-1} (12–25 kJ mol^{-1}).

[6] Belkova, N.V.; Shubina, E.S.; Epstein, L.M. *Acc. Chem. Res.* ***2005***, *38* 624. For a review of hydrogen bonding in cluster ions, see Meot-Ner (Mautner), M. *Chem. Rev.* ***2005***, *105*, 213.

[7] Steiner, T. *Angew. Chem. Int. Ed.* ***2002***, *41*, 48. See also, Damodharan, L.; Pattabhi, V. *Tetrahedron Lett.* ***2004***, *45*, 9427.

[8] See Nakahara, M.; Wakai, C. *Chem. Lett.* ***1992***, 809.

[9] Li, C.-J.; Chen, T.-H. *Organic Reactions in Aqueous Media*, Wiley, NY, ***1997***.

[10] Li, C.-J. *Chem. Rev.* ***1993***, *93*, 2023.

[11] See Curtiss, L.A.; Blander, M. *Chem. Rev.* ***1988***, *88*, 827.

[12] For a review of hydrogen bonding in carboxylic acids and acid derivatives, see Hadži, D.; Detoni, S. in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, ***1979***, pp. 213–266.

[13] Emerson, M.T.; Grunwald, E.; Kaplan, M.L.; Kromhout, R.A. *J. Am. Chem. Soc.* ***1960***, *82*, 6307.

[14] For a review of very strong hydrogen bonding, see Emsley, J. *Chem. Soc. Rev.* ***1980***, *9*, 91.

[15] Howard, J.A.K.; Hoy, V.J.; O'Hagan, D.; Smith, G.T. *Tetrahedron* ***1996***, *52*, 12613. For a discussion of the strength of such hydrogen bonds, see Perrin, C.L. *Acc. Chem. Res.* ***2010***, *43*,1550.

[16] See Sorensen, J.B.; Lewin, A.H.; Bowen, J.P. *J. Org. Chem.* ***2001***, *66*, 4105. Also see Ohshima, Y.; Sato, K.; Sumiyoshi, Y.; Endo, Y. *J. Am. Chem. Soc.* ***2005***, *127*, 1108.

The intramolecular O—H••••N hydrogen bond in hydroxy-amines is also rather strong.[17] A B—π interaction, a new type of nonclassical hydrogen bonding, has been discovered.[18] Hydrogen bond energies have been proved using mass spectrometry.[19] Ionic hydrogen bonds have been reviewed.[20] The topology of π—H hydrogen bonds has been discussed.[21]

To a first approximation, the strength of a hydrogen bond will increase with increasing acidity of A—H[22] and basicity of B, but the parallel is far from exact.[23] A quantitative measure of the strengths of hydrogen bonds has been established, involving the use of an α scale to represent hydrogen-bond donor acidities and a β scale for hydrogen-bond acceptor basicities.[24] The use of the β scale, along with another parameter, ξ, allows hydrogen bond basicities to be related to proton transfer basicities (p*K* values).[25] A database has been developed to locate all possible occurrences of bimolecular cyclic hydrogen bond motifs in the Cambridge Structural Database,[26] and donor–acceptor as well as polarity parameters have been calculated for hydrogen bonding solvents.[27] Bickelhaupt has stated that hydrogen bonds (X—H••••Y) have significant covalent interactions that stem from donor–acceptor orbital interactions between the lone pair electrons of Y and the empty σ* acceptor orbital of X—H, so they are not predominantly electrostatic phenomena.[27]

When two compounds whose molecules form hydrogen bonds with each other are both dissolved in water, the hydrogen bond between the two molecules is usually greatly weakened or completely removed.[28] This means that the molecules generally form hydrogen bonds with the water molecules (intermolecular) rather than with each other (intramolecular), presumably because the water molecules are present in such great numbers. In amides, the oxygen atom is the preferred site of protonation or complexation with water.[29] In the case of dicarboxylic acids, arguments have been presented that there is little or no evidence for strong hydrogen bonding in aqueous solution,[30] although other studies concluded that

[17] Grech, E.; Nowicka-Scheibe, J.; Olejnik, Z.; Lis, T.; Pawêka, Z.; Malarski, Z.; Sobczyk, L. *J. Chem. Soc., Perkin Trans. 2* ***1996***, 343. See Steiner, T. *J. Chem. Soc., Perkin Trans. 2* ***1995***, 1315.

[18] Zhang, X.; Dai, H.; Yan, H.; Zou, W.; Cremer, D. *J. Am. Chem. Soc.* ***2016***, *138*, 4334.

[19] Su, H.-F.; Xue, L.; Li, Y.-H.; Lin, S.-C.; Wen, Y.-M.; Huang, R.-B.; Xie, S.-Y.; Zheng, L.-S. *J. Am. Chem. Soc.* ***2013***, *135*, 6122.

[20] Meot-Ner (Mautner), M. *Chem. Rev.* ***2012***, *112*, PR22–PR103.

[21] Oliveira, B.G.; Araújo, R.C.M.U. *Monatsh. Chem.* ***2011***, *142*, 861.

[22] For a comparison of the relative strengths of OH—Cl versus OH—F hydrogen bonds, see Caminati, W.; Melandri, S.; Maris, A.; Paolo Ottaviani, P. *Angew. Chem. Int. Ed.* ***2006***, *45*, 2438.

[23] For reviews of the relationship between hydrogen bond strength and acid–base properties, see Pogorelyi, V.K.; Vishnyakova, T.B. *Russ. Chem. Rev.* ***1984***, *53*, 1154; Epshtein, L.M. *Russ. Chem. Rev.* ***1979***, *48*, 854.

[24] See Abraham, M.H.; Doherty, R.M.; Kamlet, M.J.; Taft, R.W. *Chem. Br.* ***1986***, 551; Kamlet, M.J.; Abboud, J.M.; Abraham, M.H.; Taft, R.W. *J. Org. Chem.* ***1983***, *48*, 2877. For a criticism of the β scale, see Laurence, C.; Nicolet, P.; Helbert, M. *J. Chem. Soc., Perkin Trans. 2* ***1986***, 1081. See also, Roussel, C.; Gentric, E.; Sraidi, K.; Lauransan, J.; Guihéneuf, G.; Kamlet, M.J.; Taft, R.W. *J. Org. Chem.* ***1988***, *53*, 1545; Abraham, M.H.; Grellier, P.L.; Prior, D.V.; Morris, J.J.; Taylor, P.J. *J. Chem. Soc., Perkin Trans. 2* ***1990***, 521. Deuterium exchange has been used as an indicator of hydrogen bond donors and acceptors: see Strobel, T.A.; Hester, K.C.; Sloan Jr., E.D.; Koh, C.A. *J. Am. Chem. Soc.* ***2007***, *129*, 9544; also see Zhao, C.; Parrish, R.M.; Smith, M.D.; Pellechia, P.J.; Sherrill, C.D.; Shimizu, K.D. *J. Am. Chem. Soc.* ***2012***, *134*, 14306.

[25] Kamlet, M.J.; Gal, J.; Maria, P.; Taft, R.W. *J. Chem. Soc., Perkin Trans. 2* ***1985***, 1583.

[26] Allen, F.H.; Raithby, P.R.; Shields, G.P.; Taylor, R. *Chem. Commun.* ***1998***, 1043.

[27] Joerg, S.; Drago, R.S.; Adams, J. *J. Chem. Soc., Perkin Trans. 2* ***1997***, 2431. See Guerra, C.F.; van der Wijst, T.; Bickelhaupt, F.M. *Chem. Eur. J.* ***2006***, *12*, 3032; Guerra, C.F.; Zijlstra, H.; Paragi, G.T.; Bickelhaupt, F.M. *Chem. Eur. J.* ***2011***, *17*, 12612.

[28] Stahl, N.; Jencks, W.P. *J. Am. Chem. Soc.* ***1986***, *108*, 4196.

[29] Scheiner, S.; Wang, L. *J. Am. Chem. Soc.* ***1993***, *115*, 1958.

[30] Perrin, C.L. *Annu. Rev. Phys. Org. Chem.* ***1997***, *48*, 511.

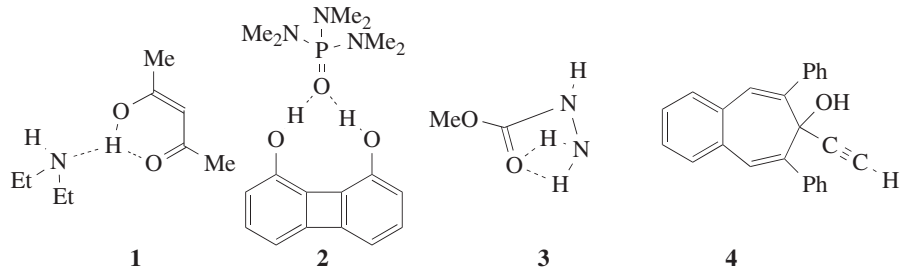
strong, intramolecular hydrogen bonding can exist in aqueous acetone solutions (0.31 mole-fraction water) of hydrogen maleate and hydrogen *cis*-cyclohexane-1,2-dicarboxylate.[31]

Many studies have been made of the geometry of hydrogen bonds,[32] and in most (though not all) cases the evidence shows that the hydrogen is on or near the straight line formed by A and B.[33] This is true both in the solid state (where X-ray crystallography and neutron diffraction have been used to determine structures),[34] and in solution.[35] It is significant that the vast majority of intramolecular hydrogen bonding occurs where six-membered rings (counting the hydrogen as one of the six) can be formed, in which linearity of the hydrogen bond is geometrically favorable. An NMR method has been developed to determine the extent of intramolecular hydrogen bonding.[36] Intramolecular hydrogen bonding is much rarer in five-membered rings, where linearity is usually not favored (although it is known). A novel nine-membered intramolecular hydrogen bond has been reported.[37] Compounds have strong hydrogen bonds if there are at least five rotatable bonds between the donor and acceptor, whereas internal H bonding became negligible for more flexible compounds.[38]

In certain cases X-ray crystallography has shown that a single H—A can form simultaneous hydrogen bonds with two B atoms (*bifurcated* or *three-center hydrogen bonds*). An example is an adduct (**1**) formed from pentane-2,4-dione in its enol form (Sec. 2.N.i) and diethylamine. In **1**, the O—H hydrogen simultaneously bonds[39] to an O and an N, where the N—H hydrogen forms a hydrogen bond with the O of another pentane-2,4-dione molecule.[40] On the other hand, the B atom (in this case oxygen) forms simultaneous hydrogen bonds with two A••••H hydrogens in the adduct (**2**) formed from 1,8-biphenylenediol and hexamethylphosphoramide (HMPA).[41] Another such case is found in methyl hydrazine carboxylate **3**.[42] Except for the special case of FH••••F^- bonds (see above), the hydrogen is not equidistant between A and B. For example, the O—H distance in ice is 0.97 Å, while the H••••O distance is 1.79 Å.[43] A theoretical study of the vinyl alcohol–vinyl alcoholate system (i.e., an enol–enolate anion system) concluded that the hydrogen bonding is strong but asymmetric.[44] The hydrogen bond in the enol of malonaldehyde, in organic solvents, is

[31] Lin, J.; Frey, P. A. *J. Am. Chem. Soc.* ***2000***, *122*, 11258.
[32] Etter, M.C. *Acc. Chem. Res.* ***1990***, *23*, 120; Taylor, R.; Kennard, O. *Acc. Chem. Res.* ***1984***, *17*, 320.
[33] Stewart, R. *The Proton: Applications to Organic Chemistry,* Academic Press, NY, ***1985***, pp. 148–153.
[34] A statistical analysis of X-ray crystallographic data has shown that most hydrogen bonds in crystals are non-linear by about 10 to 15°: Kroon, J.; Kanters, J.A.; van Duijneveldt-van de Rijdt, J.G.C.M.; van Duijneveldt, F.B.; Vliegenthart, J.A. *J. Mol. Struct.* ***1975***, *24*, 109. See also, Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* ***1983***, *105*, 5761; ***1984***, *106*, 244.
[35] For a discussion of the symmetry of hydrogen bonds in solution, see Perrin, C.L. *Pure Appl. Chem.* ***2009***, *81*, 571. For reviews of a different aspect of hydrogen bond geometry, see Legon, A.C.; Millen, D.J. *Chem. Soc. Rev.* ***1987***, *16*, 467, *Acc. Chem. Res.* ***1987***, *20*, 39.
[36] Abraham, M.H.; Abraham, R.J.; Acree Jr., W.E.; Aliev, A.E.; Leo, A.J.; Whaley, W.L. *J. Org. Chem.* ***2014***, *79*, 11075.
[37] Yoshimi, Y.; Maeda, H.; Sugimoto, A.; Mizuno, K. *Tetrahedron Lett.* ***2001***, *42*, 2341.
[38] Hubbard, T.A.; Brown, A.J.; Bell, I.A.W.; Cockroft, S.L. *J. Am. Chem. Soc.* ***2016***, *138*, 15114.
[39] Emsley, J.; Freeman, N.J.; Parker, R.J.; Dawes, H.M.; Hursthouse, M.B. *J. Chem. Soc., Perkin Trans. 1* ***1986***, 471.
[40] For some other three-center hydrogen bonds, see Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* ***1984***, *106*, 244; Jeffrey, G.A.; Mitra, J. *J. Am. Chem. Soc.* ***1984***, *106*, 5546; Staab, H.A.; Elbl, K.; Krieger, C. *Tetrahedron Lett.* ***1986***, *27*, 5719.
[41] Hine, J.; Hahn, S.; Miles, D.E. *J. Org. Chem.* ***1986***, *51*, 577.
[42] Caminati, W.; Fantoni, A.C.; Schäfer, L.; Siam, K.; Van Alsenoy, C. *J. Am. Chem. Soc.* ***1986***, *108*, 4364.
[43] Pimentel, G.C.; McClellan, A.L. *The Hydrogen Bond*, W.H. Freeman, San Francisco, ***1960***, p. 260.
[44] Chandra, A. K.; Zeegers-Huyskens, T. *J. Org. Chem.* ***2003***, *68*, 3618.

asymmetric, with the hydrogen atom closer to the basic oxygen atom.[45] There is evidence, however, that symmetrical hydrogen bonds to carboxylates should be regarded as two-center rather than three-center hydrogen bonds since the criteria traditionally used to infer three-center hydrogen bonding are inadequate for carboxylates.[46] There is also an example of cooperative hydrogen bonding [O—H••••C≡C—H••••Ph] in crystalline 2-ethynyl-6,8-diphenyl-7*H*-benzocycloheptен-7-ol (**4**).[47] Related to this discussion is the work that showed the hydrogen bond radii for OH, NH and acidic CH groups to be 0.60 ± 0.15, 0.76 ± 0.15, and 1.10 ± 0.20 Å, respectively.[48]



1 **2** **3** **4**

Hydrogen bonding has been detected in many ways, including measurements of dipole moments, solubility behavior, freezing-point lowering, and heats of mixing, but one important way is by the effect of the hydrogen bond on infrared spectroscopy (IR).[49] The IR frequencies of functional groups such as O—H or C=O are shifted when the group is hydrogen bonded. Hydrogen bonding always moves the peak toward lower frequencies, for both the A—H and the B groups, though the shift is greater for the former. For example, a free OH group of an alcohol or phenol absorbs at ~3590–3650 cm^{-1}, and a hydrogen-bonded OH group is found about 50–100 cm^{-1} lower.[50] In many cases, in dilute solution, there is partial hydrogen bonding, that is, some OH groups are free and some are hydrogen bonded. In such cases, two peaks appear.

Infrared spectroscopy can also distinguish between inter- and intramolecular hydrogen bonding, since intermolecular peaks are intensified by an increase in concentration while intramolecular peaks are unaffected. Other types of spectra that have been used for the detection of hydrogen bonding include Raman, electronic,[51] and NMR.[52] Since hydrogen bonding involves a rapid movement of protons from one atom to another, NMR records an average value that is often broadened. Hydrogen bonding can be detected because it usually produces a chemical shift to a lower field. For example, carboxylic acid–carboxylate systems arising from either mono- or diacids generally exhibit a downfield resonance

[45] Perrin, C.L.; Kim, Y.-J. *J. Am. Chem. Soc.* ***1998***, *120*, 12641.
[46] Görbitz, C.H.; Etter, M.C. *J. Chem. Soc., Perkin Trans. 2* ***1992***, 131.
[47] Steiner, T.; Tamm, M.; Lutz, B.; van der Maas, J. *Chem. Commun.* ***1996***, 1127.
[48] Lakshmi, B.; Samuelson, A.G.; Jovan Jose, K.V.; Gadre, S.R.; Arunan, E. *New J. Chem.* ***2005***, *29*, 371.
[49] See Symons, M.C.R. *Chem. Soc. Rev.* ***1983***, *12*, 1; Egorochkin, A.N.; Skobeleva, S.E. *Russ. Chem. Rev.* ***1979***, *48*, 1198; Aaron, H.S. *Top. Stereochem.* ***1979***, *11*, 1. For a review of the use of rotational spectra to study hydrogen bonding, see Legon, A.C. *Chem. Soc. Rev.* ***1990***, *19*, 197.
[50] Tichy, M. *Adv. Org. Chem.* ***1965***, *5*, 115 contains a lengthy table of free and intramolecular hydrogen-bonding peaks. For a discussion of the role of methyl groups in the formation of hydrogen bonds in DMS/methanol mixtures, see Li, Q.; Wu, G.; Yu, Z. *J. Am. Chem. Soc.* ***2006***, *128*, 1438.
[51] See Lees, W.A.; Burawoy, A. *Tetrahedron* ***1963***, *19*, 419.
[52] See Davis Jr., J.C.; Deb, K.K. *Adv. Magn. Reson.* ***1970***, *4*, 201. Also see, Kumar, G.A.; McAllister, M.A. *J. Org. Chem.* ***1998***, *63*, 6968.

(16–22 ppm), which indicates "strong" hydrogen bonding in anhydrous, aprotic solvents.[53] Hydrogen bonding changes with temperature and concentration, and comparison of spectra taken under different conditions also serves to detect and measure it. As with IR spectra, intramolecular hydrogen bonding in the NMR can be distinguished from intermolecular by its constancy when the concentration is varied. The spin–spin coupling constant across a hydrogen bond, obtained by NMR studies, has been shown to provide a "fingerprint" for hydrogen bond type.[54] Indeed, the determination of $^1J_{CH}$ correlates with the strength of the hydrogen bonds formed by an alcohol.[55] Networks of hydrogen bonds provide stabilization and a single charge center can be stabilized by multiple hydrogen bonds.[56]

Hydrogen bonds are important because of the effects they have on the properties of compounds, among them:

1. Intermolecular hydrogen bonding raises boiling points and frequently melting points.
2. If hydrogen bonding is possible between solute and solvent, this greatly increases solubility and often results in large or even infinite solubility where none would otherwise be expected.
3. Hydrogen bonding causes lack of ideality in gas and solution laws.
4. As previously mentioned, hydrogen bonding changes spectral absorption positions.
5. Hydrogen bonding, especially the intramolecular variety, changes many chemical properties. For example, it is responsible for the large amount of enol present in certain tautomeric equilibria (Sec. 2.N). Also, by influencing the conformation of molecules (see Chapter 4), it often plays a significant role in determining reaction rates.[57] Hydrogen bonding is also important in maintaining the 3D structures of protein and nucleic acid molecules.

Besides oxygen, nitrogen, and fluorine, there is evidence that weaker hydrogen bonding exists in other systems.[58] Although many searches have been made for hydrogen bonding where A is carbon,[59] only three types of C—H bonds have been found that are acidic enough to form weak hydrogen bonds.[60] These are found in terminal alkynes, RC≡CH,[61] chloroform and some other halogenated alkanes, and HCN. It has been reported that there is a relationship between intermolecular interactions and the aromaticity of H-bonded

[53] Bruck, A.; McCoy, L.L.; Kilway, K.V. *Org. Lett.* ***2000***, *2*, 2007. For a discussion of the effect of solvents on hydrogen bonding, see Cook, J.L.; Hunter, C.A.; Low, C.M.R.; Perez-Velasco, A.; Vinter, J.G. *Angew. Chem. Int. Ed.* ***2007***, *46*, 3706.

[54] Del Bene, J.E.; Perera, S.A.; Bartlett, R.J. *J. Am. Chem. Soc.* ***2000***, *122*, 3560.

[55] Maiti, N.C.; Zhu, Y.; Carmichael, I.; Serianni, A.S.; Anderson, V.E. *J. Org. Chem.* ***2006***, *71*, 2878.

[56] Shokri, A.; Schmidt, J,; Wang, X.-B.; Kass, S.R. *J. Am. Chem. Soc.* ***2012***, *134*, 2094.

[57] For the effect of hydrogen bonding on reactivity, see Hibbert, F.; Emsley, J. *Adv. Phys. Org. Chem.* ***1990***, *26*, 255; Sadekov, I.D.; Minkin, V.I.; Lutskii, A.E. *Russ. Chem. Rev.* ***1970***, *39*, 179.

[58] For a review, see Pogorelyi, V.K. *Russ. Chem. Rev.* ***1977***, *46*, 316.

[59] See Green, R.D. *Hydrogen Bonding by C–H Groups*, Wiley, NY, ***1974***. See also, Nakai, Y.; Inoue, K.; Yamamoto, G.; Öki, M. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 2923; Seiler, P.; Dunitz, J.D. *Helv. Chim. Acta* ***1989***, *72*, 1125.

[60] For a theoretical study of weak hydrogen bonds, see Calhorda, M.J. *Chem. Commun.* ***2000***, 801. For C—H—π interactions, also see Mishra, B.K.; Deshmukh, M.M.; Venkatnarayan, R *J. Org. Chem.* ***2014***, *79*, 8599; Zhao, C.; Li, P.; Smith, M.D.; Pellechia, P.J.; Shimizu, K.D. *Org. Lett.* ***2014***, *16*, 3520. See Lorand, J.P. *J. Phys. Org. Chem.* ***2011***, *24*, 267.

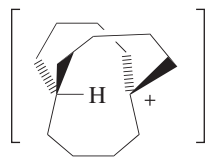
[61] See Hopkinson, A.C., in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 75–136. See also, DeLaat, A.M.; Ault, B.S. *J. Am. Chem. Soc.* ***1987***, *109*, 4232.

substrates. It has also been reported that "H-bonding interactions that increase cyclic $[4n + 2]$ π-electron delocalization boost aromaticity."[62] Halogen–heteroatom bonding interactions, including O···Cl, O···Br, O···I, N···Br, and N···I, are known.[63]

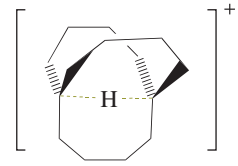
Sterically unhindered C—H groups ($CHCl_3$, CH_2Cl_2, RC≡CH) form short-contact hydrogen bonds with carbonyl acceptors, where there is a significant preference for coordination with the conventional carbonyl lone-pair direction.[64] Weak hydrogen bonds are formed by compounds containing S—H bonds.[65] There has been much speculation regarding other possibilities for B. There is evidence that Cl can form weak hydrogen bonds,[66] but Br and I form very weak bonds, if at all.[67] However, the *ions* Cl^-, Br^-, and I^- form hydrogen bonds that are much stronger than those of the covalently bonded atoms.[68] As noted above, the FH••••F^- bond is especially strong. In this case the hydrogen is equidistant from the fluorine atoms.[69] Similarly, a sulfur atom[65] can be the B component (A—B) in weak hydrogen bonds,[70] but the $^-$SH ion forms much stronger bonds.[71] There are theoretical studies of weak hydrogen bonding.[72] Hydrogen bonding has been directly observed (by NMR and IR) between a negatively charged carbon (see carbanions in Chapter 5) and an OH group in the same molecule.[73] Isocyanides ($R—^+N{\equiv}C^-$) constitute another type of molecule in which carbon is the B component that forms a rather strong hydrogen bond.[74] There is evidence that double and triple bonds, aromatic rings,[75] and even cyclopropane rings[76] may be the B component of hydrogen bonds, but these bonds are very weak. A computational study showed that changes in the (anti)aromatic character of π-conjugated heterocycles can modulate their hydrogen bond strengths.[77] An interesting case is that of the *in*-bicyclo[4.4.4]-1-tetradecyl cation **5** (see out–in isomerism, Sec. 4.L).[78] The NMR and IR spectra show that the actual structure of this ion is **6**, in which both the A and the B component of the hydrogen bond is a carbon.[79] These are sometimes called 3-center 2-electron C—H—C

[62] Wu, J.I.; Jackson, J.E.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***2014***, *136*, 13526.
[63] Widner, D.L.; Knauf, O.R.; Merucci, M.T.; Fritz, T.R.; Sauer, J.S.; Speetzen, E.D.; Bosch, E.; Bowling, N.P. *J. Org. Chem.* ***2014***, *79*, 6269.
[64] Streiner, T.; Kanters, J.A.; Kroon, J. *Chem. Commun.* ***1996***, 1277.
[65] See Zuika, I.V.; Bankovskii, Yu.A. *Russ. Chem. Rev.* ***1973***, *42*, 22; Crampton, M.R. in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, 1974, pp. 379–396; Pogorelyi, V.K. *Russ. Chem. Rev.* ***1977***, *46*, 316.
[66] Smith, J.W. in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 1; Wiley, NY, ***1973***, pp. 265–300. See Bastiansen, O.; Fernholt, L.; Hedberg, K.; Seip, R. *J. Am. Chem. Soc.* ***1985***, *107*, 7836.
[67] Fujimoto, E.; Takeoka, Y.; Kozima, K. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 991; Azrak, R.G.; Wilson, E.B. *J. Chem. Phys.* ***1970***, *52*, 5299.
[68] French, M.A.; Ikuta, S.; Kebarle, P. *Can. J. Chem.* ***1982***, *60*, 1907.
[69] In a few cases, the presence of an unsymmetrical cation causes the hydrogen to be closer to one fluorine than to the other: Williams, J.M.; Schneemeyer, L.F. *J. Am. Chem. Soc.* ***1973***, *95*, 5780.
[70] Schaefer, T.; McKinnon, D.M.; Sebastian, R.; Peeling, J.; Penner, G.H.; Veregin, R.P. *Can. J. Chem.* ***1987***, *65*, 908; Marstokk, K.; Møllendal, H.; Uggerud, E. *Acta Chem. Scand.* ***1989***, *43*, 26.
[71] McDaniel, D.H.; Evans, W.G. *Inorg. Chem,* ***1966***, *5*, 2180; Sabin, J.R. *J. Chem. Phys.* ***1971***, *54*, 4675.
[72] Calhorda, M.J. *Chem. Commun.* ***2000***, 801.
[73] Ahlberg, P.; Davidsson, O.; Johnsson, B.; McEwen, I.; Rönnqvist, M. *Bull. Soc. Chim. Fr.* ***1988***, 177.
[74] Allerhand, A.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1963***, *85*, 866.
[75] For example, see Bakke, J.M.; Chadwick, D.J. *Acta Chem. Scand. Ser. B* ***1988***, *42*, 223: Atwood, J.L.; Hamada, F.; Robinson, K.D.; Orr, G.W.; Vincent, R.L. *Nature* ***1991***, *349*, 683.
[76] Yoshida, Z.; Ishibe, N.; Kusumoto, H. *J. Am. Chem. Soc.* ***1969***, *91*, 2279.
[77] Kakeshpour, T.; Wu, J.I.; Jackson, J.E. *J. Am. Chem. Soc.* ***2016***, *138*, 3427.
[78] For a discussion of cationic noncovalent interactions, see Rodgers, M.T.; Armentrout, P.B. *Chem. Rev.* ***2016***, *116*, 5642.
[79] McMurry, J.E.; Lectka, T.; Hodge, C.N. *J. Am. Chem. Soc.* ***1989***, *111*, 8867. See also, Sorensen, T.S.; Whitworth, S.M. *J. Am. Chem. Soc.* ***1990***, *112*, 8135.

bonds.[80] A technique called *generalized population analysis* has been developed to study this type of multicenter bonding.[81]



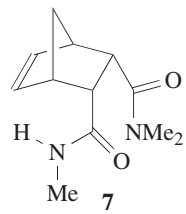
5



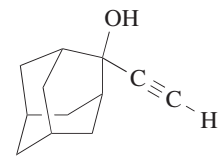
6

A weak (~1.5 kcal mol^{-1}; 6.3 kJ mol^{-1}) and rare C—H••••O═C hydrogen bond has been reported in a class of compounds known as a [6]semirubin (a dipyrrinone).[82] There is also evidence for a C—H••••N/C—H••••OH bond in the crystal structures of α,β-unsaturated ketones carrying a terminal pyridine subunit,[83] and for R_3N^+—C—H••••O═C hydrogen bonding.[84]

Deuterium also forms hydrogen bonds; in some systems these seem to be stronger than the corresponding hydrogen bonds; in others, weaker.[85] Weak hydrogen bonds can be formed between a π bond (from both alkenes and aromatic compounds) and an appropriate hydrogen. For example, IR data in dilute dichloromethane suggests that the predominant conformation for *bis*-amide **7** contains an N—H••••π hydrogen bond involving the C═C unit.[86] The strength of an intramolecular π-facial hydrogen bond between an NH group and an aromatic ring in chloroform has been estimated to have a lower limit of -4.5 ± 0.5 kcal mol^{-1} (-18.8 kJ mol^{-1}).[87] A neutron diffraction study of crystalline 2-ethynyladamantan-2-ol (**8**) shows the presence of an unusual O—H••••π hydrogen bond, which is short and linear, as well as the more common O—H••••O and C—H••••O hydrogen bonds.[88] The electric field associated with the O—H••••π hydrogen bond has been reported[89] as have the electrostatics of X—H••••π hydrogen bonds.[90]



7

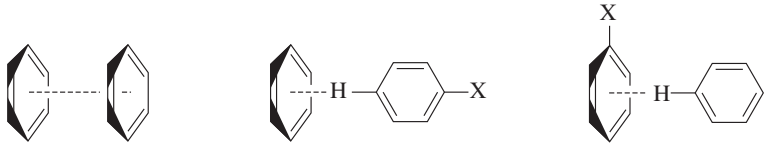


8

[80] McMurry, J.E.; Lectka, T. *Acc. Chem. Res.* ***1992***, *25*, 47.
[81] Ponec, R.; Yuzhakov, G.; Tantillo, D.J. *J. Org. Chem.* ***2004***, *69*, 2992.
[82] Huggins, M.T.; Lightner, D.A. *J. Org. Chem.* ***2001***, *66*, 8402.
[83] Mazik, M.; Bläser, D.; Boese, R. *Tetrahedron* ***2001***, *57*, 5791.
[84] Cannizzaro, C.E.; Houk, K.N. *J. Am. Chem. Soc.* ***2002***, *124*, 7163.
[85] Cummings, D.L.; Wood, J.L. *J. Mol. Struct.* ***1974***, *23*, 103.
[86] Gallo, E.A.; Gelman, S.H. *Tetrahedron Lett.* ***1992***, *33*, 7485.
[87] Adams, H.; Harris, K.D.M.; Hembury, G.A.; Hunter, C.A.; Livingstone, D.; McCabe, J.F. *Chem. Commun.* ***1996***, 2531. See Steiner, T.; Starikov, E.B.; Tamm, M. *J. Chem. Soc., Perkin Trans. 2* ***1996***.
[88] Allen, F.H.; Howard, J.A.K.; Hoy, V.J.; Desiraju, G.R.; Reddy, D.S.; Wilson, C.C. *J. Am. Chem. Soc.* ***1996***, *118*, 4081.
[89] Saggu, M.; Levinson, N.M.; Boxer, S.G. *J. Am. Chem. Soc.* ***2011***, *133*, 17414,
[90] Saggu, M.; Levinson, N.M.; Boxer, S.G. *J. Am. Chem. Soc.* ***2012***, *134*, 18986.

3.B. π–π INTERACTIONS

Many theoretical and experimental studies clearly show the importance of π—π interactions,[91] which are fundamental to many supramolecular organization and recognition processes.[92] Perhaps the simplest prototype of aromatic π—π interactions is the benzene dimer.[93] Within dimeric aryl systems such as this, possible π—π interactions are the sandwich and T-shaped interactions shown. It has been shown that all substituted sandwich dimers bind more strongly than benzene dimer, whereas the T-shaped configurations bind more or less favorably, depending on the substituent.[94] Electrostatic, dispersion, induction, and exchange–repulsion contributions are all significant to the overall binding energies,[94] and the energy component of these interactions has been reviewed.[95]



Sandwich **T-shaped (1)** **T-shaped (2)**

The π electrons of aromatic rings can interact with charged species, yielding strong cation–π interactions that are dominated by electrostatic and polarization effects.[96] An interaction with CH units is also possible. For CH—π interactions in both alkyl- and aryl-based model systems, dispersion effects dominate the interaction, but the electrostatics term is also relevant for aryl CH—π interactions.[97] Aldehyde and ketone adducts with the gaseous trifluoromethyl cation are known.[98]

Detection of π–π interactions has largely relied on NMR-based techniques such as chemical shift variations,[99] and nuclear Overhauser effect spectroscopy (NOESY) or rotating-frame NOE spectroscopy (ROESY).[100] Diffusion-ordered NMR spectroscopy (DOSY) has also been used to detect π—π stacked complexes.[101] The $n \rightarrow \pi^*$ interaction has been reviewed.[102]

[91] Tsuzuki, S.; Lüthi, H.P. *J. Chem. Phys.* ***2001***, *114*, 3949; Felker, P.M.; Maxton, P.M.; Schaeffer, M.W. *Chem. Rev.* ***1994***, *94*, 1787; Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* ***2002***, *124*, 104; Hobza, P.; Jurečka, P. *J. Am. Chem. Soc.* ***2003***, *125*, 15608.

[92] Meyer, E.A.; Castellano, R.K.; Diederich, F. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1210.

[93] Sinnokrot, M.O.; Valeev, E.F.; Sherrill, C.D. *J. Am. Chem. Soc.* ***2002***, *124*, 10887.

[94] Sinnokrot, M.O.; Sherrill, C.D. *J. Am. Chem. Soc.* ***2004***, *126*, 7690.

[95] Sherrill, C.D. *Acc. Chem. Res.* ***2013***, *46*, 1020.

[96] Lindeman, S.V.; Kosynkin, D.; Kochi, J.K. *J. Am. Chem. Soc.* ***1998***, *120*, 13268; Ma, J.C.; Dougherty, D.A. *Chem. Rev.* ***1997***, *97*, 1303; Cubero, E.; Luque, F.J.; Orozco, M. *Proc. Natl. Acad. Sci. U.S.A.* ***1998***, *95*, 5976. See Dougherty, D.A. *Acc. Chem. Res.* ***2013***, *46*, 885; Mahadevi, A.S.; Sastry, G.N. *Chem. Rev.* ***2013***, *113*, 2100. Also see Luu, Q.H.; Fiedler, T.; Gladysz, J.A. *Angew. Chem. Int. Ed.* ***2017***, *56*, 5664.

[97] Ribas, J.; Cubero, E.; Luque, F.J.; Orozco, M. *J. Org. Chem.* ***2002***, *67*, 7057. See Parrish, R.M.; Sherrill, C.D. *J. Am. Chem. Soc.* ***2014***, *136*, 17386.

[98] Oomens, J.; Morton, T.H. *Org. Lett.* ***2011***, *13*, 2176.

[99] Petersen, S.B.; Led, J.J.; Johnston, E.R.; Grant, D.M. *J. Am. Chem. Soc.* ***1982***, *104*, 5007.

[100] Wakita, M.; Kuroda, Y.; Fujiwara, Y.; Nakagawa, T. *Chem. Phys. Lipids* ***1992***, *62*, 45.

[101] Viel, S.; Mannina, L.; Segre, A. *Tetrahedron Lett.* ***2002***, *43*, 2515. See also, Ribas, J.; Cubero, E.; Luque, F.J.; Orozco, M. *J. Org. Chem.* ***2002***, *67*, 7057. For a discussion of substituent effects on aromatic stacking interactions, see Cockroft, S.L.; Perkins, J.; Zonta, C.; Adams, H.; Spey, S.E.; Low, C.M.R.; Vinter, J.G.; Lawson, K.R.; Urch, C.J.; Hunter, C.A. *Org. Biomol. Chem.* ***2007***, 5, 1062; Hwang, J.; Li, P.; Carroll, W.R.; Smith, M.D.; Pellechia, P.J.; Shimizu, K.D. *J. Am. Chem. Soc.* ***2014***, *136*, 14060. Also see Bloom, J.W.G.; Wheeler, S.E. *Angew. Chem. Int. Ed.* ***2011***, *50*, 7847.

[102] Newberry, R.W.; Raines, R.T. *Acc. Chem. Res.* ***2017***, *50*, 1838.

3.C. ADDITION COMPOUNDS

When the reaction of two compounds results in a product that contains all the mass of the two compounds, the product is called an *addition compound*. There are several kinds. The remainder of this chapter will discuss addition compounds in which the molecules of the starting materials remain more or less intact and weak bonds hold two or more molecules together. There are four broad classes: (i) electron donor–acceptor complexes, (ii) complexes formed by crown ethers and similar compounds, (iii) inclusion compounds, and (iv) catenanes.

3.C.i. Electron Donor–Acceptor (EDA) Complexes[103]

In *EDA complexes*,[104] there is always a donor molecule and an acceptor molecule. The donor may donate an unshared pair (an *n* donor) or a pair of electrons in a π orbital of a double bond or aromatic system (a π donor). The electronic spectrum constitutes a good test for the presence of an EDA complex. These complexes generally exhibit a spectrum (called a *charge-transfer spectrum*) that is not the same as the sum of the spectra of the two individual molecules.[105] Because the first excited state of the complex is relatively close in energy to the ground state, there is usually a peak in the visible or near-UV region, and EDA complexes are often colored. Many EDA complexes are unstable and exist only in solutions in equilibrium with their components, but others are stable solids. In most EDA complexes the donor and acceptor molecules are present in an integral ratio, most often 1:1, but complexes with nonintegral ratios are also known. There are several types of acceptor molecules; complexes formed by two of them will be discussed. Alkane σ complexes are known.[106]

1. *Complexes in which the acceptor is a metal ion and the donor is an alkene or an aromatic ring*. The *n* donors do not give EDA complexes with metal ions but form covalent bonds instead.[107] Many metal ions form complexes with alkenes, dienes (usually conjugated, but not always), alkynes, and aromatic rings that are often stable solids. The donor (or ligand) molecules in these complexes are classified by the prefix *hapto*[108] and/or the descriptor η^n, where *n* is the number of atoms the ligand uses to bond with the metal.[109]

[103] Foster, R. *Organic Charge-Transfer Complexes*, Academic Press, NY, ***1969***; Mulliken, R.S.; Person, W.B. *Molecular Complexes*, Wiley, NY, ***1969***; Rose, J. *Molecular Complexes*, Pergamon, Elmsford, NY, ***1967***; Poleshchuk, O.Kh.; Maksyutin, Yu.K. *Russ. Chem. Rev.* ***1976***, *45*, 1077; Banthorpe, D.V. *Chem. Rev.* ***1970***, *70*, 295; Kosower, E.M. *Prog. Phys. Org. Chem.* ***1965***, *3*, 81; Foster, R. *Chem. Br.* ***1976***, *12*, 18.

[104] These have often been called *charge-transfer complexes*, but this term implies that the bonding involves charge transfer, which is not always the case, so that the more neutral name EDA complex is preferable. See Mulliken, R.S.; Person, W.B. *J. Am. Chem. Soc.* ***1969***, *91*, 3409.

[105] Also see Bentley, M.D.; Dewar, M.J.S. *Tetrahedron Lett.* ***1967***, 5043.

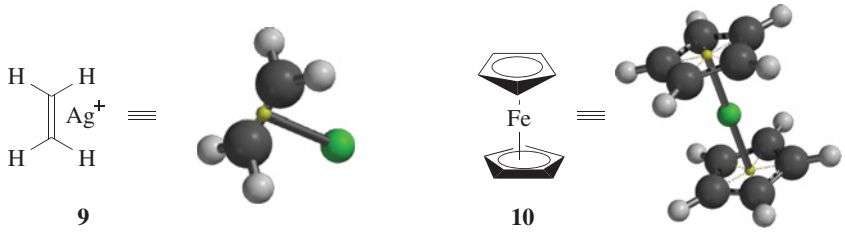
[106] Young, R.D. *Chem. Eur. J.* ***2014***, *20*, 12704.

[107] See Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed, University Science Books, Mill Valley, CA, ***1987***; Alper, H. *Transition Metal Organometallics in Organic Synthesis,* 2 Vols., Academic Press, NY, ***1976***, ***1978***. For general reviews, see Churchill, M.R.; Mason, R. *Adv. Organomet. Chem.* ***1967***, *5*, 93; Nakamura, A. *J. Organomet. Chem.* ***1990***, *400*, 35; Bennett, M.A.; Schwemlein, H.P. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1296; metal–pentadienyl ions, Powell, P. *Adv. Organomet. Chem.* ***1986***, *26*, 125; complexes of main-group metals. For a list of review articles on this subject, see Bruce, M.I. *Adv. Organomet. Chem.* ***1972***, *10*, 273 (pp. 317–321).

[108] For the origin of this system, see Cotton, F.A. *J. Organomet. Chem.* ***1975***, *100*, 29.

[109] The prefix is μ (mu) indicates that the ligand bridges two metal atoms.

The generally accepted picture of the bonding in these complexes,[110] first proposed by Dewar,[111] can be illustrated by the ethylene complex with silver, **9**, in which the alkene unit forms an η^2 complex with the silver ion (the alkene functions as a two-electron donating ligand to the metal). There is evidence of π complexation of Na^+ by C=C.[112] In the case of the silver complex, the bond is not from one atom of the C=C unit to the silver ion, but from the π center (two electrons are transferred from the alkene to the metal ion). Ethene has two π electrons and is a dihapto or η^2 ligand, as are other simple alkenes. Similarly, benzene has six π electrons and is a hexahapto or η^6 ligand. Ferrocene (**10**) is an example of a *metallocene*, with two cyclopentadienyl ligands (each is a five-electron donor or an η^5 ligand), and ferrocene is properly called bis(η^5-cyclopentadienyl)iron(II).

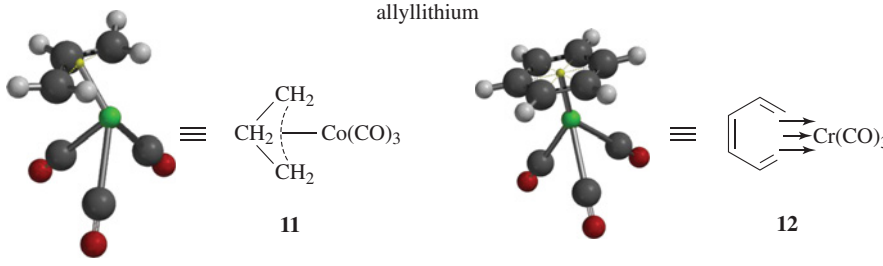


9 **10**

This system can be extended to compounds in which only a single σ bond connects the organic group to the metal, for example, C_6H_5—Li (a monohapto or η^1 ligand), and to complexes in which the organic group is an ion, for example, π-allyl complexes, such as **11**, in which the allyl ligand is trihapto or η^3. Note that in a compound such as allyllithium, where a σ bond connects the carbon to the metal, the allyl group is referred to as monohapto or η^1.

$CH_2{=}CH{-}CH_2{-}Li$

allyllithium



11 **12**

As mentioned, benzene is an η^6 ligand that forms complexes with silver and other metals.[113] When the metal involved has a coordination number >1, more than one donor molecule (ligand) participates. The CO group is a common ligand (a two-electron donating or η^2 ligand), and in metal complexes the CO group is classified as a metal carbonyl. Benzenechromium tricarbonyl (**12**) is a stable compound[114] that illustrates both benzene and carbonyl ligands. Three arrows are

[110] See Pearson, A.J. *Metallo-organic Chemistry*, Wiley, NY, ***1985***; Ittel, S.D.; Ibers, J.A. *Adv. Organomet. Chem.* ***1976***, *14*, 33; Hartley, F.R. *Chem. Rev.* ***1973***, *73*, 163; *Angew. Chem. Int. Ed.* ***1972***, *11*, 596.

[111] Dewar, M.J.S. *Bull. Soc. Chim. Fr.* ***1951***, *18*, C79.

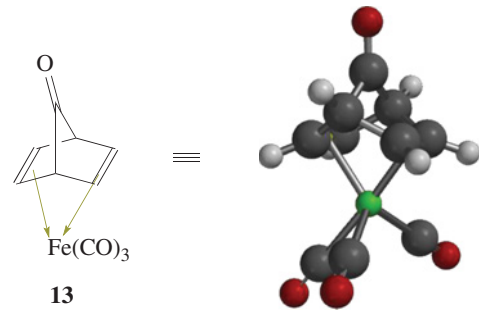
[112] Hu, J.; Gokel, G.W.; Barbour, L.J. *Chem. Commun.* ***2001***, 1858.

[113] Zeiss, H.; Wheatley, P.J.; Winkler, H.J.S. *Benzenoid–Metal Complexes*, Ronald Press, NY, ***1966***.

[114] Nicholls, B.; Whiting, M.C. *J. Chem. Soc.* ***1959***, 551. For reviews of arene–transition metal complexes, see Uemura, M. *Adv. Met.-Org. Chem.* ***1991***, *2*, 195; Silverthorn, W.E. *Adv. Organomet. Chem.* ***1975***, *13*, 47.

shown to represent the six-electron donation (an η^6 ligand), but the accompanying model gives a clearer picture of the bonding. Cyclooctatetraene is an eight-electron donating or η^8 ligand that also forms complexes with metals. Metallocenes such as **10** may be considered a special case of this type of complex, although the bonding in metallocenes is much stronger.

In a number of cases, alkenes that are too unstable to be isolated as discreet molecules have been isolated in the form of their metal complexes. As example is norbornadienone, which was isolated as its iron-tricarbonyl complex (**13**),[115] where the norbornadiene unit is an η^4 ligand, and each of the carbonyl units are η^2 ligands. The free dienone spontaneously decomposes to carbon monoxide and benzene (see reaction **17-26**).



13

2. *Complexes in which the acceptor is an organic molecule*. Picric acid (2,4,6-trinitrophenol) and similar polynitro compounds are the most important of these.[116] Picric acid forms addition compounds with many aromatic hydrocarbons, aromatic amines, aliphatic amines, alkenes, and other compounds. These addition compounds are usually solids that have definite melting points and have been used as derivatives of the compounds in question. These complexes are called picrates, and they are *addition compounds* and not salts of picric acids. Unfortunately, the actual salts of picric acid are also called picrates. Similar complexes are formed between phenols and quinones (quinhydrones).[117] Alkenes that contain electron-withdrawing substituents also act as acceptor molecules, as do carbon tetrahalides[118] and certain anhydrides.[119] A particularly strong alkene acceptor is tetracyanoethylene.[120]

   The bonding in these cases is more difficult to explain than in the previous case, and indeed no truly satisfactory explanation is available.[121] The difficulty is that the donor has a pair of electrons to contribute (both *n* donors and π donors are found

[115] Landesberg, J.M.; Sieczkowski, J. *J. Am. Chem. Soc.* ***1971***, *93*, 972.

[116] See Parini, V.P. *Russ. Chem. Rev.* ***1962***, *31*, 408; for a review of complexes in which the acceptor is an organic cation, see Kampar, V.E. *Russ. Chem. Rev.* ***1982***, *51*, 107; also see, Ref. 103.

[117] For a review of quinone complexes, see Foster, R.; Foreman, M.I. in Patai, S. *The Chemistry of the Quinonoid Compounds*, pt. 1, Wiley, NY, ***1974***, pp. 257–333. There are also complexes between phenols and benzene. See Nikolova, V.; Ilieva, S.; Galabov, B.; Henry F. Schaefer III, H.F. *J. Org. Chem.* ***2014***, *79*, 6823.

[118] See Blackstock, S.C.; Lorand, J.P.; Kochi, J.K. *J. Org. Chem.* ***1987***, *52*, 1451.

[119] Foster, R. in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, ***1979***, pp. 175–212.

[120] See Melby, L.R. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 639–669. See also, Fatiadi, A.J. *Synthesis* ***1987***, 959.

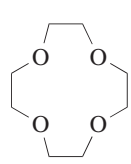
[121] For reviews, see Bender, C.J. *Chem. Soc. Rev.* ***1986***, *15*, 475; Kampar, E.; Neilands, O. *Russ. Chem. Rev.* ***1986***, *55*, 334; Bent, H.A. *Chem. Rev.* ***1968***, *68*, 587.

here), but the acceptor does not have a vacant orbital. Simple attraction of the dipole–induced dipole type accounts for some of the bonding,[122] but is too weak to explain the bonding in all cases.[123] Nitromethane, with about the same dipole moment as nitrobenzene, is an example of a molecule that forms much weaker complexes. Some other type of bonding clearly must also be present in many EDA complexes. The exact nature of this bonding, called *charge-transfer bonding*, is not well understood, but it presumably involves some kind of donor–acceptor interaction.

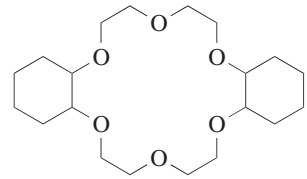
3.C.ii. Crown Ether Complexes and Cryptates[124]

Crown ethers are large-ring compounds that contain several oxygen atoms, usually in a regular pattern. Examples are 12-crown-4 (**14**; where 12 is the size of the ring and 4 represents the number of coordinating atoms, here oxygen),[125] dicyclohexano-18-crown-6 (**15**), and 15-crown-5 (**16**). These compounds have the property[126] of forming complexes with positive ions, generally metallic ions (but usually not the ions of transition metals), or ammonium and substituted ammonium ions.[127] The crown ether is called the *host* and the ion is the *guest*. In most cases, the ions are held tightly in the center of the cavity.[128] Each crown ether binds different ions, depending on the size of the cavity. For example, **14** binds Li^+[129] but not K^+,[130] while **15** binds K^+ but not Li^+.[131] Similarly, **15** binds Hg^{2+} but not Cd^{2+} or Zn^{2+}, and Sr^{2+} but not Ca^{2+}.[132] 18-Crown-5 binds alkali and ammonium cations >1000 times weaker than 18-crown-6, presumably because the larger 18-crown-6 cavity involves more hydrogen bonds.[133] Interlocked molecules are bound by bromopyrido-24-crown-8.[134] The complexes can frequently be prepared as well-defined sharp-melting solids. It has been shown that crown ether complexation is enhanced in water that contains ice.[135]

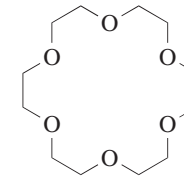
[122] See, for example, Le Fevre, R.J.W.; Radford, D.V.; Stiles, P.J. *J. Chem. Soc. B* ***1968***, 1297.
[123] Mulliken, R.S.; Person, W.B. *J. Am. Chem. Soc.* ***1969***, *91*, 3409.
[124] See Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, 3 Vols., Academic Press, NY, ***1984***; Vögtle, F. *Host Guest Complex Chemistry I, II, and III (Top. Curr. Chem. 98*, *101*, *121)*, Springer, Berlin, ***1981***, ***1982***, ***1984***; Vögtle, F.; Weber, E. *Host Guest Complex Chemistry/Macrocycles*, Springer, Berlin, ***1985***; Izatt, R.M.; Christensen, J.J. *Synthetic Multidentate Macrocyclic Compounds*, Academic Press, NY, ***1978***. For reviews, see McDaniel, C.W.; Bradshaw, J.S.; Izatt, R.M. *Heterocycles,* ***1990***, *30*, 665; Sutherland, I.O. *Chem. Soc. Rev.* ***1986***, *15*, 63; Cram, D.J. *Angew. Chem. Int. Ed.* ***1986***, *25*, 1039; Gutsche, C.D. *Acc. Chem. Res.* ***1983***, *16*, 161; Tabushi, I.; Yamamura, K. *Top. Curr. Chem.* ***1983***, *113*, 145; Cram, D.J.; Cram, J.M. *Acc. Chem. Res.* ***1978***, *11*, 8; Lehn, J.M. *Struct. Bonding (Berlin)* ***1973***, *16*, 1; Christensen, J.J.; Eatough, D.J.; Izatt, R.M. *Chem. Rev.* ***1974***, *74*, 351; See *Angew. Chem. Int. Ed.* ***1988***, *27*, 89, 1009, 1021; and *Chem. Scr.,* ***1988***, *28*, 229, 237, 263. The series *Advances in Supramolecular Chemistry*.
[125] Cook, F.L.; Caruso, T.C.; Byrne, M.P.; Bowers, C.W.; Speck, D.H.; Liotta, C. *Tetrahedron Lett.* ***1974***, 4029.
[126] Discovered by Pedersen, C.J. *J. Am. Chem. Soc.* ***1967***, *89*, 2495, 7017. For an account of the discovery, see Schroeder, H.E.; Petersen, C.J. *Pure Appl. Chem.* ***1988***, *60*, 445.
[127] See Inoue, Y.; Gokel, G.W. *Cation Binding by Macrocycles*, Marcel Dekker, NY, ***1990***.
[128] See Izatt, R.M.; Bradshaw, J.S.; Nielsen, S.A.; Lamb, J.D.; Christensen, J.J.; Sen, D. *Chem. Rev.* ***1985***, *85*, 271; Parsonage, N.G.; Staveley, L.A.K. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 3, Academic Press, NY, ***1984***, pp. 1–36.
[129] Anet, F.A.L.; Krane, J.; Dale, J.; Daasvatn, K.; Kristiansen, P.O. *Acta Chem. Scand.* ***1973***, *27*, 3395.
[130] See Dale, J.; Eggestad, J.; Fredriksen, S.B.; Groth, P. *J. Chem. Soc., Chem. Commun.* ***1987***, 1391; Dale, J.; Fredriksen, S.B. *Pure Appl. Chem.* ***1989***, *61*, 1587.
[131] Izatt, R.M.; Nelson, D.P.; Rytting, J.H.; Haymore, B.L.; Christensen, J.J. *J. Am. Chem. Soc.* ***1971***, *93*, 1619.
[132] Kimura, Y.; Iwashima, K.; Ishimori, T.; Hamaguchi, H. *Chem. Lett.* ***1977***, 563.
[133] Raevsky, O.A.; Solov'ev, V.P.; Solotnov, A.F.; Schneider, H.-J.; Rüdiger, V. *J. Org. Chem.* ***1996***, *61*, 8113.
[134] Delmas, L.C.; Payne, N.A.; Williams, A.R. *Tetrahedron Lett.* ***2016***, *57*, 513.
[135] Tasaki, Y.; Okada, T. *J. Am. Chem. Soc.* ***2012***, *134*, 6128.



14

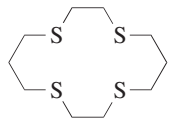


15

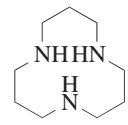


16

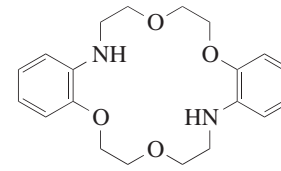
Apart from their obvious utility in separating mixtures of cations,[136] crown ethers are widely used in organic synthesis (see the discussion in Sec. 10.G.v). Chiral crown ethers have been used for the resolution of racemic mixtures (Sec. 4.A). Although crown ethers are most frequently used to complex cations, amines, phenols, and other neutral molecules have also been complexed[137] (see Sec. 4.L for the complexing of anions).[138] Macrocycles containing nitrogen (azacrown ethers) or sulfur atoms (thiacrown ethers),[139] such as **17** and **18**,[140] have complexing properties similar to other crown ethers, as do mixed heteroatom crown ethers such as **19**,[141] **20**,[142] or **21**.[143] Enantiomerically pure P-stereogenic diphosphacrowns have been prepared.[144]



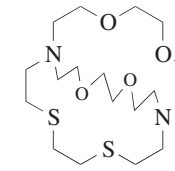
17



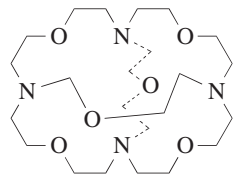
18



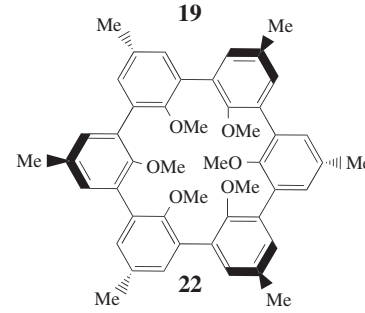
19



20



21



22

[136] Crown ethers have been used to separate isotopes of cations, e.g., ^{44}Ca from ^{40}Ca. For a review, see Heumann, K.G. *Top. Curr. Chem.* ***1985***, *127*, 77.

[137] For reviews, see Vögtle, F.; Müller, W.M.; Watson, W.H. *Top. Curr. Chem.* ***1984***, *125*, 131; Weber, E. *Prog. Macrocycl. Chem.* ***1987***, *3*, 337; Diederich, F. *Angew. Chem. Int. Ed.* ***1988***, *27*, 362.

[138] See van Staveren, C.J.; van Eerden, J.; van Veggel, F.C.J.M.; Harkema, S.; Reinhoudt, D.N. *J. Am. Chem. Soc.* ***1988***, *110*, 4994. See also, Rodrigue, A.; Bovenkamp, J.W.; Murchie, M.P.; Buchanan, G.W.; Fortier, S. *Can. J. Chem.* ***1987***, *65*, 2551; Fraser, M.E.; Fortier, S.; Markiewicz, M.K.; Rodrigue, A.; Bovenkamp, J.W. *Can. J. Chem.* ***1987***, *65*, 2558.

[139] Voronkov, M.G.; Knutov, V.I. *Sulfur Rep.* ***1986***, *6*, 137, *Russ. Chem. Rev.* ***1982***, *51*, 856; Reid, G.; Schröder, M. *Chem. Soc. Rev.* ***1990***, *19*, 239.

[140] For a review of **17** and its derivatives, see Chaudhuri, P.; Wieghardt, K. *Prog. Inorg. Chem.* ***1987***, *35*, 329. *N*-Aryl-azacrown ethers are known, see Zhang, X.-X.; Buchwald, S.L. *J. Org. Chem.* ***2000***, *65*, 8027.

[141] Gersch, B.; Lehn, J.-M.; Grell, E. *Tetrahedron Lett.* ***1996***, *37*, 2213.

[142] Newcomb, M.; Gokel, G.W.; Cram, D.J. *J. Am. Chem. Soc.* ***1974***, *96*, 6810.

[143] Ragunathan, K.G.; Shukla, R.; Mishra, S.; Bharadwaj, P.K. *Tetrahedron Lett.* ***1993***, *34*, 5631.

[144] Morisak, Y.; Imoto, H.; Hirano, K.; Hayashi, T.; Chujo, Y. *J. Org. Chem.* ***2011***, *76*, 1795.

Bicyclic molecules such as **20** can surround the enclosed ion in three dimensions, binding it even more tightly than the monocyclic crown ethers. Bicyclics and cycles of higher order[145] are called *cryptands* and the complexes formed are called *cryptates* (monocyclic compounds are sometimes called *cryptands*). When the molecule contains a cavity that can accommodate a *guest molecule*,[146] usually through hydrogen-bonding interactions, it is sometimes called a *cavitand*.[147] The tricyclic cryptand **21** has ten binding sites and a spherical cavity.[116] Another molecule with a spherical cavity (though not a cryptand) is **22**, which complexes Li^+ and Na^+ (preferentially Na^+), but not K^+, Mg^{2+}, or Ca^{2+}.[148] Molecules such as these, whose cavities can be occupied only by spherical entities, have been called *spherands*.[99] Other types are *calixarenes*,[149] for example **23**.[150] Spherand-type calixarenes are known.[151] There is significant hydrogen bonding involving the phenolic OH units in [4]calixarenes, but this diminishes as the size of the cavity increases in larger ring calixarenes.[152] There are also calix[6]arenes[153] that have been shown to have conformational isomers (Sec. 4.O) in equilibrium (cone versus alternate) that can sometimes be isolated:[154] calix[8]arenes,[155] azacalixarenes,[156] homooxacalixarenes,[157] and calix[9-20]arenes.[158] Note that substitution of the unoccupied "meta" positions immobilizes calix[4]arenes and the conformational mobility (Sec. 4.O.iv) in calix[8]arenes is substantially diminished.[159] Amide-bridged calix[4]arenes[160] calix[4]azulene,[161] and

[145] See Potvin, P.G.; Lehn, J.M. *Prog. Macrocycl. Chem.* ***1987***, *3*, 167; Kiggen, W.; Vögtle, F. *Prog. Macrocycl. Chem.* ***1987***, *3*, 309; Dietrich, B. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, ***1984***, pp. 337–405; Lehn, J.M. *Acc. Chem. Res.* ***1978***, *11*, 49, *Pure Appl. Chem.* ***1977***, *49*, 857.

[146] For a review of cryptand-based hosts for organic guests, see Han, Y.; Jiang, Y.; Chen, C.-F. *Tetrahedron* ***2015***, *71*, 503.

[147] Shivanyuk, A.; Spaniol, T.P.; Rissanen, K.; Kolehmainen, E.; Böhmer, V. *Angew. Chem. Int. Ed.* ***2000***, *39*, 3497. For a cavitand-based coordination cage, see Pinalli, R.; Boccini, F.; Dalcanale, E. *Isr J. Chem.* ***2011***, *51*, 781.

[148] Bryany, J.A.; Ho, S.P.; Knobler, C.B.; Cram, D.J. *J. Am. Chem. Soc.* ***1990***, *112*, 5837.

[149] Shinkai, S. *Tetrahedron* ***1993***, *49*, 8933.

[150] See Vicens, J.; Böhmer, V. *Calixarenes: A Versatile Class of Macrocyclic Compounds*, Kluver: Dordrecht, ***1991***; Gutsche, C.D. *Calixarenes*; Royal Society of Chemistry, Cambridge, ***1989***; Gutsche, C.D. *Prog. Macrocycl. Chem.* ***1987***, *3*, 93. Also see, Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* ***1995***, *36*, 5429; Zhong, Z.-L.; Chen, Y.-Y.; Lu, X.-R. *Tetrahedron Lett.* ***1995***, *36*, 6735; No, K.; Kim, J.E.; Kwon, K.M. *Tetrahedron Lett.* ***1995***, *36*, 8453.

[151] Agbaria, K.; Aleksiuk, O.; Biali, S.E.; Böhmer, V.; Frings, M.; Thondorf, I. *J. Org. Chem.* ***2001***, *66*, 2891. See Agbaria, K.; Biali, S.E.; Böhmer, V.; Brenn, J.; Cohen, S.; Frings, M.; Grynszpan, F.; Harrowfield, J.Mc B.; Sobolev, A.N.; Thondorf, I. *J. Org. Chem.* ***2001***, *66*, 2900.

[152] Cerioni, G.; Biali, S.E.; Rappoport, Z. *Tetrahedron Lett.* ***1996***, *37*, 5797; Molard, Y.; Bureau, C.; Parrot-Lopez, H.; Lamartine, R.; Regnourf-de-Vains, J.-B. *Tetrahedron Lett.* ***1999***, *40*, 6383.

[153] Otsuka, H.; Araki, K.; Matsumoto, H.; Harada, T.; Shinkai, S. *J. Org. Chem.* ***1995***, *60*, 4862.

[154] Kanamathareddy, S.; Gutsche, C.D. *J. Org. Chem.* ***1994***, *59*, 3871.

[155] Cunsolo, F.; Consoli, G.M.L.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* ***1996***, *37*, 715.

[156] Miyazaki, Y.; Kanbara, T.; Yamamoto, T. *Tetrahedron Lett.* ***2002***, *43*, 7945; Khan, I.U.; Takemura, H.; Suenaga, M.; Shinmyozu, T.; Inazu, T. *J. Org. Chem.* ***1993***, *58*, 3158.

[157] Masci, B. *J. Org. Chem.* ***2001***, *66*, 1497; Seri, N.; Thondorf, I.; Biali, S.E. *J. Org. Chem.* ***2004***, *69*, 4774; Tsubaki, K.; Morimoto, T.; Otsubo, T.; Kinoshita, T.; Fuji, K. *J. Org. Chem.* ***2001***, *66*, 4083.

[158] Stewart, D.R.; Gutsche, C.D. *J. Am. Chem. Soc.* ***1999***, *121*, 4136.

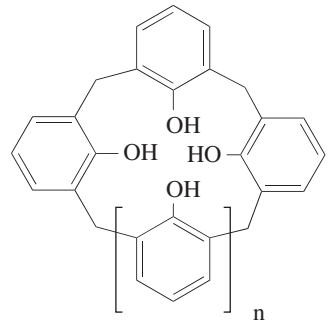
[159] Mascal, M.; Naven, R.T.; Warmuth, R. *Tetrahedron Lett.* ***1995***, *36*, 9361.

[160] Wu, Y.; Shen, X.-P.; Duan, C.-y.; Liu, Y.-i.; Xu, Z. *Tetrahedron Lett.* ***1999***, *40*, 5749.

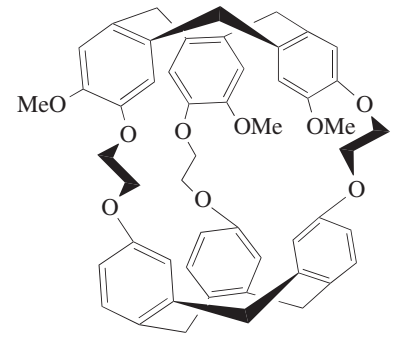
[161] Colby, D.A.; Lash, T.D. *J. Org. Chem.* ***2002***, 67, 1031.

quinone-bridged calix[6]arenes[162] are known, and diammoniumcalix[4]arene has been prepared.[163] Enantiopure calix[4]resorcinarene derivatives are known,[164] and water-soluble calix[4]arenes have been prepared.[165] There are also a variety of calix[*n*]crown ethers,[166] some of which are cryptands.[167] The binding affinity between quaternary ammonium cations and water-soluble calix[4]resorcionarene has been determined.[168] There is also evidence for formation of a calix[4]arene–proton complex.[169] Calixarene-based [3]rotaxanes have been prepared.[170]

calix[4]arene, n = 1
calix[6]arene, n = 3
calix[8]arene, n = 5



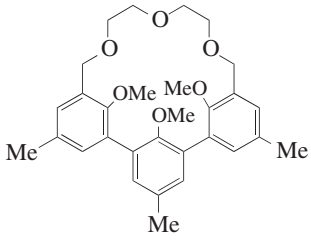
23



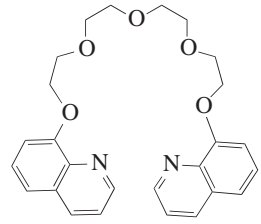
24

Other molecules include *cryptophanes* (for example, **24**),[171] *hemispherands* (an example is **25**[172]), and *podands*.[173] The last-named are host compounds in which two or more arms come out of a central structure. Examples are **26**[174] and **27**[175] and the latter molecule binds simple cations such as Na^+, K^+, and Ca^{2+}. *Lariat ethers*[176] are compounds containing a crown ether ring with one or more side chains that can also serve as ligands, for example, **28**.[177] There is also a class of ortho cyclophanes that are crown ethers (see **29**) and have been given the name *starands*.[178]

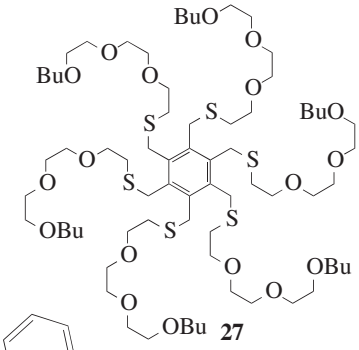
[162] Akine, S.; Goto, K.; Kawashima, T. *Tetrahedron Lett.* ***2000***, *41*, 897.
[163] Aeungmaitrepirom, W.; Hagège, A.; Asfari, Z.; Bennouna, L.; Vicens, J.; Leroy, M. *Tetrahedron Lett.* ***1999***, *40*, 6389.
[164] Shirakawa, S.; Moriyama, A.; Shimizu, S. *Eur. J. Org. Chem.* ***2008***, 5957.
[165] Shimizu, S.; Shirakawa, S.; Sasaki, Y.; Hirai, C. *Angew. Chem. Int. Ed.* ***2000***, *39*, 1256.
[166] Stephan, H.; Gloe, K.; Paulus, E.F.; Saadioui, M.; Böhmer, V. *Org. Lett.* ***2000***, *2*, 839; Asfari, Z.; Thuéry, P.; Nierlich, M.; Vicens, J. *Tetrahedron Lett.* ***1999***, *40*, 499.
[167] Pulpoka, B.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* ***1996***, *37*, 6315.
[168] Hong, M.; Zhang, Y.-M.; Liu, Y. *J. Org. Chem.* ***2015***, *80*, 1849.
[169] Maklik, E.; Vañura, P. *Monat. Chemie* ***2006***, *137*, 1185.
[170] Talotta, C.; Gaeta, C.; Neri, P. *Org. Lett.* ***2012***, *14*, 3104.
[171] See Collet, A. *Tetrahedron* ***1987***, *43*, 5725, in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 1, Academic Press, NY, ***1984***, pp. 97–121.
[172] Lein, G.M.; Cram, D.J. *J. Am. Chem. Soc.* ***1985***, *107*, 448.
[173] Kron, T.E.; Tsvetkov, E.N. *Russ. Chem. Rev.* ***1990***, *59*, 283; Menger, F.M. *Top. Curr. Chem.* ***1986***, *136*, 1.
[174] Tümmler, B.; Maass, G.; Weber, E.; Wehner, W.; Vögtle, F. *J. Am. Chem. Soc.* ***1977***, *99*, 4683.
[175] Vögtle, F.; Weber, E. *Angew. Chem. Int. Ed.* ***1974***, *13*, 814.
[176] For the synthesis of *N*-pivot lariat ethers, see Elwahy, A.H.M.; Abbas, A.A. *J. Het. Chem.* ***2008***, *45*, 1.
[177] Gatto, V.J.; Gokel, G.W. *J. Am. Chem. Soc.* ***1984***, *106*, 8240; Nakatsuji, Y.; Nakamura, T.; Yonetani, M.; Yuya, H.; Okahara, M. *J. Am. Chem. Soc.* ***1988***, *110*, 531.
[178] Lee, W.Y.; Park, C.H. *J. Org. Chem.* ***1993***, *58*, 7149.



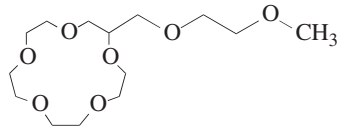
25



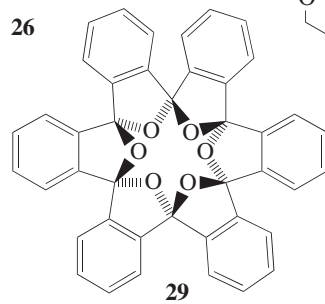
26



27



28

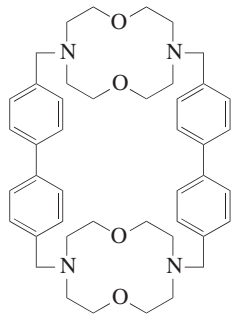


29

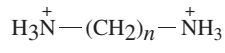
The bonding in these complexes is the result of ion–dipole attractions between the heteroatoms and the positive ions. The parameters of the host–guest interactions can sometimes be measured by NMR.[179] Another important interaction is $n \rightarrow \pi^*$ interactions, whose strength may be competitive with hydrogen bonds.[180]

It has been implied that the ability of these host molecules to bind guests is often very specific, often linked to the hydrogen-bonding ability of the host,[181] enabling the host to pull just one molecule or ion out of a mixture. This is called *molecular recognition*.[182] The H-bond acceptor parameters of anions has been discussed.[183] In general, cryptands, with their well-defined 3D cavities, are better for this than monocyclic crown ethers or ether derivatives. An example is the host **30**, which selectively binds the dication **31** ($n = 5$) rather than **31** ($n = 4$), and **31** ($n = 6$) rather than **31** ($n = 7$).[184] The host **32**, which is water soluble, forms 1:1 complexes with neutral aromatic hydrocarbons such as pyrene and fluoranthene, and even (though more weakly) with biphenyl and naphthalene, and is able to transport them through an aqueous phase.[185]

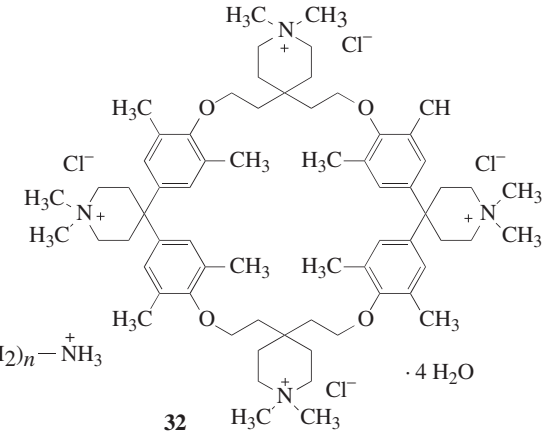
[179] Wang, T.; Bradshaw, J.S.; Izatt, R.M. *J. Heterocylic Chem.* ***1994***, *31*, 1097.
[180] Newberry, R.W.; Orke, S.J.; Raines, R.T. *Org. Lett.* ***2016***, *18*, 3614.
[181] Fujimoto, T.; Yanagihara, R.; Koboyashi, K.; Aoyama, Y. *Bull. Chem. Soc. Jpn.* ***1995***, *68*, 2113.
[182] For reviews, see Rebek Jr., J. *Angew. Chem. Int. Ed.* ***1990***, *29*, 245; *Acc. Chem. Res.* ***1990***, *23*, 399; *Top. Curr. Chem.* ***1988***, *149*, 189; Diederich, F. *J. Chem. Educ.* ***1990***, *67*, 813; Hamilton, A.D. *J. Chem. Educ.* ***1990***, *67*, 821; Raevskii, O.A. *Russ. Chem. Rev.* ***1990***, *59*, 219.
[183] Pike, S.J.; Hutchinson, J.J.; Hunter, C.A. *J. Am. Chem. Soc.* ***2017***, *139*, 6700.
[184] Mageswaran, R.; Mageswaran, S.; Sutherland, I.O. *J. Chem. Soc., Chem. Commun.* ***1979***, 722.
[185] Diederich, F.; Dick, K. *J. Am. Chem. Soc.* ***1984***, *106*, 8024; Diederich, F.; Griebe, D. *J. Am. Chem. Soc.* ***1984***, *106*, 8037. See also, Vögtle, F.; Müller, W.M.; Werner, U.; Losensky, H. *Angew. Chem. Int. Ed.* ***1987***, *26*, 901.



30

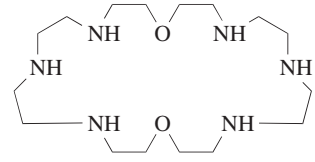


31



32

Of course, it has long been known that molecular recognition is very important in biochemistry. The action of enzymes and various other biological molecules is extremely specific because these molecules also have host cavities that are able to recognize only one or a few particular types of guest molecules. Now, organic chemists can synthesize nonnatural hosts that can also perform crude (compared to biological molecules) molecular recognition. The macrocycle **33** has been used as a catalyst for the hydrolysis of acetyl phosphate and the synthesis of pyrophosphate.[186]



33

No matter what type of host, the strongest attractions occur when combination with the guest causes the smallest amount of distortion of the host.[187] That is, a fully preorganized host will bind better than a host whose molecular shape must change in order to accommodate the guest.

3.C.iii. Inclusion Compounds

This type of addition compound is different from either the EDA complexes or the crown ether type of complexes previously discussed. Here, the host forms a crystal lattice that has spaces large enough for the guest to fit into. *van der Waals forces* constitute the only bonding between the host and the guest. There are two main types, depending on the shape of the space.[188] The spaces in *inclusion compounds* are in the shape of long tunnels or channels, while the other type, often called *clathrate*[189] or *cage compounds*, have spaces that are

[186] Hosseini, M.W.; Lehn, J.M. *J. Am. Chem. Soc.* ***1987***, *109*, 7047. For a discussion, see Mertes, M.P.; Mertes, K.B. *Acc. Chem. Res.* ***1990***, *23*, 413.

[187] See Cram, D.J. *Angew. Chem. Int. Ed.* ***1986***, *25*, 1039.

[188] See Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 1–3, Academic Press, NY, ***1984***; Weber, E. *Top. Curr. Chem.* ***1987***, *140*, 1; Gerdil, R. *Top. Curr. Chem.* ***1987***, *140*, 71; Mak, T.C.W.; Wong, H.N.C. *Top. Curr. Chem.* ***1987***, *140*, 141; Bishop, R.; Dance, I.G. *Top. Curr. Chem.* ***1988***, *149*, 137.

[189] For reviews, see Goldberg, I. *Top. Curr. Chem.* ***1988***, *149*, 1; Weber, E.; Czugler, M. *Top. Curr. Chem.* ***1988***, *149*, 45; MacNicol, D.D.; McKendrick, J.J.; Wilson, D.R. *Chem. Soc. Rev.* ***1978***, *7*, 65.

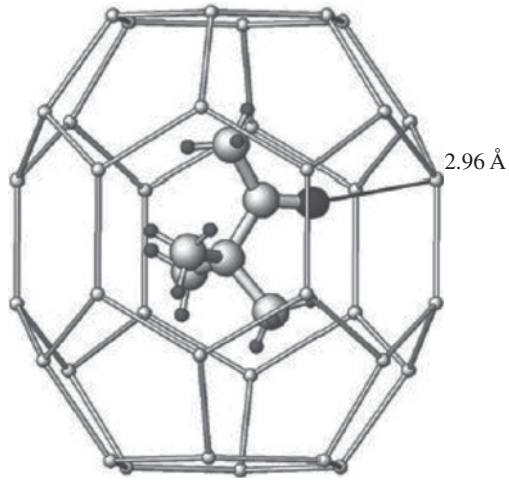


FIGURE 3.1. X-ray structure of pinacolone in a H_2S hexagonal clathrate hydrate cage molecule at 100 K.[192]
[Reprinted with permission from Alavi, S.; Udachin, K.; Ripmeester, J.A. *Chem. Eur. J.* ***2010****, 16*, 1017, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. Copyright © ***2010*** by Wiley-VCH Verlag.]

completely enclosed. In both types the guest molecule must fit into the space and potential guests that are too large or too small will not go into the lattice, so that the addition compound will not form. Such structures need not be restricted to large molecules. Indeed, the structure and stability of the hydrogen clathrate hydrate with cyclohexanone is known.[190]

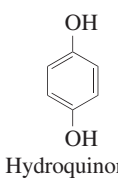
Several important host molecules are known, and inclusion compounds include small molecules such as urea.[191] Hydrogen sulfide forms hexagonal clathrate hydrate cages, and a guest molecule such as pinacolone, may be present, as shown in Figure 3.1.[192] Commonly, van der Waals forces between the host and the guest, while small, are essential to the stability of the structure. Which molecules can be a guest is usually dependent on their shapes and sizes and not necessarily on any electronic or chemical effects. For example, octane and 1-bromooctane are suitable guests for urea, but 2-bromooctane, 2-methylheptane, and 2-methyloctane are not. Also, both dibutyl maleate and dibutyl fumarate are guests; neither diethyl maleate or diethyl fumarate is a guest, but dipropyl fumarate is a guest and dipropyl maleate is not.[193] In these complexes, there is usually no integral molar ratio (though, by chance, there may be). For example, the octane/urea ratio is 1:6.73.[194] A deuterium quadrupole echo spectroscopy study of a urea complex showed that the urea molecules do not remain rigid, but undergo 180° flips about the C═O axis at the rate of more than 10^6 s^{-1} at 30 °C.[195]

The complexes are solids, but are not useful as derivatives, since they melt, with decomposition of the complex, at the melting point of urea. They are useful, however, in separating isomers that would be quite difficult to separate otherwise. Thiourea also forms inclusion

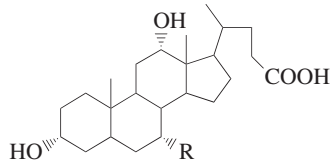
[190] Strobel, T.A.; Hester, K.C.; Sloan Jr., E.D.; Koh, C.A. *J. Am. Chem. Soc.* ***2007***, *129*, 9544.
[191] For a review of urea and thiourea inclusion compounds, see Takemoto, K.; Sonoda, N. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, ***1984***, pp. 47–67.
[192] Taken from Alavi, S.; Udachin, K.; Ripmeester, J.A. *Chem. Eur. J.* ***2010***, *16*, 1017.
[193] Radell, J.; Connolly, J.W.; Cosgrove Jr., W.R. *J. Org. Chem.* ***1961***, *26*, 2960.
[194] Redlich, O.; Gable, C.M.; Dunlop, A.K.; Millar, R.W. *J. Am. Chem. Soc.* ***1950***, *72*, 4153.
[195] Heaton, N.J.; Vold, R.L.; Vold, R.R. *J. Am. Chem. Soc.* ***1989***, *111*, 3211.

compounds though with channels of larger diameter, so that *n*-alkanes cannot be guests but, for example, 2-bromooctane, cyclohexane, and chloroform readily fit.

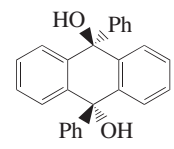
Hydroquinone is a useful host for clathrates.[196] Three molecules, held together by hydrogen bonding, make a cage in which fits one molecule of guest. Typical guests are methanol (but not ethanol), SO_2, CO_2, and argon (but not neon). One important use is the isolation of anhydrous hydrazine as a complex.[197] Anhydrous hydrazine is highly explosive, so preparation by distillation of aqueous hydrazine solutions is both difficult and dangerous. The inclusion complex can be readily isolated and reactions done in the solid state, such as the reaction with esters to give hydrazides (reaction **16-74**).[198] In contrast to the inclusion compounds, the crystal lattices here can exist partially empty. Another host is water. Usually six molecules of water form the cage and many guest molecules, among them Cl_2, propane, and methyl iodide, can fit. The water clathrates (see Figure 3.1), which are solids, can normally be kept only at low temperatures; at room temperature, they decompose.[198] Methane hydrate, which is a promising energy source that exists in vast quantities in the seabed of various oceans,[199] is an example of this type of clathrate. Another inorganic host is sodium chloride (and some other alkali halides), which can encapsulate organic molecules such as benzene, naphthalene, and diphenylmethane.[200]



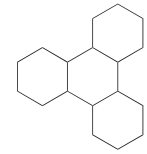
Hydroquinone

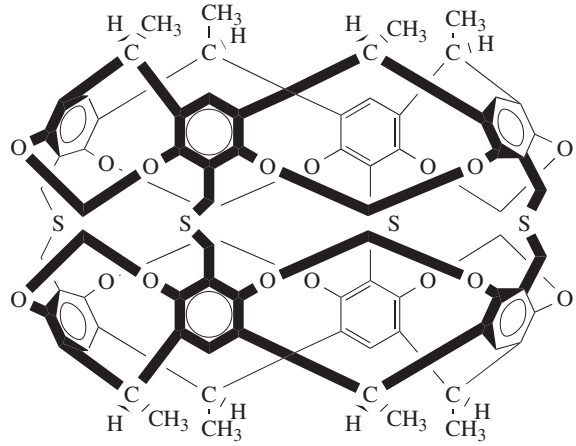


Cholic acid (R = OH)
Deoxycholic acid (R = H)



34


Perhydrotriphenylene


35

[196] For a review, see MacNicol, D.D. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, ***1984***, pp. 1–45.

[197] Toda, F.; Hyoda, S.; Okada, K.; Hirotsu, K. *J. Chem. Soc., Chem. Commun.* ***1995***, 1531.

[198] For a monograph on water clathrates, see Berecz, E.; Balla-Achs, M. *Gas Hydrates*; Elsevier, NY, ***1983***. For reviews, see Jeffrey, G.A. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 1, Academic Press, NY, ***1984***, pp. 135–190; Cady, G.H. *J. Chem. Educ.* ***1983***, *60*, 915.

[199] Sloan, E.D. *Clathrate Hydrate of Natural Gases*, Marcel Dekker, Inc., ***1998***.

[200] Kirkor, E.; Gebicki, J.; Phillips, D.R.; Michl, J. *J. Am. Chem. Soc.* ***1986***, *108*, 7106.

Among other hosts[201] for inclusion and/or clathrate compounds are deoxycholic acid,[202] cholic acid,[203] anthracene compounds, such as **34**,[204] dibenzo-24-crown-8,[205] and the compound **35**, which has been called a *carcerand*.[206] When carcerand-type molecules trap ions or other molecules (called guests), the resulting complex is called a carciplex.[207] It has been shown that in some cases, the motion of the guest within the carciplex is restricted.[208] Inclusion complexes with polycyclic aromatic hydrocarbons are possible with an "extended pyridinium-based, cage-like host ($ExCage^{6+}$) that contains a total of six π-electron-deficient pyridinium units connected in a pairwise fashion by three bridging *p*-xylylene linkers."[209] Crown ether-based cryptand/tropylium cation inclusion compounds are known.[210]

3.C.iv. Cyclodextrins

There is one type of host that can form both channel and cage complexes. This type is called *cyclodextrins* or *cycloamyloses*.[211] The host molecules are made up of six, seven, or eight glucose units connected in a large ring, called, respectively, α-, β-, or γ-cyclodextrin. Figure 3.2 shows the β or seven-membered ring compound.

The three molecules are in the shape of hollow truncated cones (Figure 3.3, top), with primary OH groups projecting from the narrow side of the cones and secondary OH groups from the wide side. As expected for carbohydrate molecules, all of them are soluble in water and the cavities normally fill with water molecules held in place by hydrogen bonds (6, 12, and 17 H_2O molecules for the α, β, and γ forms, respectively). However, the insides of the cones are less polar than the outsides, so that nonpolar organic molecules readily displace the water. The polarity of such cavities has been probed by a chemical reaction: the solvolysis of benzoyl halides (**16-56**).[212] Thus the cyclodextrins form 1:1 cage complexes

[201] See also, Toda, F. *Pure Appl. Chem.* ***1990***, *62*, 417, *Top. Curr. Chem.* ***1988***, *149*, 211; ***1987***, *140*, 43; Davies, J.E.; Finocchiaro, P.; Herbstein, F.H. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, ***1984***, pp. 407–453.

[202] For a review, see Giglio, E. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 2, Academic Press, NY, ***1984***, pp. 207–229.

[203] See Miki, K.; Masui, A.; Kasei, N.; Miyata, M.; Shibakami, M.; Takemoto, K. *J. Am. Chem. Soc.* ***1988***, *110*, 6594.

[204] Barbour, L.J.; Caira, M.R.; Nassimbeni, L.R. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 2321. Also see, Barbour, L.J.; Caira, M.R.; Nassimbeni, L.R. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 1413.

[205] Lämsä, M.; Suorsa, T.; Pursiainen, J.; Huuskonen, J.; Rissanen, K. *Chem. Commun.* ***1996***, 1443.

[206] Sherman, J.C.; Knobler, C.B.; Cram, D.J. *J. Am. Chem. Soc.* ***1991***, *113*, 2194.

[207] van Wageningen, A.M.A.; Timmerman, P.; van Duynhoven, J.P.M.; Verboom, W.; van Veggel, F.C.J.M.; Reinhoudt, D.N. *Chem. Eur. J.* ***1997***, *3*, 639; Place, D.; Brown, J.; Deshayes, K. *Tetrahedron Lett.* ***1998***, *39*, 5915. See also: Jasat, A.; Sherman, J.C. *Chem. Rev.* ***1999***, *99*, 931.

[208] Chapman, R.G.; Sherman, J.C. *J. Org. Chem.* ***2000***, *65*, 513.

[209] Dale, E.J.; Vermeulen, N.A.; Thomas, A.A.; Barnes, J.C.; Juríček, M.; Blackburn, A.K.; Strutt, N.L; Sarjeant, A.A.; Stern, C.L.; Denmark, S.E.; Stoddart, J.F. *J. Am. Chem. Soc.* ***2014***, *136*, 10669.

[210] Wu, X.; Li, J.; Yan, X.; Zhou, Q. *Tetrahedron.* ***2013***, *69*, 9573.

[211] See Bender, M.L.; Komiyama, M. *Cyclodextrin Chemistry*, Springer, NY, ***1978***. For reviews, see Crini, G. *Chem. Rev.* ***2014***, *114*, 10940; in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Academic Press, NY, ***1984***, the reviews, by Saenger, W. Vol. 2, 231–259, Bergeron, R.J. Vol. 3, 391–443, Tabushi, I. Vol. 3, 445–471, Breslow, R. Vol. 3, 473–508; Croft, A.P.; Bartsch, R.A. *Tetrahedron* ***1983***, *39*, 1417; Tabushi, I.; Kuroda, Y. *Adv. Catal.,* ***1983***, *32*, 417; Tabushi, I. *Acc. Chem. Res.* ***1982***, *15*, 66.

[212] García-Río, L.; Hall, R.W.; Mejuto, J.C.; Rodriguez-Dafonte, P. *Tetrahedron* ***2007***, *63*, 2208.

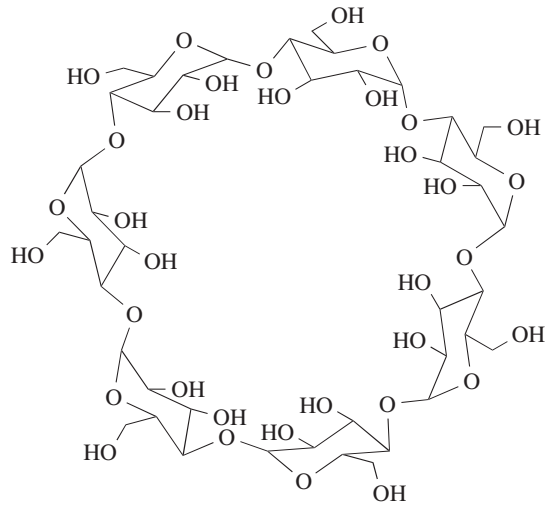


FIGURE 3.2. β-Cyclodextrin.

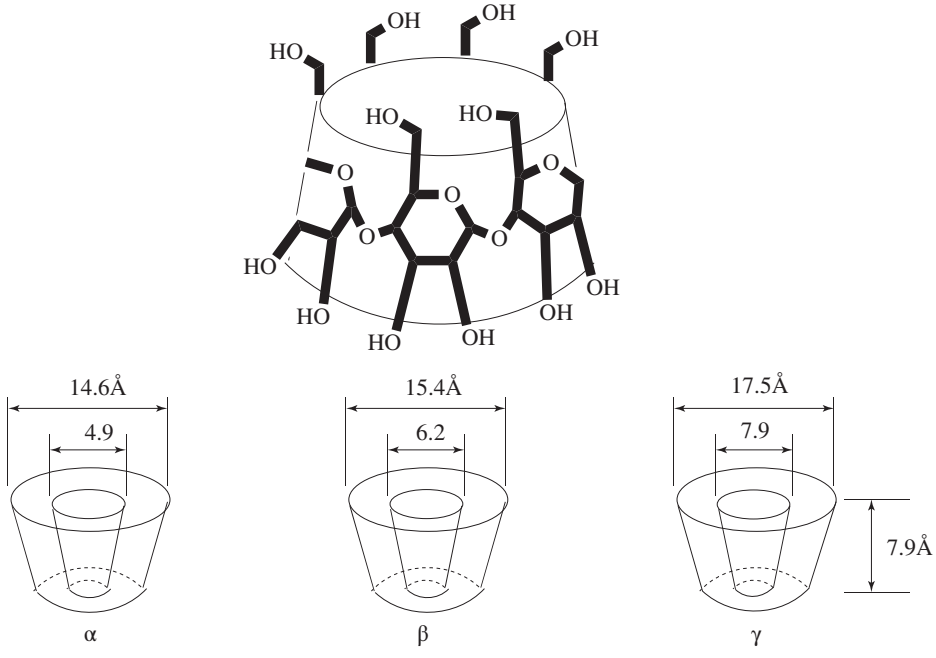


FIGURE 3.3. Shape and dimensions of the α-, β-, and γ-cyclodextrin molecules.[213]

with many guests, ranging in size from the noble gases to large organic molecules. A guest molecule must not be too large or it will not fit, though many stable complexes are known in which one end of the guest molecule protrudes from the cavity (Figure 3.4). On the other hand, if the guest is too small, it may go through the bottom hole (though some small polar

[213] Szejtli, J. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 3, Academic Press, NY, ***1984***, p. 332; Nickon, A.; Silversmith, E.F. *The Name Game*, Pergamon, Elmsford, NY, p. 235.

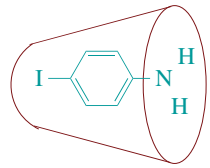


FIGURE 3.4. Schematic drawing of the complex of α-cyclodextrin and *p*-iodoaniline.[214]

molecules, e.g., methanol, do form complexes in which the cavity also contains some water molecules). Since the cavities of the three cyclodextrins are of different sizes (see Figure 3.3), a large variety of guests can be accommodated. As cyclodextrins are nontoxic (they are actually small starch molecules), they are now used industrially to encapsulate foods and drugs.[215]

The cyclodextrins also form channel-type complexes, in which the host molecules are stacked on top of each other, like coins in a row.[216] For example, α-cyclodextrin (cyclohexaamylose) forms cage complexes with acetic, propionic, and butyric acids, but channel complexes with valeric and higher acids. Capped cyclodextrins are known.[217]

3.D. CATENANES AND ROTAXANES[218]

A [2]-catenane A [3]-catenane A rotaxane

These compounds contain two or more independent portions that are not bonded to each other by any valence forces but nevertheless must remain linked. [*n*]*Catenanes* (where *n* corresponds to the number of linked rings) are made up of two or more rings held together as links in a chain, while in *rotaxanes* a linear portion is threaded through a ring[219] and cannot get away because of bulky end groups. Among several types of bulky molecular units, porphyrin units have been used to cap rotaxanes[220] as have C_{60} fullerenes.[221] [2]Rotaxanes, including large [2]rotaxanes,[222] and [2]catenanes are quite common, and [3]catenanes

[214] Modified from Saenger, W.; Beyer, K.; Manor, P.C. *Acta Crystallogr. Sect. B* ***1976***, *32*, 120.
[215] For reviews, see Pagington, J.S. *Chem. Br.,* ***1987***, *23*, 455; Szejtli, J. in Atwood, J.L.; Davies, J.E.; MacNicol, D.D. *Inclusion Compounds*, Vol. 3, Academic Press, NY, ***1984***, 331–390.
[216] See Saenger, W. *Angew. Chem. Int. Ed.* ***1980***, *19*, 344.
[217] Engeldinger, E.; Armspach, D.; Matt, D. *Chem. Rev.* ***2003***, *103*, 4147.
[218] For a monograph, see Schill, G. *Catenanes, Rotaxanes, and Knots*, Academic Press, NY, ***1971***. For a review, see Schill, G. in Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, ***1971***, pp. 229–239.
[219] For a discussion of the kinetic barriers for threading/dethreading, see Carrasco-Ruiz, A.; Tiburcio, J. *Org. Lett.* ***2015***, *17*, 1858.
[220] Solladié, N.; Chambron, J.-C.; Sauvage, J.-P. *J. Am. Chem. Soc.* ***1999***, *121*, 3684.
[221] Sasabe, H.; Kihara, N.; Furusho, Y.; Mizuno, K.; Ogawa, A.; Takata, T. *Org. Lett.* ***2004***, *6*, 3957.
[222] Saito, S.; Takahashi, E.; Wakatsuki, K.; Inoue, K.; Orikasa, T.; Sakai, K.; Yamasaki, R.; Mutoh, Y.; Kasama, T. *J. Org. Chem.* ***2013***, *78*, 3553.

are known, having rather robust amide linkages.[223] Triply threaded [4]rotaxanes have been prepared.[224] A ferrocene-based [1]rotaxane is known.[225] Biscalix[4]arene derivatives have been used as gelators for oil-spill recovery.[226] More intricate variants, such as oligocatenanes,[227] molecular necklaces (a cyclic oligorotaxane in which a number of small rings are threaded onto a large ring),[228] and cyclic daisy chains (an interwoven chain in which each monomer unit acts as a donor and an acceptor for a threading interaction)[229] are known. Ring-in-ring complexes have also been reported.[230] Molecular thread, ribbon, and belt assemblies have been synthesized,[231] as have molecular dirotors.[232] Rotaxanes have been used as the basis for molecular switches,[233] and a rotaxane exciplex has been generated that may have applications to molecular-scale photonic devices.[234] A bistable symmetric [2](2)rotaxane was prepared and molecular dynamics simulations were carried out both in protonated (stretched) and in neutral (contracted) forms.[235] "The system can mimic the stretching and contractional molecular motion performed by skeletal muscle accompanied by a molecular rotary motion in response to external acid−base stimuli."[li2014] Such compounds often form the basis of molecular machines.[236] Liquid crystalline catenanes and rotaxanes are known.[237]

Transitional isomers are possible in [2]rotaxanes.[238] Catenanes and rotaxanes can be prepared by statistical methods or directed syntheses.[239] Catenanes can contain heteroatoms and heterocyclic units. In some cases, the catenane exists in equilibrium with the cyclic–non-catenane structures and in some cases this exchange is thought to proceed by ligand exchange and a Möbius-strip mechanism.[240] An example of a statistical synthesis of a

[223] Iwamoto, H.; Takizawa, W.; Itoh, K.; Hagiwara, T.; Tayama, E.; Hasegawa, E.; Haino, T. *J. Org. Chem.* ***2013***, *78*, 5205. See Zhao, Y.; Li, Y.; Lai, S.-W.;Yang, J.; Liu, C.; Lium H.; Che, C.-M.; Li, Y. *Org. Biomol. Chem.* ***2011***, *9*, 7500.

[224] Danon, J.J.; Leigh, D.A.; McGonigal, P.R.; Ward, J.W.; Wu, J. *J. Am. Chem. Soc.* ***2016***, *138*, 12643.

[225] Li, H.; Zhang, H.; Zhang, Q.; Zhang, Q.-W.; Qu, D.-H. *Org. Lett.* ***2012***, *14*, 5900.

[226] Tsai, C.-C.; Cheng, Y.-T.; Shen, L.-C.; Chang, K.-C.; Ho, I.-T.; Chu, J.-H.; Chung, W.-S. *Org. Lett.* ***2013***, *15*, 5830.

[227] Amabilino, D.B.; Ashton, P.R.; Balzani, V.; Boyd, S.E.; Credi, A.; Lee, J.Y.; Menzer, S.; Stoddart, J.F.; Venturi, M.; Williams, D.J. *J. Am. Chem. Soc.* ***1998***, *120*, 4295.

[228] Chiu, S.-H.; Rowan, S.J.; Cantrill, S.J.; Ridvan, L.; Ashton, R.P.; Garrell, R.L.; Stoddart, J.-F. *Tetrahedron* ***2002***, *58*, 807; Roh, S.-G.; Park, K.-M.; Park, G.-J.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem. Int. Ed.* ***1999***, *38*, 638.

[229] See Onagi, H.; Easton, C.J.; Lincoln, S.F. *Org. Lett.* ***2001***, *3*, 1041; Cantrill, S.J.; Youn, G.J.; Stoddart, J.F.; Williams, D.J. *J. Org. Chem.* ***2001***, *66*, 6857. See Bozdemir, O.A.; Barin, G.; Belowich, M.E.; Basuray, A.N.; Beuele, F.; Stoddart, J.F. *Chem. Commun.* ***2012***, *48*, 10401.

[230] Chiu, S.-H.; Pease, A.R.; Stoddart, J.F.; White, A.J.P.; Williams, D.J. *Angew. Chem. Int. Ed.* ***2002***, *41*, 270.

[231] Schwierz, H.; Vögtle, F. *Synthesis* ***1999***, 295.

[232] Hughs, M.; Jimenez, M.; Khan, S.; Garcia-Garibay, M.A. *J. Org. Chem.* ***2013***, *78*, 5293.

[233] Elizarov, A.M.; Chiu, S.-H.; Stoddart, J.-F. *J. Org. Chem.* ***2002***, *67*, 9175.

[234] MacLachlan, M.J.; Rose, A.; Swager, T.M. *J. Am. Chem. Soc.* ***2001***, *123*, 9180.

[235] Erbas-Cakmak, S.; Leigh, D.A.; McTernan, C.T.; Nussbaumer, A.L. *Chem. Rev.* ***2015***, *115*, 10081; Li, H.; Li, X.; Wu, Y.; Ågren, H.; Qu, D.-H. *J. Org. Chem.* ***2014***, *79*, 6996.

[236] Zerbetto, F. *Angew. Chem. Int. Ed.* ***2013***, *52*, 7917.

[237] Sakuda, J.; Yasuda, T.; Kato, T. *Isr J. Chem.* ***2012***, *52*, 854.

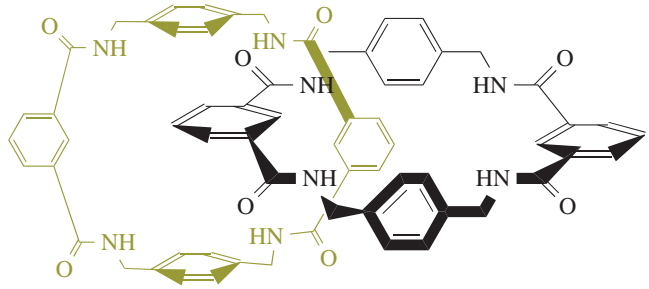
[238] Amabilino, D.B.; Ashton, P.R.; Boyd, S.E.; Gómez-López, M.; Hayes, W.; Stoddart, J.F. *J. Org. Chem.* ***1997***, *62*, 3062.

[239] For discussions, see Schill, G. *Catenanes, Rotaxanes, and Knots*, Academic Press, NY, ***1971***. For a review, see Schill, G. in Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, ***1971***, pp. 229–239; Walba, D.M. *Tetrahedron* ***1985***, *41*, 3161.

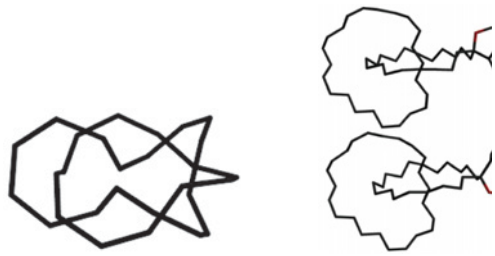
[240] Fujita, M.; Ibukuro, F.; Seki, H.; Kamo, O.; Imanari, M.; Ogura, K. *J. Am. Chem. Soc.* ***1996***, *118*, 899.

rotaxane is a reaction where a compound **A** is bonded at two positions to another compound **B** in the presence of a large ring **C**. It is hoped that some **A** molecules would by chance be threaded through **C** before combining with the two **B** molecules, so that some rotaxane (**D**) would be formed along with the normal product **E**.[241] In a directed synthesis,[242] the separate parts of the molecule are held together by other bonds that are later cleaved.

Rotation of one unit through the other catenanes is complex,[243] often driven by making and breaking key hydrogen bonds or π–π interactions.[244] In the case of the isophthaloyl [2]catenane, **36**, the rate-determining steps do not necessarily correspond to the passage of the bulkiest groups.[245]



36



37 **38**

Singly and doubly interlocked [2]catenanes[246] can exist as *topological stereoisomers*[247] (Sec. 4.G). Catenanes **37** and **38** are such stereoisomers, and would be expected to have

[241] See Schill, G.; Beckmann, W.; Schweikert, N.; Fritz, H. *Chem. Ber.* ***1986***, *119*, 2647. See also, Agam, G.; Graiver, D.; Zilkha, A. *J. Am. Chem. Soc.* ***1976***, *98*, 5206.
[242] For a synthesis of a rotaxane, see Schill, G.; Zürcher, C.; Vetter, W. *Chem. Ber.* ***1973***, *106*, 228.
[243] Bauer, J.; Hou, L.; Kistemaker, J.C.M.; Feringa, B.L. *J. Org. Chem.* ***2014***, *79*, 4446.
[244] Stepwise motion in [2](3)catenanes has been reported. See Meng, Z.; Han, Y.; Wang, L.-N.; Xiang, J.-F.; He, S.-G.; Chen, C.-F. *J. Am. Chem. Soc.* ***2015***, *137*, 9739.
[245] Deleuze, M.S.; Leigh, D.A; Zerbetto, F. *J. Am. Chem. Soc.* ***1999***, *121*, 2364.
[246] For the synthesis of a doubly interlocking [2]catenane, see Ibukuro, F.; Fujita, M.; Yamaguchi, K.; Sauvage, J.-P. *J. Am. Chem. Soc.* ***1999***, *121*, 11014.
[247] See Lukin, O.; Godt, A.; Vögtle, F. *Chem. Eur. J.,* ***2004***, *10*, 1879.

identical mass spectra. Analysis showed that **37** is more constrained and cannot readily accommodate an excess of energy during the mass spectrometry ionization process and, hence, breaks more easily. Neutral [2]catenanes with sliding interlocked electron-rich rings have been prepared.[248]

Catenanes, molecular knots, and other molecules in these structural categories can exist as enantiomers. In other words, stereoisomers can be generated in some cases. This phenomenon was first predicted by Frisch and Wassermann,[249] and the first stereoisomeric catenanes and molecular knots were synthesized by Sauvage et al.[250] Enantiomeric resolution has been achieved.[251] A chiral rotaxane containing two achiral wheels, mechanically bonded, has been reported,[252] generating a cyclodiastereomeric compound, and the enantiomers were separated using chiral HPLC. The terms "cycloenantiomerism" and "cyclodiastereomerism" were introduced by Prelog and co-workers.[253] This type of stereoisomerism occurs in cyclic arrangements of several centrally chiral elements in combination with an orientation of the macrocycle.[252] A self-assembled, metal-organic [3]rotaxane has been reported.[254] "Molecular turnstiles, composed of two stators with pyridyl binding sites and a different-sized triptycene rotor have been synthesized."[255] Other molecular rotors are known.[256]

A rotaxane can also be an inclusion compound.[257] Such molecules contain bulky end groups (or "stoppers" such as triisopropylsilyl groups, $i\text{-Pr}_3\text{Si}—$) and a chain that consists of a series of $—O—CH_2CH_2—O—$ groups, but also contains two benzene rings. Cyclodextrins have been threaded onto axle molecules.[258] The ring (or "bead") around the chain is a macrocycle containing two benzene rings and four pyridine rings, and is preferentially attracted to one of the benzene rings in the chain. The benzene moiety serves as a "station" for the "bead." However, symmetry of the chain can make the two "stations" equivalent, so that the "bead" is equally attracted to them, and the "bead" actually moves back and forth rapidly between the two "stations," as shown by the temperature dependence of the NMR spectrum.[259] This molecule has been called a *molecular shuttle*. A copper(I)-complexed

[248] Fernando, I.R.; Frasconi, M.; Wu, Y.; Liu, W.-G.; Wasielewski, M.R.; Goddard III, W.A.; Stoddart, J.F. *J. Am. Chem. Soc.* ***2016***, *138*, 10214. Also see Li, Z.; Liu, W.; Wu, J.; Liu, S.-H.; Yin, J. *J. Org. Chem.* ***2012***, *77*, 7129–7135.

[249] Frisch, H.L.; Wasserman, E. *J. Am. Chem. Soc.* ***1961***, *83*, 3789.

[250] *Molecular Catenanes, Rotaxanes and Knots* (ed. Sauvage, J.-P.; Dietrich-Buchecker, C.O.) Wiley-VCH, Weinheim, ***1999***; Ashton, P.R.; Bravo, J.A.; Raymo, F.M.; Stoddart, J.F.; White, A.J.P.; Williams, D.J. *Eur. J. Org. Chem.* ***1999***, 899; Chen, C.-T.; Gantzel, P.; Siegel, J.S.; Baldridge, K.K.; English, R.B.; Ho, D.M. *Angew. Chem. Int. Ed.* ***1995***, *34*, 2657.

[251] Kaida, T.; Okamoto, Y.; Chambron, J.-C.; Mitchell, D.K.; Sauvage, J.-P. *Tetrahedron Lett.* ***1993***, *34*, 1019.

[252] Schmieder, R.; Hübner, G.; Seel, C.; Vögtle, F. *Angew. Chem. Int. Ed.* ***1999***, *38*, 3528.

[253] Prelog, V.; Gerlach, H. *Helv. Chim. Acta* ***1964***, *47*, 2288; Gerlach, H.; Owtischinnkow, J.A.; Prelog, V. *Helv. Chim. Acta* ***1964***, *47*, 2294; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, ***1994***, pp. 1176–1181; Chorev, M.; Goodman, M. *Acc. Chem. Res.* ***1993***, *26*, 266; Mislow, K. *Chimia* ***1986***, *40*, 395.

[254] Yang, Y.-D.; Fan, C.-C.; Rambo, B.M.; Gong, H.-Y.; Xu, L.-J.; Xiang, J.-F.; Sessler, J.L. *J. Am. Chem. Soc.* ***2015***, *137*, 12966.

[255] Wang, G.; Xiao, H.; He, J.; Xiang, J.; Wang, Y.; Chen, X.; Che, Y.; Jiang, H. *J. Org. Chem.* ***2016***, *81*, 3364.

[256] Dial, B.E.; Rasberry, R.D.; Bullock, B.N.; Smith, M.D.; Pellechia, P.J.; Profeta Jr., S.; Shimizu, K.D. *Org. Lett.* ***2011***, *13*, 244.

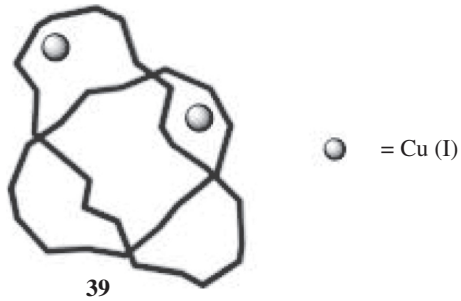
[257] For an example, see Anelli, P.L.; Spencer, N.; Stoddart, J.F. *J. Am. Chem. Soc.* ***1991***, *113*, 5131.

[258] Oshikiri, T.; Takashima, Y.; Yamaguchi, H.; Harada, A. *J. Am. Chem. Soc.* ***2005***, *127*, 12186.

[259] Anelli, P.L.; Spencer, N.; Stoddart, J.F. *J. Am. Chem. Soc.* ***1991***, *113*, 5131. For a review of the synthesis and properties of molecules of this type, see Philp, D.; Stoddart, J.F. *Synlett* ***1991***, 445.

rotaxane has been prepared with two fullerene (see Sec. 2.L) stoppers.[260] DNA rotaxanes are known,[261] as are hetero[*n*]rotaxanes.[262] Gyrotops are macrocage molecules with a bridged π-electron system that can rotate within the cage.[263] Rotocatenanes are known.[264]

Another variation of these molecules are called molecular knots,[265] such as **39**, where the ○ represents a metal [in this case, copper(I)].[266] This is particularly interesting since knotted forms of deoxyribonucleic acid (DNA) have been reported.[267] There are mechanically interlocked molecules, and one example is known as suit[2]ane.[268]



39

3.E. CUCURBIT[*n*]URIL-BASED GYROSCANE

A molecule called gyroscane has been proposed as a new supramolecular form.[269] The cucurbit[*n*]urils, abbreviated Q_n (**40**),[270] are condensation products of glycoluril and formaldehyde[271] that can act as molecular hosts. This "supramolecular form is one in which a smaller macrocycle, Q5, is located inside a larger macrocycle, Q10, with facile rotation of one relative to the other in solution (see **41**).[269] The image of a ring rotating independently inside another ring, which resembles a gyroscope, suggests the name gyroscane for this

[260] Diederich, F.; Dietrich-Buchecker, C.O.; Nierengarten, S.-F.; Sauvage, J.-P. *J. Chem. Soc., Chem. Commun.* ***1995***, 781.

[261] Ackermann, D.; Schmidt, T. L.; Hannam, J. S.; Purohit, C. S.; Heckel, A.; Famulok, M. *Nat. Nanotechnol.* ***2010***, *5*, 436; Lohmann, F.; Ackermann, D.; Famulok, M. *J. Am. Chem. Soc.* ***2012***, *134*, 11884.

[262] Li, Z.; Liu, G.; Xue, W.; Wu, D.; Yang, Y.-W.; Wu, J.; Liu, S.H.; Yoon, J.; Yin, J. *J. Org. Chem.* ***2013***, *78*, 11560; Fa, S.-X.; Wang, L.-X.; Wang, D.-X.; Zhao, L.; Wang, M.-X. *J. Org. Chem.* ***2014***, *79*, 3559; Chen, P.-N.; Lai, C.-C.; Chiu, S.-H. *Org. Lett.* ***2011***, *13*, 4660.

[263] Nishiyama, Y.; Inagaki, Y.; Yamaguchi, K.; Setaka, W. *J. Org. Chem.* ***2015***, *80*, 9959.

[264] Xue, W.; Li, Z.; Li, G.; Chen, X.; Li, T.; Liu, T.L.; Yin, J. *Org. Biomol. Chem.* ***2014***, *12*, 4862.

[265] For an example of a trefoil knot, see Ayme, J.-F.; Gil-Ramírez, G.; Leigh, D.A.; Lemonnier, J.-F.; Markevicius, A.; Muryn, C.A.; Zhang, G. *J. Am. Chem. Soc.* ***2014***, *136*, 13142.

[266] Dietrich-Buchecker, C.O.; Nierengarten, J.-F.; Sauvage, J.-P. *Tetrahedron Lett.* ***1992***, *33*, 3625. See Dietrich-Buchecker, C.O.; Guilhem, J.; Pascard, C.; Sauvage, J.-P. *Angew. Chem. Int. Ed.* ***1990***, *29*, 1154.

[267] Liu, L.F.; Depew, R.E.; Wang, J.C. *J. Mol. Biol.* ***1976***, *106*, 439.

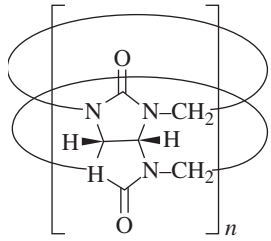
[268] Williams, A.R.; Northrop, B.N.; Chang, T.; Stoddart, J.F.; White, A.J.P.; Williams, D.J. *Angew. Chem. Int. Ed.* ***2006***, *45*, 6665.

[269] Day, A.I.; Blanch, R.J.; Arnold, A.P.; Lorenzo, S.; Lewis, G.R.; Dance, I. *Angew. Chem. Int. Ed.* ***2002***, *41*, 275.

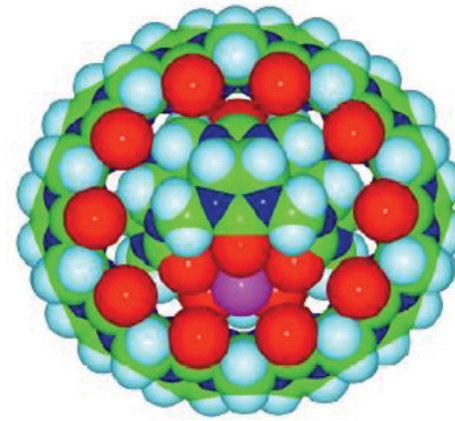
[270] Mock, W.L. *Top. Curr. Chem.* ***1995***, *175*, 1; Mock, W.L. in *Comprehensive Supramolecular Chemistry, Vol. 2* (ed. Atwood, J.L.; Davies, J.E.D.; MacNicol, D.D.; Vogtle, F.), Pergamon, Oxford, ***1996***, pp. 477–493; Day, A.; Arnold, A.P.; Blanch, R.J.; Snushall, B. *J. Org. Chem.* ***2001***, *66*, 8094. For cucurbit[10]uril, see Liu, S.; Zavalij, P.Y.; Isaacs, L. *J. Am. Chem. Soc.* ***2005***, *127*, 16798.

[271] See Barrow, S.J.; Kasera, S.; Rowland, M.J.; del Barrio, J.; Scherman, O.A. *Chem. Rev.* ***2015***, *115*, 12320.

new class of supramolecular system."[270] A hemimethyl-substituted cucurbit[7]uril has been prepared.[272] New, tunable, luminescent materials based on a cucurbit[8]uril supermolecular approach have been developed.[273] Supramolecular cages from aryl-bisimidazolium compounds and cucurbit[8]uril have also been developed.[274] Cucurbit[8]uril rotaxanes are known.[275]



40



41

[Reprinted with permission from Day, A.I.; Blanch, R.J.; Arnold, A.P.; Lorenzo, S.; Lewis, G.R.; Dance, I. *Angew. Chem. Int. Ed.* ***2002****, 41,* 275, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. Copyright © ***2002*** by Wiley-VCH Verlag]

[272] Zhao, W.-Z.; Wang, C.-Z.; Chen, L.-X.; Cong, H.; Xiao, X.; Zhang, Y.-Q.; Xue, S.-F.; Huang, Y.; Tao, Z.; Zhu, Q.-J. *Org. Lett.* ***2015***, *17*, 5072.

[273] Ni, X.-L.; Chen, S.; Yang, Y. Tao, Z. *J. Am. Chem. Soc.* ***2016***, *138*, 6177.

[274] Jiao, D.; Biedermann, F.; Scherman, O.A. *Org. Lett.* ***2011***, *13*, 3044.

[275] Ramalingam, V.; Urbach, A.R. *Org. Lett.* ***2011***, *13*, 4898. See also Senler, S.; Cheng, B.; Kaifer A.E. *Org. Lett.* ***2014***, *16*, 5834; Huang, X.; Huang, S.; Zhai, B.; Zhang, Y.; Xu, Y.; Wang, Q. *Tetrahedron Lett.* ***2012***, *53*, 6414.

CHAPTER 4

Stereochemistry and Conformation

The discussion in chapters 1–3 focused on electron distribution in organic molecules. In this chapter, the focus will be on the 3D structure of organic compounds.[1] The structure may be such that *stereoisomerism*[2] is possible. Stereoisomers are compounds made up of the same atoms bonded by the same sequence of bonds but having different 3D structures that are not interchangeable. These structures are called *configurations*.

4.A. OPTICAL ACTIVITY AND CHIRALITY[3]

Any material that rotates the plane of polarized light is said to be *optically active*.[4] If a pure compound is optically active, the molecule is nonsuperimposable on its mirror image. If a molecule is superimposable on its mirror image, the two structures constitute the same compound. Such a compound does not rotate the plane of polarized light; it is *optically inactive*. The property of nonsuperimposability of an object on its mirror image is called *chirality*. If a molecule is not superimposable on its mirror image, it is *chiral*. If it is superimposable on its mirror image, it is *achiral*. The relationship between optical activity and chirality is absolute. No exceptions are known, and many thousands of cases have been found in accord with it (however, see 4.C). The ultimate criterion, then, for optical activity is chirality (*nonsuperimposability on the mirror imag*e). *This criterion is both a necessary and a sufficient condition*.[5] This fact has been used as evidence for the structure determination of many compounds, and historically the tetrahedral nature of carbon was deduced

[1] See Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***; Sokolov, V.I. *Introduction to Theoretical Stereochemistry*, Gordon and Breach, NY, ***1991***; Nógrádi, M. *Stereochemistry*, Pergamon, Elmsford, NY, ***1981***; Kagan, H. *Organic Sterochemistry*, Wiley, NY, ***1979***; Testa, B. *Principles of Organic Stereochemistry*, Marcel Dekker, NY, ***1979***; Izumi, Y.; Tai, A. *Stereo-Differentiating Reactions*, Academic Press, NY, Kodansha Ltd.: Tokyo, ***1977***; Natta, G.; Farina, M. *Stereochemistry*, Harper and Row, NY, ***1972***; Eliel, E.L. *Elements of Stereochemistry*, Wiley, NY, ***1969***; Mislow, K. *Introduction to Stereochemistry*, W.A. Benjamin, NY, ***1965***. For a historical treatment, see Ramsay, O.B. *Stereochemistry*, Heyden & Son, Ltd., London, ***1981***.

[2] See *Pure Appl. Chem.* ***1976***, *45*, 13 and in *Nomenclature of Organic Chemistry*, Pergamon, Elmsford, NY, ***1979*** (the "Blue Book"). See, however, Fujita, S. *Bull. Chem. Soc. Jpn.* ***2014***, *87*, 1367.

[3] See Cintas, P. *Angew. Chem. Int. Ed.* ***2007***, *46*, 4016.

[4] For a discussion of Hückel theory and optical activity, see Murphy, V.L.; Kahr, B. *J. Am. Chem. Soc.* ***2015***, *137*, 5177.

[5] For a discussion of the conditions for optical activity in liquids and crystals, see O'Loane, J.K. *Chem. Rev.* ***1980***, *80*, 41. For a discussion of chirality as applied to molecules, see Quack, M. *Angew. Chem. Int. Ed.* ***1989***, *28*, 571.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

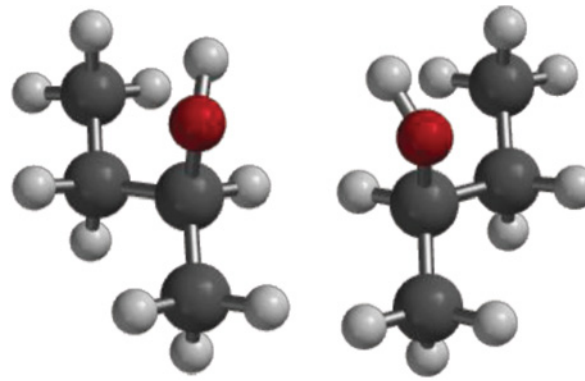


FIGURE 4.1. Enantiomers of butan-2-ol.

from the hypothesis that the relationship might be true. Note that parity violation represents an essential property of particle and atomic handedness, and has been related to chirality.[6]

If a molecule is nonsuperimposable on its mirror image, the mirror image must be a different molecule, since superimposability is the same as identity. In each case of optical activity of a pure compound there are two and only two isomers, called *enantiomers* (sometimes *enantiomorphs*), which differ in structure only in the left- and right-handedness of their orientations (see the enantiomers for butan-2-ol in Figure 4.1). Enantiomers have identical[7] physical and chemical properties, except in two important respects:

1. Enantiomers rotate the plane of polarized light in opposite directions, although in equal amounts. The isomer that rotates the plane to the left (counterclockwise) is called the *levo* isomer and is designated (−), while the one that rotates the plane to the right (clockwise) is called the *dextro* isomer and is designated (+). Because they differ in this property they are often called *optical antipodes*.
2. They may react at different rates with other chiral compounds. These rates may be so close together that the distinction is practically useless, or they may be so far apart that one enantiomer undergoes the reaction at a convenient rate while the other does not react at all. This is the reason that many compounds are biologically active while their enantiomers are not. Enantiomers react at the same rate with achiral compounds.[8]

In general, it may be said that enantiomers have identical properties in a symmetrical environment, but their properties may differ in an unsymmetrical environment.[9] Besides the important differences previously noted, enantiomers may react at different rates with achiral molecules if an optically active *catalyst* is present; they may have different solubilities in an

[6] Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J.L.; Palacios, J.C. *Tetrahedron Asymmetry* ***2000***, *11*, 2845.

[7] Interactions between electrons, nucleons, and certain components of nucleons (e.g., bosons), called *weak interactions*, violate parity; that is, mirror image interactions do not have the same energy. It has been contended that interactions of this sort cause one of a pair of enantiomers to be (slightly) more stable than the other. See Tranter, G.E. *J. Chem. Soc., Chem. Commun.* ***1986***, 60, and references cited therein. See also, Barron, L.D. *Chem. Soc. Rev.* ***1986***, *15*, 189.

[8] For a reported exception, see Hata, N. *Chem. Lett.* ***1991***, 155.

[9] See Craig, D.P.; Mellor, D.P. *Top. Curr. Chem.* ***1976***, *63*, 1.

optically active *solvent*; they may have different indexes of refraction or absorption spectra *when examined with circularly polarized light*, etc. In most cases these differences are too small to be useful and are often too small to be measured.

Although pure compounds are always optically active if they are composed of chiral molecules, mixtures of equal amounts of enantiomers are optically inactive since the equal and opposite rotations cancel. Such mixtures are called *racemic mixtures*[10] or *racemates*.[11] Their properties are not always the same as those of the individual enantiomers. The properties in the gaseous or liquid state or in solution usually are the same, since such a mixture is nearly ideal, but properties involving the solid state,[12] such as melting points, solubilities, and heats of fusion, are often different. Thus racemic tartaric acid has a melting point of 204–206 °C and a solubility in water at 20 °C of 206 g L^{-1} while for the (+) or the (−) enantiomer, the corresponding figures are 170 °C and 1390 g L^{-1}. The separation of a racemic mixture into its two optically active components is called *resolution*. The presence of optical activity always proves that a given compound is chiral, but its absence does not prove that the compound is achiral. A compound that is optically inactive may be achiral, or it may be a racemic mixture (see also, Sec. 4.C).

It has been reported that molecules with and without aromatic resonance structure representations, in tautomers, and in certain other compounds, aromaticity is correlated to diminished optical activity.[13]

4.B. DEPENDENCE OF ROTATION ON CONDITIONS OF MEASUREMENT

The *amount* of rotation α is not a constant for a given enantiomer; it depends on the length of the sample vessel, the temperature, the solvent[14] and concentration (for solutions), the pressure (for gases), and the wavelength of light.[15] Of course, rotations determined for the same compound under the same conditions are identical. The length of the vessel and the concentration or pressure determine the number of molecules in the path of the beam, and α is linear with this. To make it possible for one value of α for a pure compound to be compared with another α for that compound taken under different circumstances, a physical property is defined, called the *specific rotation* [α], which is

$$[\alpha] = \frac{\alpha}{lc} \quad \text{for solutions and } [\alpha] = \frac{\alpha}{ld} \quad \text{for pure compounds}$$

where α is the observed rotation, l is the cell length in decimeters, c is the concentration in grams per milliliter, and d is the density in the same units. The specific rotation is usually given along with the temperature and wavelength of light used for the measurement, in this manner: $[\alpha]_{546}^{25}$, where the superscript is the temperature in °C and the subscript is the

[10] Strictly speaking, the term *racemic mixture* applies only when the mixture of molecules is present as separate solid phases, but in this book this expression refers to any equimolar mixture of enantiomeric molecules, whether liquid, solid, gaseous, or in solution.

[11] See Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers*, *Racemates*, *and Resolutions*, Wiley, NY, ***1981***.

[12] See Wynberg, H.; Lorand, J.P. *J. Org. Chem.* ***1981***, *46*, 2538 and references cited therein.

[13] Murphy, V.L.; Reyes, A.; Kahr, B. *J. Am. Chem. Soc.* ***2016***, *138*, 25.

[14] For an example, see Kumata, Y.; Furukawa, J.; Fueno, T. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 3920.

[15] For a review of polarimetry see Lyle, G.G.; Lyle, R.E. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 13–27.

wavelength in nm. These conditions must be duplicated for comparison of rotations, since there is no way to put them into a simple formula. The expression $[\alpha]_D$ means that the rotation was measured with sodium D light; that is, $\lambda = 589$ nm. The *molar rotation* $[M]^t_\lambda$ is the specific rotation multiplied by the molecular weight and divided by 100.

It must be emphasized that the value of α changes with conditions, but the molecular structure is unchanged, even when the changes in conditions are sufficient to change not only the amount of rotation but even the direction. Thus one of the enantiomers of aspartic acid, when dissolved in water, has $[\alpha]_D$ equal to +4.36° at 20 °C and −1.86° at 90 °C, but the molecular structure is unchanged. A consequence of such cases is that there is a temperature at which there is *no* rotation (e.g., 75 °C for aspartic acid). Of course, the other enantiomer exhibits the opposite behavior.

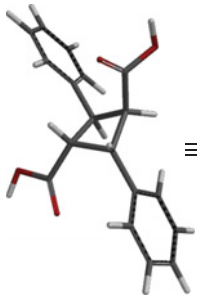
Other cases are known in which the direction of rotation is reversed by changes in wavelength, solvent, and even concentration.[16] In theory, there should be no change in [α] with concentration, since concentration is taken into account in the formula, but associations, dissociations, and solute–solvent interactions often cause nonlinear behavior. For example, $[\alpha]^{24}_D$ for (−)-2-ethyl-2-methylsuccinic acid in $CHCl_3$ is −5.0° at $c = 16.5$ g/100 mL (0.165 g/mL), −0.7° at $c = 10.6$, +1.7° at $c = 8.5$, and +18.9° at $c = 2.2$.[17] Note that the concentration is sometimes reported in g/100 mL (as shown) or as g/dL (deciliters) rather than the standard g/mL. One should always check the concentration term to be certain. Note that calculation of the optical rotation of (*R*)-(−)-3-chlorobut-1-ene found a remarkably large dependence on the C═C─C─C torsional angle.[18] However, the observed rotations are a factor of 2.6 smaller than the calculated values, independent of both conformation and wavelength from 589 to 365 nm.

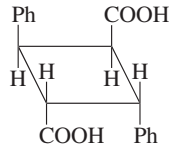
4.C. WHAT KINDS OF MOLECULES DISPLAY OPTICAL ACTIVITY?

Although the ultimate criterion is, of course, nonsuperimposability on the mirror image (chirality), other tests may be used that are simpler to apply but not always accurate. One such test is the presence of a *plane of symmetry*.[19] A plane of symmetry[20] (also called a *mirror plane*) is a plane passing through an object such that the part on one side of the plane is the exact reflection of the part on the other side (the plane acting as a mirror). *Compounds possessing such a plane are always optically inactive*, but there are a few cases known in which compounds lack a plane of symmetry and are nevertheless inactive. Such compounds possess a *center of symmetry*, such as in α-truxillic acid, or an *alternating axis of symmetry*, as in **1**.[21] A center of symmetry[20] is a point within an object such that a straight line drawn from any part or element of the object to the center and extended an equal distance on the other side encounters an equal part or element. An alternating axis of symmetry[20] of order *n* is an axis such that when an object containing such an axis is rotated by 360°/*n* about the

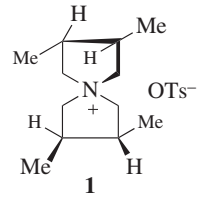
[16] For examples, see Shriner, R.L.; Adams, R.; Marvel, C.S. in Gilman, H. *Advanced Organic Chemistry*, vol 1, 2nd ed., Wiley, NY, ***1943***, pp. 291–301.
[17] Krow, G.; Hill, R.K. *Chem. Commun.* ***1968***, 430.
[18] Wiberg, K.B.; Vaccaro, P.H.; Cheeseman, J.R. *J. Am. Chem. Soc.* ***2003***, *125*, 1888.
[19] See Barron L.D. *Chem. Soc. Rev.* ***1986***, *15*, 189.
[20] The definitions of plane, center, and alternating axis of symmetry are taken from Eliel, E.L. *Elements of Stereochemistry*, Wiley, NY, ***1969***, pp. 6,7. See also, Lemière, G.L.; Alderweireldt, F.C. *J. Org. Chem.* ***1980***, *45*, 4175.
[21] McCasland, G.E.; Proskow, S. *J. Am. Chem. Soc.* ***1955***, *77*, 4688.

axis and then reflection is effected across a plane at right angles to the axis, a new object is obtained that is indistinguishable from the original one. Compounds that lack an alternating axis of symmetry are always chiral.

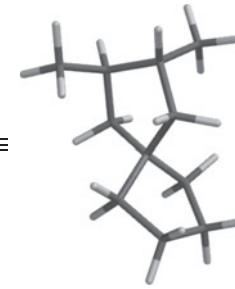




α-truxillic acid



1



A molecule that contains just one *stereogenic carbon atom* (defined as a carbon atom connected to four different groups; also called a *chiral atom or* an *asymmetric carbon atom*) is always chiral, and hence is optically active.[22] As seen in Figure 4.1, such a molecule *cannot* have a plane of symmetry, whatever the identity of W, X, Y, and Z, as long as they are all different. However, optical activity may be present in molecules with no stereogenic atom.[23] Some molecules with two or more stereogenic carbon atoms, however, are superimposable on their mirror images (these are called *meso* compounds) and hence are inactive principally because there is symmetry.

Optically active compounds may be classified into several categories.

1. *Compounds with a stereogenic carbon atom*. If there is only one such atom, the molecule must be optically active, no matter how slight the differences are among the four groups. An example is 1,12-dibromo-6-methyldodecane, which has one stereogenic carbon and will be optically active. Optical activity has been detected even in cases[24] such as butan-1-ol-1-*d*, where one group is hydrogen and another deuterium:[25] the stereogenic carbon is connected to OH, H, D, and a propyl group.

   Although enantiomers will exhibit specific rotation of equal magnitude but opposite sign, the difference may be too small to be measured accurately. In optically active compounds, the amount of rotation is greatly dependent on the nature of the four groups, in general increasing with increasing differences in polarizabilities among the groups. Alkyl groups have very similar polarizabilities[26] and the optical activity of 5-ethyl-5-propylundecane is too low to be measurable at any wavelength between 280 and 580 nm.[27]

[22] For discussions of the relationship between a chiral carbon and chirality, see Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* ***1984***, *106*, 3319; Brand, D.J.; Fisher, J. *J. Chem. Educ.* ***1987***, *64*, 1035.

[23] For a review of such molecules, see Nakazaki, M. *Top. Stereochem.* ***1984***, *15*, 199.

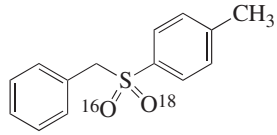
[24] See Barth, G.; Djerassi, C. *Tetrahedron* ***1981***, *24*, 4123; Verbit, L. *Prog. Phys. Org. Chem.* ***1970***, *7*, 51; Floss, H.G.; Tsai, M.; Woodard, R.W. *Top. Stereochem.* ***1984***, *15*, 253.

[25] Streitwieser Jr., A.; Schaeffer, W.D. *J. Am. Chem. Soc.* ***1956***, *78*, 5597.

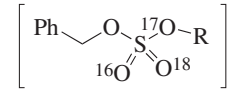
[26] For a discussion of optical activity in paraffins, see Brewster, J.H. *Tetrahedron* ***1974***, *30*, 1807.

[27] Ten Hoeve, W.; Wynberg, H. *J. Org. Chem.* ***1980***, *45*, 2754.

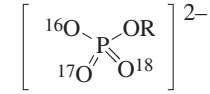
2. *Compounds with other quadrivalent stereogenic atoms*.[28] Any molecule with an atom that has four bonds pointing to the corners of a tetrahedron will be optically active if the four groups are different. Among atoms in this category are Si,[29] Ge, Sn,[30] and N (in quaternary salts or *N*-oxides).[31] In sulfones, the sulfur bonds have a tetrahedral array, but since two of the groups are always oxygen, no chirality results. However, the preparation[32] of an optically active sulfone (**2**) in which one oxygen is ^{16}O and the other ^{18}O illustrates the point that slight differences in groups are all that is necessary. This point has been taken even further with the preparation of the ester **3**, both enantiomers of which have been prepared.[33] Optically active chiral phosphates **4** have similarly been made.[34]



2



3



4

3. *Compounds with tervalent stereogenic atoms*. Atoms with pyramidal bonding[35] might be expected to give rise to optical activity if the atom is connected to three different groups, since the unshared pair of electrons is analogous to a fourth group, necessarily different from the others. A secondary or tertiary amine where X, Y, and Z are different and the fourth group is the electron pair would be expected to be chiral and thus resolvable. Many attempts have been made to resolve such compounds, but until 1968 all of them failed because of *pyramidal inversion* (also called *fluxional inversion*), which is a rapid oscillation of the unshared pair from one side of the XYZ plane to the other, thus converting the molecule into its enantiomer.[36] For ammonia there are 2×10^{11} inversions every second. The inversion is less rapid in substituted ammonia derivatives[37] (amines, amides, etc.). The interconversion barrier for *endo* versus *exo* methyl in *N*-methyl-2-azabicyclo[2.2.1]heptane, for example, is

[28] For compounds with asymmetric atoms other than carbon, see Aylett, B.J. *Prog. Stereochem.* ***1969***, *4*, 213; Belloli, R. *J. Chem. Educ.* ***1969***, *46*, 640; Sokolov, V.I.; Reutov, O.A. *Russ. Chem. Rev.* ***1965***, *34*, 1.

[29] See Corriu, R.J.P.; Guérin, C.; Moreau, J.J.E. in Patai, S.; Rappoport, Z. *The Chemistry of Organic Silicon Compounds*, pt. 1, Wiley, NY, ***1989***, pp. 305–370, *Top. Stereochem.* ***1984***, *15*, 43; Maryanoff, C.A.; Maryanoff, B.E. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 4, Academic Press, NY, ***1984***, pp. 355–374.

[30] See Gielen, M. *Top. Curr. Chem.* ***1982***, *104*, 57; *Top. Stereochem.* ***1981***, *12*, 217.

[31] See Davis, F.A.; Jenkins Jr., R.H. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 4, Academic Press, NY, ***1984***, pp. 313–353; Pope, W.J.; Peachey, S.J. *J. Chem. Soc.* ***1899***, *75*, 1127.

[32] Stirling, C.J.M. *J. Chem. Soc.* ***1963***, 5741; Sabol, M.A.; Andersen, K.K. *J. Am. Chem. Soc.* ***1969***, *91*, 3603; Annunziata, R.; Cinquini, M.; Colonna, S. *J. Chem. Soc., Perkin Trans. 1* ***1972***, 2057.

[33] Lowe, G.; Parratt, M.J. *J. Chem. Soc., Chem. Commun.* ***1985***, 1075.

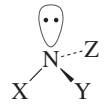
[34] Abbott, S.J.; Jones, S.R.; Weinman, S.A.; Knowles, J.R. *J. Am. Chem. Soc.* ***1978***, *100*, 2558; Cullis, P.M.; Lowe, G. *J. Chem. Soc., Chem. Commun.* ***1978***, 512. See Lowe, G. *Acc. Chem. Res.* ***1983***, *16*, 244.

[35] For a review of the stereochemistry at trivalent nitrogen, see Raban, M.; Greenblatt, J. in Patai, S. *The Chemistry of Functional Groups*, *Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 53–83.

[36] See Lambert, J.B. *Top. Stereochem.* ***1971***, *6*, 19; Rauk, A.; Allen, L.C.; Mislow, K. *Angew. Chem. Int. Ed.* ***1970***, *9*, 400; Lehn, J.M. *Fortschr. Chem. Forsch.* ***1970***, *15*, 311.

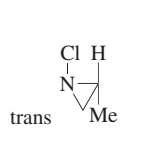
[37] See Stackhouse, J.; Baechler, R.D.; Mislow, K. *Tetrahedron Lett.* ***1971***, 3437, 3441.

0.3 kcal mol^{-1} (1.26 kJ mol^{-1}).[38] In this case, torsional strain plays a significant role, along with angle strain, in determining inversion barriers.

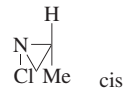


N-Methyl-2-azabicyclo[2.2.1]heptane

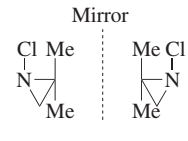
Two types of nitrogen atom invert particularly slowly, namely, a nitrogen atom in a three-membered ring and a nitrogen atom connected to another atom bearing an unshared pair. Even in such compounds, however, pyramidal inversion proved too rapid to permit isolation of separate isomers for many years. This goal was accomplished[31] only when compounds were synthesized in which both features are combined: a nitrogen atom in a three-membered ring connected to an atom containing an unshared pair. For example, the two isomers of 1-chloro-2-methylaziridine (**5** and **6**) were separated and do not interconvert at room temperature.[39] In suitable cases, this barrier to inversion can result in compounds that are optically active solely because of a chiral tervalent nitrogen atom. For example, **7** has been resolved into its separate enantiomers.[40] Note that in this case too, the nitrogen is connected to an atom with an unshared pair. Conformational stability has also been demonstrated for oxaziridines,[41] diaziridines (e.g., **8**),[42] triaziridines (e.g. **9**),[43] and 1,2-oxazolidines (e.g., **10**),[44] even although in this case the ring is five-membered. However, note that the nitrogen atom in **10** is connected to two oxygen atoms.



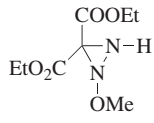
5



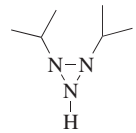
6



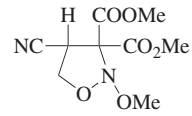
7



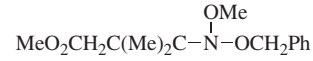
8



9



10



11

[38] Forsyth, D.A.; Zhang, W.; Hanley, J.A. *J. Org. Chem.* ***1996***, *61*, 1284. Also see, Adams, D.B. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 567.

[39] Brois, S.J. *J. Am. Chem. Soc.* ***1968***, *90*, 506, 508. See also, Shustov, G.V.; Kadorkina, G.K.; Kostyanovsky, R.G.; Rauk, A. *J. Am. Chem. Soc.* ***1988***, *110*, 1719; Lehn, J.M.; Wagner, J. *Chem. Commun.* ***1968***, 148; Felix, D.; Eschenmoser, A. *Angew. Chem. Int. Ed.* ***1968***, *7*, 224. For a review, see Brois, S.J. *Trans. N.Y. Acad. Sci.* ***1969***, *31*, 931.

[40] Schurig, V.; Leyrer, U. *Tetrahedron: Asymmetry* ***1990***, *1*, 865.

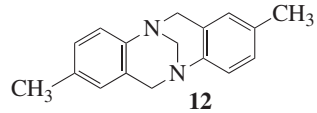
[41] Bucciarelli, M.; Forni, A.; Moretti, I.; Torre, G.; Brückner, S.; Malpezzi, L. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 1595; Forni, A.; Schmitz, E. *Adv. Heterocycl. Chem.* ***1979***, *24*, 63.

[42] Shustov, G.V.; Denisenko, S.N.; Chervin, I.I.; Asfandiarov, N.L.; Kostyanovsky, R.G. *Tetrahedron* ***1985***, *41*, 5719 and cited references.

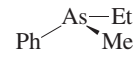
[43] Hilpert, H.; Hoesch, L.; Dreiding, A.S. *Helv. Chim. Acta* ***1985***, *68*, 1691; ***1987***, *70*, 381.

[44] See Wu, G.; Huang, M. *Chem. Rev.* ***2006***, *106*, 2596.

Compound **11** is another example in which nitrogen is connected to two oxygen atoms. In this case there is no ring at all, but it has been resolved into (+) and (−) enantiomers ($[\alpha]_D^{20} \approx \pm 3°$).[45] This compound and several similar ones reported in the same paper are the first examples of compounds whose optical activity is solely due to an acyclic tervalent chiral nitrogen atom. However, **11** is not optically stable and racemizes at 20 °C with a half-life of 1.22 hours. A similar compound (**11**, with OCH_2Ph replaced by OEt) has a longer half-life, 37.5 hours at 20 °C.



12



13

For molecules in which the nitrogen atom is at a bridgehead, pyramidal inversion is of course prevented. Such molecules, if chiral, can be resolved even without the presence of the two structural features noted above. For example, optically active **12** (*Tröger's base*) has been prepared.[46] Phosphorus inverts more slowly and arsenic still more slowly.[47] Nonbridgehead phosphorus,[48] arsenic, and antimony compounds have also been resolved, for example, **13**.[49] Sulfur exhibits pyramidal bonding in sulfoxides, sulfinic esters, sulfonium salts, and sulfites.

Examples of each of these have been resolved.[50] An interesting example is (+)-$Ph^{12}CH_2SO^{13}CH_2Ph$, a sulfoxide in which the two alkyl groups differ only in ^{12}C versus ^{13}C, but which has $[\alpha]_{280} = +0.71°$.[51] A computational study indicates that base-catalyzed inversion at sulfur in sulfoxides is possible via a tetrahedral intermediate.[52]

4. *Suitably substituted adamantanes*. Adamantanes bearing four different substituents at the bridgehead positions are chiral and optically active and **14**, for example, has

[45] Kostyanovsky, R.G.; Rudchenko, V.F.; Shtamburg, V.G.; Chervin, I.I.; Nasibov, S.S. *Tetrahedron* ***1981***, *37*, 4245; Kostyanovsky, R.G.; Rudchenko, V.F. *Doklad. Chem.* ***1982***, *263*, 121. See also, Rudchenko, V.F.; Ignatov, S.M.; Chervin, I.I.; Kostyanovsky, R.G. *Tetrahedron* ***1988***, *44*, 2233.

[46] Prelog, V.; Wieland, P. *Helv. Chim. Acta* ***1944***, *27*, 1127.

[47] For reviews, see Yambushev, F.D.; Savin, V.I. *Russ. Chem. Rev.* ***1979***, *48*, 582; Gallagher, M.J.; Jenkins, I.D. *Top. Stereochem.* ***1968***, *3*, 1; Kamai, G.; Usacheva, G.M. *Russ. Chem. Rev.* ***1966***, *35*, 601.

[48] See Valentine Jr., D.J. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 4, Academic Press, NY, ***1984***, pp. 263–312.

[49] Horner, L.; Fuchs, H. *Tetrahedron Lett.* ***1962***, 203.

[50] See Andersen, K.K. in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 55–94; and in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, pt. 1, Wiley, NY, ***1981***, pp. 229–312; Barbachyn, M.R.; Johnson, C.R. in Morrison, J.D. *Asymmetric Synthesis* Vol. 4, Academic Press, NY, ***1984***, pp. 227–261; Cinquini, M.; Cozzi, F.; Montanari, F. in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, ***1985***, pp. 355–407; Mikołajczyk, M.; Drabowicz, J. *Top. Stereochem.* ***1982***, *13*, 333.

[51] Andersen, K.K.; Colonna, S.; Stirling, C.J.M. *J. Chem. Soc., Chem. Commun.* ***1973***, 645.

[52] Balcells, D.; Maseras, F.; Khiar, N. *Org. Lett.* ***2004***, *6*, 2197.

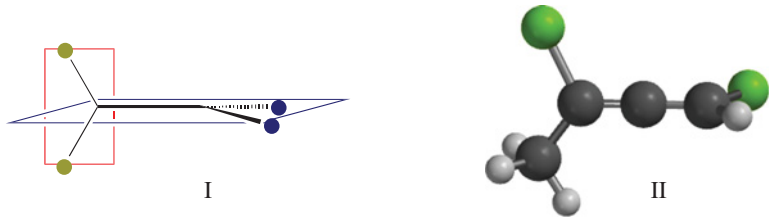
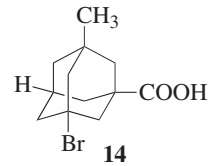


FIGURE 4.2. Perpendicular dissymmetric planes and a chiral molecule with no stereogenic center.

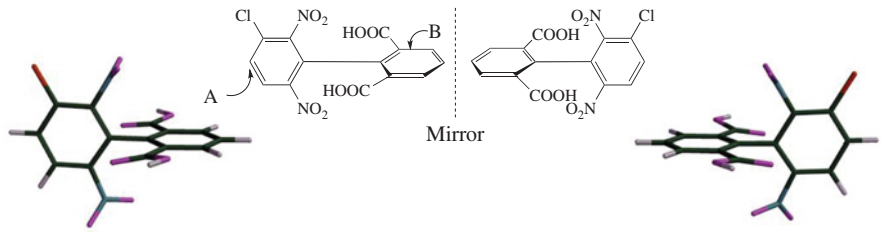
been resolved.[53] This type of molecule is a kind of expanded tetrahedron and has the same symmetry properties as any other tetrahedron.



14

5. *Restricted rotation giving rise to perpendicular disymmetric planes*. Certain compounds that do not contain asymmetric atoms are nevertheless chiral, as illustrated in Figure 4.2. For such compounds there are two perpendicular planes (see **I**), neither of which can be bisected by a plane of symmetry (as illustrated by **II**). If either plane could be so bisected, the molecule would be superimposable on its mirror image, since such a plane would be a plane of symmetry.

   Biphenyls that contain four large groups in the ortho positions cannot freely rotate about the central bond because of steric hindrance.[54] For example, the activation energy (rotational barrier) for the enantiomerization process of the chiral 2-carboxy-2′-methoxy-6-nitrobiphenyl was determined, $\Delta G^{\ddagger} = 21.8 \pm 0.1$ kcal mol^{-1} (91.3 ± 0.1 kJ mol^{-1}).[55] In such compounds the two rings are in perpendicular planes. If either ring is symmetrically substituted, the molecule has a plane of symmetry. For example, consider the biaryl, 2-carboxy-6-carboxy-6-nitro-6′-nitrobiphenyl:

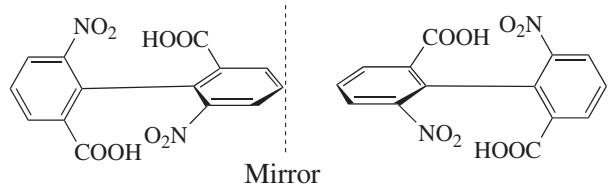


[53] Hamill, H.; McKervey, M.A. *Chem. Commun.* ***1969***, 864; Applequist, J.; Rivers, P.; Applequist, D.E. *J. Am. Chem. Soc.* ***1969***, *91*, 5705.

[54] When the two rings of a biphenyl are connected by a bridge, rotation is of course impossible. For a review of such compounds, see Hall, D.M. *Prog. Stereochem.* ***1969***, *4*, 1. For a discussion of the factors that control the stereochemistry of biphenyl, see Jia, J.; Wu, H.-S.; Chen, Z.; Mo, Y. *Eur. J. Org. Chem.* ***2013***, 611.

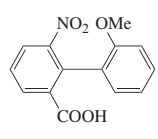
[55] Ceccacci, F.; Mancini, G.; Mencarelli, P.; Villani, C. *Tetrahedron Asymmetry* ***2003***, *14*, 3117.

Ring B is symmetrically substituted. A plane drawn perpendicular to ring B contains all the atoms and groups in ring A; hence, it is a plane of symmetry and the compound is achiral. On the other hand, consider 2-carboxy-6-nitro-2′-carboxy-6′-nitrobiphenyl:

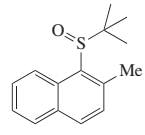


In this molecule there is no plane of symmetry and the molecule is chiral; many such compounds have been resolved. Note that groups in the para position cannot cause lack of symmetry. Isomers that can be separated only because rotation about single bonds is prevented or greatly slowed are called *atropisomers*.[56] 9,9′-Bianthryls also show hindered rotation and exhibit atropisomers.[57] Low-temperature NMR is sometimes used to detect atropisomers in certain systems (1,2,4,5-tetra(*o*-tolyl)benzene, for example).[58] Configurationally stable atropisomers are known.[59]

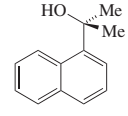
It is not always necessary for four large ortho groups to be present in order for rotation to be prevented. Compounds with three and even two groups, if large enough, can have hindered rotation and, if suitably substituted, can be resolved. An example is biphenyl-2,2′-bis-sulfonic acid.[60] In some cases, the groups may be large enough to slow rotation greatly but not to prevent it completely. In such cases, optically active compounds can be prepared that slowly racemize on standing. Thus, **15** loses its optical activity with a half-life of 9.4 min in ethanol at 25 °C.[61] Compounds with greater rotational stability can often be racemized if higher temperatures are used to supply the energy necessary to force the groups past each other.[62]



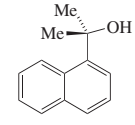
15



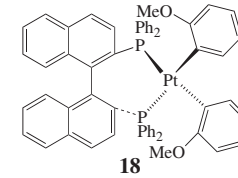
16



17a



17b

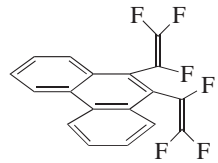


18

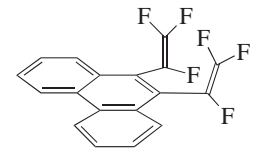
[56] For a review, see Öki, M. *Top. Stereochem.* ***1983***, *14*, 1. Also see Miljanić, O.S.; Han, S.; Holmes, D.; Schaller, G.R.; Vollhardt, K.P.C. *Chem. Commun.* ***2005***, 2606.
[57] Becker, H.-D.; Langer, V.; Sieler, J.; Becker, H.-C. *J. Org. Chem.* ***1992***, *57*, 1883.
[58] Lunazzi, L.; Mazzanti, A.; Minzoni, M. *J. Org. Chem.* ***2005***, *70*, 10062.
[59] Casarini, D.; Coluccini, C.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* ***2005***, *70*, 5098.
[60] Patterson, W.I.; Adams, R. *J. Am. Chem. Soc.* ***1935***, *57*, 762.
[61] Stoughton, R.W.; Adams, R. *J. Am. Chem. Soc.* ***1932***, *54*, 4426.
[62] See Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***.

Atropisomerism occurs in other systems as well,[63] including monopyrroles.[64] Sulfoxide **16**, for example, forms atropisomers with an interconversion barrier with its atropisomer of 18–19 kcal mol^{-1} (75.4–79.5 kJ mol^{-1}).[65] The atropisomers of hindered naphthyl alcohols such as **17** exist as the *sp*-atropisomer (**17a**) and the *ap*-atropisomer (**17b**).[66] Atropisomers can also be formed in organometallic compounds, such as the *bis*-phosphinoplatinum complex (see **18**) generated by reaction with R-BINAP (see **19-36**).[67]

It is possible to isolate isomers in some cases, often due to restricted rotation. In 9,10-bis-(trifluorovinyl)phenanthrene (**19**), torsional diastereomers (Sec. 4.G) are formed. The value of K for interconversion of **19a** and **19b** is 0.48, with $\Delta G^\circ = 15.1$ kcal mol^{-1} (63.2 kJ mol^{-1}).[68] The ability to isolate atropisomers can depend on interactions with solvent, as in the isolation of atropisomeric colchicinoid alkaloids, which have been isolated, characterized, and their dichroic behavior described.[69]



19a



19b

In allenes, the central carbon is *sp* hybridized. The remaining two *p* orbitals are mutually perpendicular so that each overlaps with the *p* orbital of one adjacent carbon atom, forcing the two remaining bonds of each carbon into perpendicular planes. Thus allenes fall into the category represented by Figure 4.2. Like biphenyls, allenes are chiral *only* if both sides are unsymmetrically substituted.[70] These cases are completely different from the *cis–trans* isomerism of compounds with one double bond (Sec. 4.K). In the latter cases, the four groups are all in one plane, the isomers are not enantiomers, and neither is chiral, while in allenes the groups are in two perpendicular planes and the isomers are a pair of optically active enantiomers. Chiral allenes have been used for chirality transfer reactions.[71]

[63] For a discussion of the photochemistry of non-biaryl atropisomers, see Clay, A.; Kumarasamy, E.; Ayitou, A.J.-L.; Sivaguru, J. *Chem. Lett.* ***2014***, *43*, 1816.

[64] Boiadjiev, S.E.; Lightner, S.A. *Tetrahedron Asymmetry* ***2002***, *13*, 1721.

[65] Casarini, D.; Foresti, E.; Gasparrini, F.; Lunazzi, L.; Macciantelli, D.; Misiti, D.; Villani, C. *J. Org. Chem.* ***1993***, *58*, 5674.

[66] See Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev.* ***2005***, *105*, 1801. For a review of BINOL, see Brunel, J.M. *Chem. Rev.* ***2005***, *105*, 857.

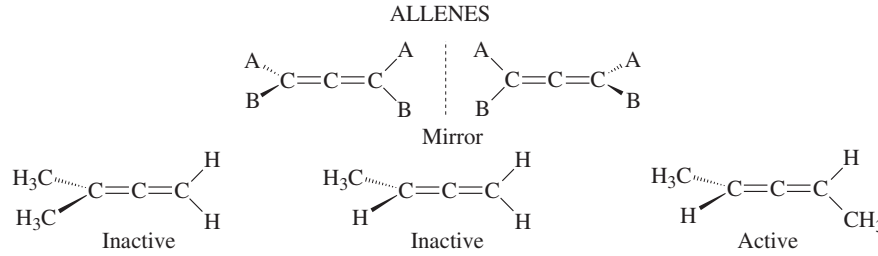
[67] Alcock, N.W.; Brown, J.M.; Pérez-Torrente, J.J. *Tetrahedron Lett.* ***1992***, *33*, 389. See also, Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J.J.; Yamanaka, M. *Synlett* ***2002***, 1561.

[68] Dolbier Jr., W.R.; Palmer, K.W. *Tetrahedron Lett.* ***1992***, *33*, 1547.

[69] Cavazza, M.; Zandomeneghi, M.; Pietra, F. *Tetrahedron Lett.* ***2000***, *41*, 9129.

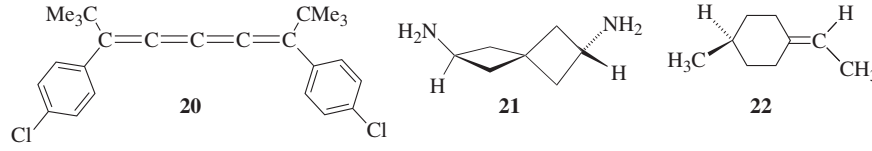
[70] For reviews of allene chirality, see Runge, W. in Landor, S.R. *The Chemistry of the Allenes*, Vol. 3, Academic Press, NY, ***1982***, pp. 579–678, and in Patai, S. *The Chemistry of Ketenes, Allenes, and Related Compounds*, pt. 1, Wiley, NY, ***1980***, pp. 99–154; Rossi, R.; Diversi, P. *Synthesis* ***1973***, 25.

[71] Neff, R.K.; Frantz, D.E. *Tetrahedron* ***2015***, *71*, 7.



When a molecule has three, five, or any *odd* number of cumulative double bonds, orbital overlap causes the four groups to occupy one plane and *cis–trans* isomerism is observed. When four, six, or any *even* number of cumulative double bonds exist, the situation is analogous to that in the allenes and optical activity is possible. Compound **20** has been resolved.[72]

Other types of compounds that contain the system illustrated in Figure 4.2 and that are similarly chiral if both sides are dissymmetric include spiranes, e.g., **21**, and compounds with exocyclic double bonds, e.g., **22**. Atropisomerism exists in (1,5)-bridged calix[8]arenes (Sec. 3.C.ii).[73]

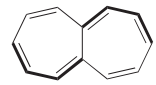


6. *Chirality due to a helical shape*.[74] Several compounds have been prepared that are chiral because they have a shape that is actually helical and can therefore be left-handed or right-handed in orientation. The entire molecule is usually less than one full turn of the helix, but this does not alter the possibility of left- and right-handedness. An example is hexahelicene,[75] in which one side of the molecule must lie above the other because of crowding.[76] The rotational barrier for helicene is about 22.9 kcal mol^{-1} (95.9 kJ mol^{-1}), and significantly higher when substituents are present,[77] and it has been shown that the dianion of helicene retains its chirality.[78] Chiral discrimination of helicenes is possible.[79] 1,16-Diazo[6]helicene has also been prepared and, interestingly, does not act as a proton sponge (Sec. 8.F) because the helical structure leaves the basic nitrogen atoms too far apart. Heptalene is another

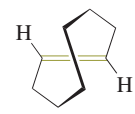
[72] Nakagawa, M.; Shingū, K.; Naemura, K. *Tetrahedron Lett.* ***1961***, 802.
[73] Consoli, G.M.L.; Cunsolo, F.; Geraci, C.; Gavuzzo, E.; Neri, P. *Org. Lett.* ***2002***, *4*, 2649.
[74] For a review, see Meurer, K.P.; Vögtle, F. *Top. Curr. Chem.* ***1985***, *127*, 1. See also, Laarhoven, W.H.; Prinsen, W.J.C. *Top. Curr. Chem.* ***1984***, *125*, 63; Martin, R.H. *Angew. Chem. Int. Ed.* ***1974***, *13*, 649. For stereocontrol in the synthesis of a fully aromatic helicene, see Šámal, M; Chercheja, S.; Rybáček, J.; Chocholoušová, J.V.; Vacek, J.; Bednárová, L.; Šaman, D.; Stará, I.G.; Starý, I. *J. Am. Chem. Soc.* ***2015***, *137*, 8469.
[75] Martin, R.H.; Baes, M. *Tetrahedron* ***1975***, *31*, 2135; Martin, R.H. *Bull. Soc. Chim. Belg.* ***1984***, *93*, 313; Bestmann, H.J.; Roth, W. *Chem. Ber.* ***1974***, *107*, 2923.
[76] For reviews of the helicenes, see Laarhoven, W.H.; Prinsen, W.J.C. *Top. Curr. Chem.* ***1984***, *125*, 63; Martin, R.H. *Angew. Chem. Int. Ed.* ***1974***, *13*, 649.
[77] Janke, R.H.; Haufe, G.; Würthwein, E.-U.; Borkent, J.H. *J. Am. Chem. Soc.* ***1996***, *118*, 6031.
[78] Frim, R.; Goldblum, A.; Rabinovitz, M. *J. Chem. Soc., Perkin Trans. 2* ***1992***, 267.
[79] Murguly, E.; McDonald, R.; Branda, N.R. *Org. Lett.* ***2000***, *2*, 3169.

compound that is not planar (Sec. 2.I.iii). The twisted structure makes heptalene chiral, but the enantiomers rapidly interconvert.[80]

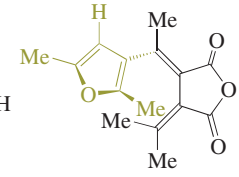
Hexahelicene



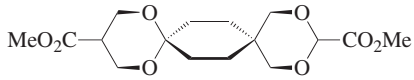
Heptalene



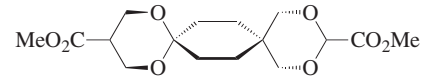
trans-Cyclooctene



23



24a



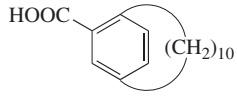
24b

trans-Cyclooctene (see also 4.K.i) also exhibits helical chirality because the carbon chain must lie above the double bond on one side and below it on the other.[81] Similar helical chirality also appears in fulgide, **23**,[82] and dispiro-1,3-dioxane, **24**, shows two enantiomers, **24a** and **24b**.[83]

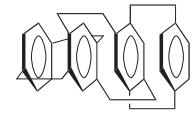
7. *Optical activity caused by restricted rotation of other types*. Substituted paracyclophanes may be optically active[84] and **25**, for example, has been resolved.[85] In this case, chirality results because the benzene ring cannot rotate in such a way that the carboxyl group goes through the alicyclic ring. Compound **25** has been prepared in optically active form[86] and is another case where chirality is due to isotopic substitution. Many chiral layered cyclophanes (e.g., **26**) have been prepared,[87] as well as cyclophanes with planar and helical chirality.[88] Another cyclophane[89] with a different type of chirality is [12][12]paracyclophane (**27**), where the chirality arises from the relative orientation of the two rings attached to the central benzene ring.[90] An acetylenic cyclophane was shown to have helical chirality.[91] Metallocenes (Sec. 2.I.ii) substituted with at least two different groups on one ring are also chiral.[92] Several hundred such compounds have been resolved, one being **28**. Chirality is

[80] Staab, H.A.; Diehm, M.; Krieger, C. *Tetrahedron Lett.* ***1994***, *35*, 8357.
[81] Cope, A.C.; Ganellin, C.R.; Johnson Jr., H.W.; Van Auken, T.V.; Winkler, H.J.S. *J. Am. Chem. Soc.* ***1963***, *85*, 3276. Also see, Levin, C.C.; Hoffmann, R. *J. Am. Chem. Soc.* ***1972***, *94*, 3446.
[82] Yokoyama, Y.; Iwai, T.; Yokoyama, Y.; Kurita, Y. *Chem. Lett.* ***1994***, 225.
[83] Grosu, I.; Mager, S.; Plé, G.; Mesaros, E. *Tetrahedron* ***1996***, *52*, 12783.
[84] For an example, see Rajakumar, P.; Srisailas, M. *Tetrahedron* ***2001***, *57*, 9749.
[85] Blomquist, A.T.; Stahl, R.E.; Meinwald, Y.C.; Smith, B.H. *J. Org. Chem.* ***1961***, *26*, 1687. For a review of chiral cyclophanes and related molecules, see Schlögl, K. *Top. Curr. Chem.* ***1984***, *125*, 27.
[86] Lightner, D.A.; Paquette, L.A.; Chayangkoon, P.; Lin, H.; Peterson, J.R. *J. Org. Chem.* ***1988***, *53*, 1969.
[87] Nakazaki, M.; Yamamoto, K.; Tanaka, S.; Kametani, H. *J. Org. Chem.* ***1977***, *42*, 287. Also see Pelter, A.; Crump, R.A.N.C.; Kidwell, H. *Tetrahedron Lett.* ***1996***, *37*, 1273 for an example of a chiral [2.2]paracyclophane.
[88] Liu, X.; Ma, Y.; Duan, W.; He, F.; Zhao, L.; Song, C. *J. Org. Chem.* ***2011***, *76*, 1953.
[89] For a treatise on the quantitative chirality of helicenes, see Katzenelson, O.; Edelstein, J.; Avnir, D. *Tetrahedron Asymmetry* ***2000***, *11*, 2695.
[90] Chan, T.-L.; Hung, C.-W.; Man, T.-O.; Leung, M.-k. *J. Chem. Soc., Chem. Commun.* ***1994***, 1971.
[91] Collins, S.K.; Yap, G.P.A.; Fallis, A.G. *Org. Lett.* ***2000***, *2*, 3189.
[92] For reviews on the stereochemistry of metallocenes, see Schlögl, K. *J. Organomet. Chem.* ***1986***, *300*, 219; *Top. Stereochem.* ***1967***, *1*, 39; *Pure Appl. Chem.* ***1970***, *23*, 413.

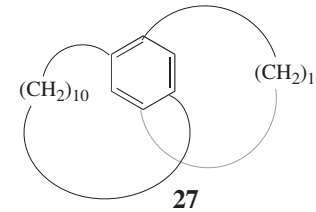
also found in other metallic complexes of suitable geometry.[93] Fumaric acid–iron tetracarbonyl (**29**) has been resolved,[94] and 1,2,3,4-tetramethylcyclooctatetraene (**30**) is also chiral.[95] This molecule, which exists in the tub form (Sec. 2.K.iii), has neither a plane nor an alternating axis of symmetry. Another compound that is chiral solely because of hindered rotation is the propeller-shaped perchlorotriphenylamine, which has been resolved.[96] The 2,5-dideuterio derivative (**31**) of barrelene is chiral, although the parent hydrocarbon and the monodeuterio derivative are not.



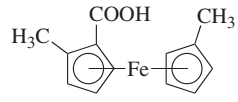
25



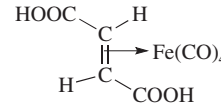
26



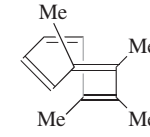
27



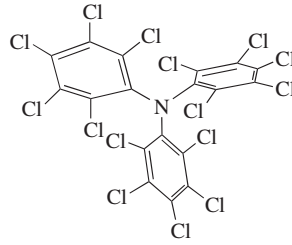
28



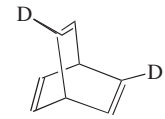
29



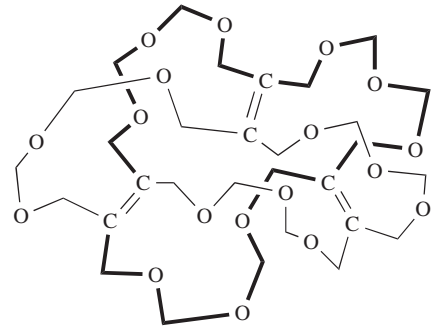
30



Perchlorotriphenylamine



31



32

[93] For reviews of such complexes, see Paiaro, G. *Organomet. Chem. Rev. Sect. A* ***1970***, *6*, 319.

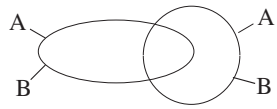
[94] Paiaro, G.; Palumbo, R.; Musco, A.; Panunzi, A. *Tetrahedron Lett.* ***1965***, 1067. Also see, Paiaro, G.; Panunzi, A. *J. Am. Chem. Soc.* ***1964***, *86*, 5148.

[95] Paquette, L.A.; Gardlik, J.M.; Johnson, L.K.; McCullough, K.J. *J. Am. Chem. Soc.* ***1980***, *102*, 5026.

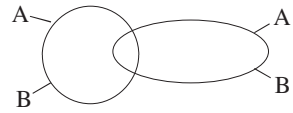
[96] Okamoto, Y.; Yashima, E.; Hatada, K.; Mislow, K. *J. Org. Chem.* ***1984***, *49*, 557. See Grilli, S.; Lunazzi, L.; Mazzanti, A.; Casarini, D.; Femoni, C. *J. Org. Chem.* ***2001***, *66*, 488.

The main molecular chain in compound **32** has the form of a Möbius strip (see Figure 15.7).[97] This molecule has no stereogenic carbons, nor does it have a rigid shape, a plane, nor an alternating axis of symmetry. However, **32** has been synthesized and shown to be chiral.[98] Rings containing 50 or more members should be able to exist as knots (**33**, and see **39** in Sec. 3.D). Such a knot would be nonsuperimposable on its mirror image. Calixarenes,[99] crown ethers,[100] catenanes, and rotaxanes (Sec. 3.D) can also be chiral if suitably substituted.[101] For example, **34** and **35** are nonsuperimposable mirror images.

33



34



35

A stereogenic center may be created from an achiral molecule via a chemical reaction. One example is the α-bromination of a carboxylic acid (Hell-Volhardt-Zelenskii reaction, **12-5**) to form the α-bromo acid:

$$CH_3CH_2COOH + Br_2 \xrightarrow{P} CH_3CHBrCOOH$$

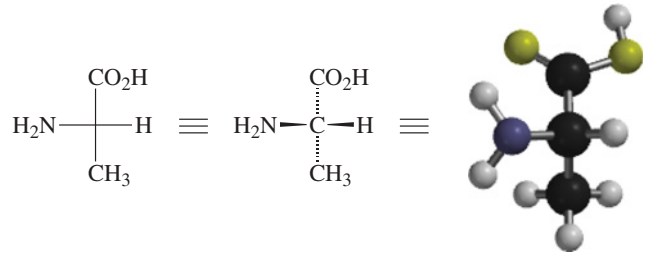
In this case, the α-carbon in the product is the stereogenic carbon. If there are no asymmetric components in the reaction, the product must be racemic. This means that no optically active material can be created if all starting materials and conditions are optically inactive.[102] This statement also holds when one begins with a racemic mixture, unless there is kinetic resolution (Sec. 4.I). Thus racemic butan-2-ol, treated with HBr, must give racemic 2-bromobutane.

4.D. THE FISCHER PROJECTION

For a thorough understanding of stereochemistry it is useful to examine molecular models (like those depicted in Figure 4.1). In 1891, long before molecular modeling was possible, Emil Fischer displayed amino acids and some carbohydrates in a particular way known as a *Fischer projection*. This is simply a method of representing an "edge-viewed" tetrahedral on paper. By this convention, the model is held so that the two bonds in front of the paper

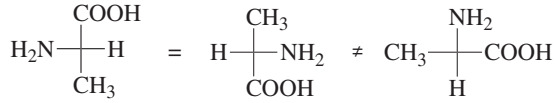
[97] See Walba, D.M. *Tetrahedron* ***1985***, *41*, 3161.
[98] Walba, D.M.; Richards, R.M.; Haltiwanger, R.C. *J. Am. Chem. Soc.* ***1982***, *104*, 3219.
[99] Iwanek, W.; Wolff, C.; Mattay, J. *Tetrahedron Lett.* ***1995***, *36*, 8969.
[100] de Vries, E.F.J.; Steenwinkel, P.; Brussee, J.; Kruse, C.G.; van der Gen, A. *J. Org. Chem.* ***1993***, *58*, 4315; Pappalardo, S.; Palrisi, M.F. *Tetrahedron Lett.* ***1996***, *37*, 1493; Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* ***1996***, *37*, 7627.
[101] See Schill, G. *Catenanes*, *Rotaxanes*, *and Knots*, Academic Press, NY, ***1971***, pp. 11–18.
[102] There is one exception to this statement. In a very few cases racemic mixtures may crystalize from solution in such a way that all the (+) molecules go into one crystal and the (−) molecules into another. If one of the crystals crystallizes before the other, a rapid filtration results in optically active material. For a discussion, see Pincock, R.E.; Wilson, K.R. *J. Chem. Educ.* ***1973***, *50*, 455.

are horizontal and those behind the paper are vertical, as shown for 2-aminopropanoic acid (alanine).

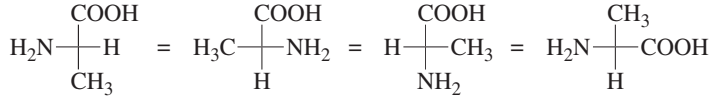


With modern computers, molecular models are readily available, but the ability to write structures in two dimensions to represent a three-dimensional form remains important.

In order to obtain proper results with these formulas, it should be remembered that they are projections and must be treated differently from the models in testing for superimposability. Every plane is superimposable on its mirror image; hence with these formulas there must be added the restriction that they may not be taken out of the plane of the blackboard or paper. Also they may not be rotated 90°, although 180° rotation is permissible:



It is also permissible to keep any one group fixed and to rotate the other three clockwise or counterclockwise, as shown with the Fischer projection for the following amino acid (alanine):

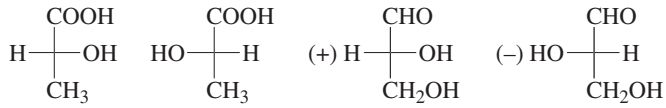


However, the *interchange* of any two groups results in the conversion of an enantiomer into its mirror image (this applies to models as well as to the Fischer projections).

With these restrictions, Fischer projections may be used instead of models to test whether a molecule containing a stereogenic carbon is superimposable on its mirror image. However, there are no such conventions for molecules whose chirality arises from anything other than stereogenic atoms (category 5 in Sec. 4.C).

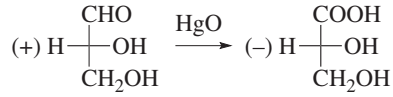
4.E. ABSOLUTE CONFIGURATION

Suppose there are two test tubes, one containing (−)-lactic acid and the other the (+) enantiomer. One test tube contains **36** and the other **37**. How can they be distinguished?



36 **37** **38** **39**

To generate a model to answer this question, Rosanoff proposed that one compound be chosen as a standard and a configuration arbitrarily assigned to it. The compound chosen was glyceraldehyde because of its relationship to the sugars. The (+) isomer was assigned the configuration shown in **38** and given the label D. The (−) isomer, designated to be **39**, was given the label L. With a standard, other compounds could then be related to it. For example, (+)-glyceraldehyde, oxidized with mercuric oxide, gives (−)-glyceric acid:



Since it is highly improbable that the configuration at the central carbon changed, it can be concluded that (−)-glyceric acid has the same configuration as (+)-glyceraldehyde and therefore (−)-glyceric acid is also called D. This example emphasizes that molecules with the same configuration need not rotate the plane of polarized light in the same direction. This fact should not surprise when it is remembered that the same compound can rotate the plane in opposite directions under different conditions.

Once the configuration of the glyceric acids was known (in relation to the glyceraldehydes), it was then possible to relate other compounds to either of these, and each time a new compound was related, others could be related to *it*. In this way, many thousands of compounds were related, indirectly, to D- or L-glyceraldehyde, and it was determined that **36**, which has the D configuration, is the isomer that rotates the plane of polarized light to the left. Even compounds without asymmetric atoms, such as biphenyls and allenes, have been placed in the D or L series.[103] When a compound has been placed in the D or L series, its *absolute configuration* is said to be known.[104]

In 1951, it became possible to determine that Rosanoff's guess was right. Ordinary X-ray crystallography cannot distinguish between a D and a L isomer, but by use of a special technique, Bijvoet was able to examine sodium rubidium tartrate, compared it with glyceraldehyde, and found that Rosanoff had made the correct choice.[105] It was perhaps historically fitting that the first true absolute configuration should have been determined on a salt of tartaric acid, since Pasteur made his great discoveries on another salt of this acid.

In spite of the former widespread use of D and L to denote absolute configuration, the method is not without faults. This method does not apply to all compounds that have a

[103] The use of small *d* and *l* is now discouraged, since some authors used it for rotation, and some for configuration. However, a racemic mixture is still a *dl* mixture, since there is no ambiguity here.

[104] For lists of absolute configurations of thousands of compounds, with references, mostly expressed as (*R*) or (*S*) rather than D or L, see Klyne, W.; Buckingham, J. *Atlas of Stereochemistry*, 2nd ed., 2 Vols, Oxford University Press, Oxford, ***1978***; Jacques, J.; Gros, C.; Bourcier, S.; Brienne, M.J.; Toullec, J. *Absolute Configurations* (Vol. 4 of Kagan, H. *Stereochemistry*), Georg Thieme Publishers, Stuttgart, ***1977***.

[105] Bijvoet, J.M.; Peerdeman, A.F.; van Bommel, A.J. *Nature (London)* ***1951***, *168*, 271. For a list of organic structures whose absolute configurations have been determined by this method, see Neidle, S.; Rogers, D.; Allen, F.H. *J. Chem. Soc. C* ***1970***, 2340.

stereogenic center, but only those that can be structurally related to glyceraldehyde. The DL system is rarely used, therefore, except for certain groups of compounds, such as carbohydrates and amino acids. A more general model is required to distinguish the stereogenic centers of enantiomers. A method has been reported for the interconversion of (*S*)- and (*R*)-α-amino acids.[106]

4.E.i. The Cahn-Ingold-Prelog System

The system that is used universally is the *Cahn-Ingold-Prelog* system (or the CIP system), in which the four groups on a stereogenic carbon are ranked (prioritized) according to a set of sequence rules.[107] For the most part, only a few of these rules are sufficient to deal with the vast majority of chiral compounds.

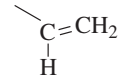
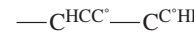
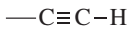
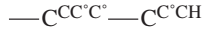
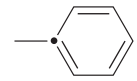
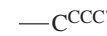
1. Prioritize substituents in order of decreasing atomic number of the atom directly joined to the carbon.
2. A tritium atom takes precedence over deuterium, which in turn takes precedence over ordinary hydrogen. Similarly, any higher isotope (e.g., ^{14}C) takes precedence over any lower one.
3. Where two or more of the atoms connected to the stereogenic carbon are the same, the atomic number of the second atom determines the order. For example, in the molecule $Me_2CH{-}CHBr{-}CH_2OH$, the CH_2OH group takes precedence over the Me_2CH group because oxygen has a higher atomic number than carbon. Note that this is so even although there are two carbons in Me_2CH, and only one oxygen in CH_2OH. If two or more atoms connected to the second atom are the same, the third atom determines the precedence, and so on.
4. All atoms except hydrogen are formally given a valence of 4. Where the actual valence is less (as in nitrogen, oxygen, or a carbanion), phantom atoms (designated by a superscript °) are used to bring the valence up to four. These phantom atoms are assigned an atomic number of zero and necessarily rank lowest. Thus the ligand $-^{+}NHMe_2$ ranks higher than $-NMe_2$.
5. Double and triple bonds are counted as if they were split into two or three single bonds, respectively, as in the examples in Table 4.1 (note the treatment of the phenyl group). Note that in a C=C double bond, the two carbon atoms are *each* regarded as being connected to two carbon atoms and that one of the latter is counted as having three phantom substituents.

The use of phantom atoms is shown in Table 4.1, which shows four functional groups with π bonds. The carbon of the aldehyde CHO is treated as if it is $-CHOO^{\circ}$ and the carbon of the $-CH{=}CH_2$ group is treated as if it is $-CHCC^{\circ}{-}CC^{\circ}CH$. The alkyne unit, $-C{\equiv}C-$

[106] Sorochinsky, A.E.; Ueki, H.; Aceña, J.L.; Ellis, T.K.; Mriwaki, H.; Sato, T.; Soloshonok, V.A. *Org. Biomol. Chem.* ***2013***, *11*, 4503.

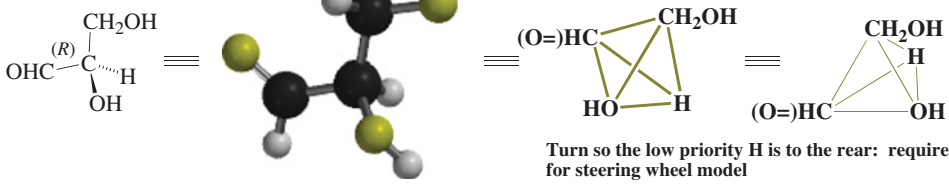
[107] For descriptions of the system and sets of sequence rules, see *Pure Appl. Chem.* ***1976***, *45*, 11; *Nomenclature of Organic Chemistry*, Pergamon, Elmsford, NY, ***1979*** (the "Blue Book"); Cahn, R.S.; Ingold, C.K.; Prelog, V. *Angew. Chem. Int. Ed.* ***1966***, *5*, 385; Cahn, R.S. *J. Chem. Educ.* ***1964***, *41*, 116; Fernelius, W.C.; Loening, K.; Adams, R.M. *J. Chem. Educ.* ***1974***, *51*, 735. See also, Prelog, V.; Helmchen, G. *Angew. Chem. Int. Ed.* ***1982***, *21*, 567. Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 101–147. Also see, Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, England, ***2017***, pp. 10–18. See, however, Fujita, S. *Tetrahedron: Asymmetry* ***2014***, *25*, 1153, 1169, 1190; ***2017***, *28*, 1.

TABLE 4.1 How four common groups are treated in the Cahn-Ingold-Prelog system

Group	Treated as If It Were	Group	Treated as If It Were
			
			

is treated as if it is —CCC°C°—CC°C°H. The highlighted carbon (•) of the benzene ring is treated as if it is —CCCC°.

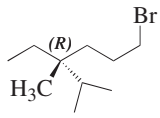
By application of the above rules, some groups in descending order of precedence are COOH, COPh, COMe, CHO, $CH(OH)_2$, *o*-tolyl, *m*-tolyl, *p*-tolyl, phenyl, C≡CH, *tert*-butyl, cyclohexyl, vinyl, isopropyl, benzyl, neopentyl, allyl, *n*-pentyl, ethyl, methyl, deuterium, and hydrogen. Using the CIP rules, the four groups of glyceraldehyde are arranged in the sequence: OH, CHO, CH_2OH, H.



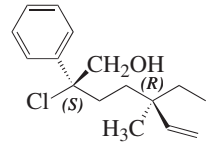
Turn so the low priority H is to the rear: required for steering wheel model

Once the order is determined, a model is required to determine the absolute configuration (i.e., which structure correlates to which enantiomer). The model used is known as the *steering wheel model,* where the molecule is held so that the lowest group in the sequence is pointed away from the viewer. Once the lowest priority group is held in that position, if the other groups, in the order listed, are oriented clockwise, the molecule is designated (*R*), and if counterclockwise, (*S*). For glyceraldehyde, the (+) enantiomer is shown here and the CIP rules and the steering wheel model was used to assign an absolute configuration of (*R*).

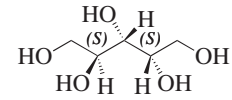
The CIP rules and steering wheel model are used to assign an absolute configuration to the following molecules. In **A**, the isopropyl carbon is higher in priority than the bromine-containing chain, and the methyl group is the lowest priority. Turning the molecule to place the methyl group to the rear makes this a (*R*) configuration. In **B**, there are two stereogenic centers, where the (*S*) center has the chain containing the (*R*) center as the lowest priority, and the (*R*) center has the methyl group as the low priority. In **C**, there are two (*S*) centers, but the hydroxyl-bearing carbon in the middle of the molecule is *not* a stereogenic carbon. Close inspection of **C** shows that this carbon has two identical groups [$CH(OH)CH_2OH$].



A

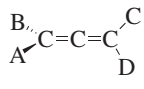


B

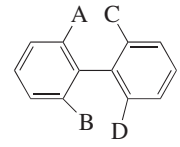


C

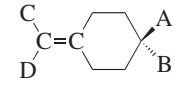
The Cahn-Ingold-Prelog system is unambiguous and easily applicable in most cases. The Cahn-Ingold-Prelog system has also been extended to chiral compounds that do not contain stereogenic centers, but rather have a chiral axis.[108] Compounds having a chiral axis include unsymmetrical allenes, biaryls that exhibit atropisomerism (Sec. 4.C, category 5), and alkylidene cyclohexane derivatives, molecular propellers and gears, helicenes, cyclophanes, annulenes, *trans*-cycloalkenes, and metallocenes. A series of rules have been proposed to address these cases based on what is called an "extended tetrahedron mode," but the rules can be ambiguous in the case of cyclophanes and a few other systems.[109]



Allenes



Biaryls



Alkylidene Cyclohexanes

4.E.ii. Methods Of Determining Configuration[110]

In all the methods,[111] it is necessary to relate the compound of unknown configuration to another whose configuration is known. The most important methods of doing this are:

1. *Conversion of the unknown to, or formation of the unknown from, a compound of known configuration without disturbing the stereogenic center*. The glyceraldehyde–glyceric acid example above is one example. The stereogenic center was not disturbed, and the configuration of the product (glyceric acid) is the same as the starting material (glyceraldehyde). Retention of the same absolute configuration such as with glyceraldehyde-to-glyceric acid is not always the case. If the reaction sequence does not disturb (change) the stereogenic center, the absolute configuration depends on the nature of the groups. For example, when (*R*)-1-bromobutan-2-ol is reduced

[108] Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, ***1994***, pp 1119–1190. See Krow, G. *Top. Stereochem.* ***1970***, *5*, 31.

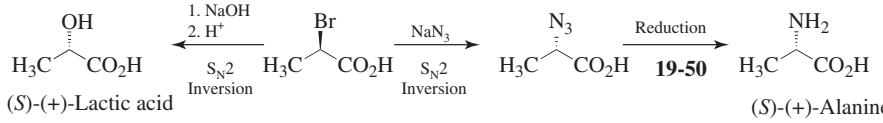
[109] Mata, P.; Lobo, A.M.; Marshall, C.; Johnson, A.P. *Tetrahedron Asymmetry* ***1993***, *4*, 657; Perdih, M.; Razinger, M. *Tetrahedron Asymmetry* ***1994***, *5*, 835.

[110] See Kagan, H.B. *Determination of Configuration by Chemical Methods* (Vol. 3 of Kagan, H.B. *Stereochemistry*), Georg Thieme Publishers, Stuttgart, ***1977***; Brewster, J.H. in Bentley, K.W.; Kirby, G.W. *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), pt. 3, Wiley, NY, ***1972***, pp. 1–249; Klyne, W.; Scopes, P.M. *Prog. Stereochem.* ***1969***, *4*, 97; Schlenk Jr., W. *Angew. Chem. Int. Ed.* ***1965***, *4*, 139. Also see Addadi, L.; Berkovitch-Yellin, Z.; Weissbuch, I.; Lahav, M.; Leiserowitz, L. *Top. Stereochem.* ***1986***, *16*, 1. See Zhu, H.-J. *Organic Stereochemistry. Experimental and Computational Methods*, Wiley-VCH, Weinheim, ***2015***; For a discussion of methods to assign the configuration of natural products, see Molinski, T.F.; Morinaka, B.I. *Tetrahedron* ***2012***, *68*, 9307.

[111] Except the X-ray method of Bijvoet.

to (*S*)-butan-2-ol without disturbing the stereogenic center, the product is the (*S*) enantiomer because CH_3CH_2 ranks lower than $BrCH_2$, but higher than CH_3.

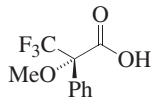
2. *Conversion at the stereogenic center if the mechanism is known*. An S_N2 mechanism proceeds with inversion of configuration at a stereogenic carbon (Sec. 10.A.i). Indeed, a series of such transformations allowed the stereogenic center in lactic acid to be correlated to that in alanine.



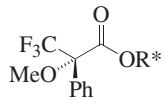
3. *Biochemical methods*. In a series of similar compounds, such as amino acids or certain types of steroids, a given enzyme will usually attack only molecules with one kind of configuration. If the enzyme attacks only the L form of eight amino acids, say, then attack on the unknown ninth amino acid will demonstrate that it is also the L form.
4. *Optical comparison*. It is sometimes possible to use the sign and extent of rotation to determine which isomer has which configuration. In a homologous series, the rotation usually changes gradually and in one direction. If the configurations of enough members of the series are known, the configurations of the missing ones can be determined by extrapolation. Also, certain groups contribute more or less fixed amounts to the rotation of the parent molecule, especially when the parent is a rigid system, such as a steroid.
5. *The special X-ray method of Bijvoet*. This method gives direct answers and has been used in a number of cases.[92]
6. *Derivatize the alcohol with a chiral nonracemic reagent and examine the ratio of resulting diastereomers*.[112] This is one of the most useful methods for determining enantiomeric composition. Many derivatizing agents are available, but one widely used class are derivatives of α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA, *Mosher's acid*, **40**).[113] Reaction with a chiral nonracemic alcohol (R*OH) generates a *Mosher's ester* (**41**) that can be analyzed for diastereomeric composition by ^1H or ^{19}F NMR, as well as by chromatographic techniques.[114] Complexation with lanthanide shift reagents allow the signals of the MTPA ester to be resolved and used to determine enantiomeric composition.[115] This NMR method, as well as other related

[112] Parker, D. *Chem. Rev.* ***1991***, *91*, 1441.
[113] Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.* ***1969***, 34, 2543; Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* ***1973***, *95*, 512.
[114] See Mori, K.; Akao, H. *Tetrahedron Lett.* ***1978***, 4127; Plummer, E.L.; Stewart, T.E.; Byrne, K.; Pearce, G.T.; Silverstein, R.M. *J. Chem. Ecol.* ***1976***, *2*, 307. See also, Seco, J.M.; Quiñoá, E.; Riguera, R. *Tetrahedron Asymmetry* ***2000***, *11*, 2695.
[115] Yasuhara, F.; Yamaguchi, S. *Tetrahedron Lett.* ***1980***, *21*, 2827; Yamaguchi, S.; Yasuhara, F. *Tetrahedron Lett.* ***1977***, 89.

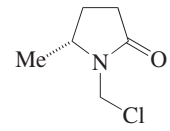
methods,[116] are effective for determining the absolute configuration of an alcohol of interest (R*OH, where R* is a group containing a stereogenic center).[117] Two of many other reagents that have been developed to determine the enantiopurity of alcohols and amines are **42** and **43**. Chloromethyl lactam **42** reacts with R*OH or R*NHR (R*NH_2),[118] forming derivatives that allow analysis by ^{1}H NMR and **43** reacts with alkoxides (R*O^-)[119] to form a derivative that can be analyzed by ^{31}P NMR.[120] For a more detailed discussion of methods to determine optical purity, see Sec. 4.J.



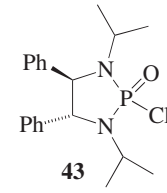
40



41



42



43

7. *Other methods*. Other methods used for determining absolute configuration in a variety of molecules include optical rotatory dispersion,[121] circular dichroism,[122] and asymmetric synthesis (Sec. 4.H). The use of co-crystals has also been used.[123] Optical rotatory dispersion (ORD) is a measurement of specific rotation, [α], as a function of wavelength.[124] The change of specific rotation [α] or molar rotation [Φ] with wavelength is measured, and a plot of either versus wavelength is often related to the sense of chirality or the substance under consideration. In general, the absolute value of the rotation increases as the wavelength decreases. The plot of circular dichroism (CD) is the differential absorption of left and right circularly polarized radiation by a nonracemic sample, taking place only in spectral regions in which absorption bands are found in the isotropic UV or visible electronic spectrum.[125] The primary application of both ORD and CD is for the assignment of configuration or conformation.[126]

[116] Latypov, S.K.; Ferreiro, M.J.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* ***1998***, *120*, 4741; Latypov, S.K.; Seco, J.M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* ***1995***, *60*, 1538.

[117] Seco, J.M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* ***2004***, *104*, 17.

[118] Smith, M.B.; Dembofsky, B.T.; Son, Y.C. *J. Org. Chem.* ***1994***, *59*, 1719; Latypov, S.K.; Riguera, R.; Smith, M.B.; Polivkova, J. *J. Org. Chem.* ***1998***, *63*, 8682. For a chiral compound used to determine the enantiomeric purity of primary amines, see Pérez-Fuertes, Y.; Kelly, A.M.; Johnson, A.L.; Arimori, S.; Bull, S.D.; James, T.D. *Org. Lett.* ***2006***, *8*, 609.

[119] Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* ***1992***, *57*, 1224.

[120] For a discussion of ^{31}P NMR used to determine absolute configuration, see Szyszkowiak, J.; Majewska, P. *Tetrahedron: Asymmetry* ***2014***, *25*, 103.

[121] See Ref. 306 for books and reviews on optical rotatory dispersion and CD. For predictions about anomalous ORD, see Polavarapu, P.L.; Zhao, C. *J. Am. Chem. Soc.* ***1999***, *121*, 246.

[122] Gawronski, J.; Grajewski, J. *Org. Lett.* ***2003***, *5*, 3301. See Ref. 306; Stephens, P.J.; Aamouche, A.; Devlin, F.J.; Superchi, S.; Donnoli, M.I.; Rosini, C. *J. Org. Chem.* ***2001***, *66*, 3671.; McCann, D.M.; Stephens, P.J. *J. Org. Chem.* ***2006***, *71*, 6074.

[123] Eccles, K.S.; Deasy, R.E.; Fábián, L.; Maguire. A.R.; Lawrence, S.E. *J. Org. Chem.* ***2011***, *76*, 1159.

[124] Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, ***1994***, pp. 1203, 999–1003.

[125] Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, ***1994***, pp. 1195, 1003–1007.

[126] Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley, NY, ***1994***, pp. 1007–1071; Nakanishi, K.; Berova, N.; Woody, R.W. *Circular Dichroism: Principles and Applications*, VCH, NY, ***1994***;

Configurational and conformational analyses have been carried out using infrared (IR) and vibrational circular dichroism (VCD) spectroscopies.[127]

One example, and one of the more effective methods for derivatizing 1,2-diols, is the method employing dimolybdenum tetraacetate [$Mo_2(AcO)_4$] developed by Snatzke and Frelek (Ac = acetyl).[128] Exposure of the resulting complex to air leads, in most cases, to a significant induced CD spectrum (known as ICD). The method can be used for a variety of 1,2-diols.[129] Enantiomeric pairs of molecularly imprinted polymers allows the determination of absolute configuration of amino acid derivatives, hydroxy acids, amino alcohols, alcohols, and carboxylic acids.[130] A chiroptical probe, a complex tertiary amine, has been used for chirality detection of primary amines.[131] The chirality in solutions has been determined.[132] Enantioselective acylation reactions have been used to determine the absolute configuration of alcohols.[133]

8. *NMR databases*. Kishi and co-workers[134] developed an NMR database[135] of various molecules in chiral solvents, for the assignment of relative and absolute stereochemistry without derivatization or degradation. Kishi referred to this database as a "universal NMR database."[136] The diagram provided for diols **44** illustrates the method (see Figure 4.3). The graph presents the difference in carbon chemical shifts between the average and the values for **44** (100 MHz) in DMBA (*N*,α-dimethylbenzylamine). Spectra were recorded in both enantiomers of the solvent, where the solid bar was recorded in (*R*)-DMBA and the shaded bar in (*S*)-DMBA. The *x*- and *y*-axes represent carbon number and $\Delta\delta$ ($\delta_{\mathbf{45a\text{-}h}} - \delta_{ave}$ in ppm), respectively. The graphs are taken from "the ^{13}C NMR database in (*R*)- and (*S*)-DMBA as a deviation in chemical shift for each carbon of a given diastereomer from the average chemical shift of the carbon in question. Each diastereomer exhibits an almost identical NMR profile for (*R*)- and (*S*)-DMBA, but shows an NMR profile distinct and differing from the other diastereomers, demonstrating that the database in (*R*)- and/or (*S*)-DMBA can be used for prediction of the relative stereochemistry of structural motifs in an intact form."[137]

Purdie, N.; Brittain, H.G. *Analytical Applications of Circular Dichroism*, Elsevier, Amsterdam, The Netherlands, ***1994***.

[127] Devlin, F.J.; Stephens, P.J.; Osterle, C.; Wiberg, K.B.; Cheeseman, J.R.; Frisch, M.J. *J. Org. Chem.* ***2002***, *67*, 8090; Lüdeke, S.; Pfeifer, M.; Fischer, P. *J. Am. Chem. Soc.* ***2011***, *133*, 5704.

[128] Frelek, J.; Geiger, M.; Voelter, W. *Curr. Org. Chem.* ***1999***, *3*, 117–146 and references therein; Pakulski, Z.; Zamojski, A. *Tetrahedron: Asymmetry* ***1996***, *7*, 1363; Frelek, J.; Ikekawa, N.; Takatsuto, S.; Snatzke, G. *Chirality* ***1997***, *9*, 578.

[129] Di Bari, L.; Pescitelli, G.; Pratelli, C.; Pini, D.; Salvadori, P. *J. Org. Chem.* ***2001***, *66*, 4819.

[130] Meador, D.S.; Spivak, D.A. *Org. Lett.* ***2014***, *16*, 1402.

[131] Kuwahara, S.; Nakamura, M.; Yamaguchi, A.; Ikeda, A.; Habata, Y. *Org. Lett.* ***2013***, *15*, 5738; Anyika, M.; Gholami, H.; Ashtekar, K.D.; Acho, R.; Borhan, B. *J. Am. Chem. Soc.* ***2014***, *136*, 550.

[132] Partovi, T. *Chem. Lett.* ***2012***, *41*, 760.

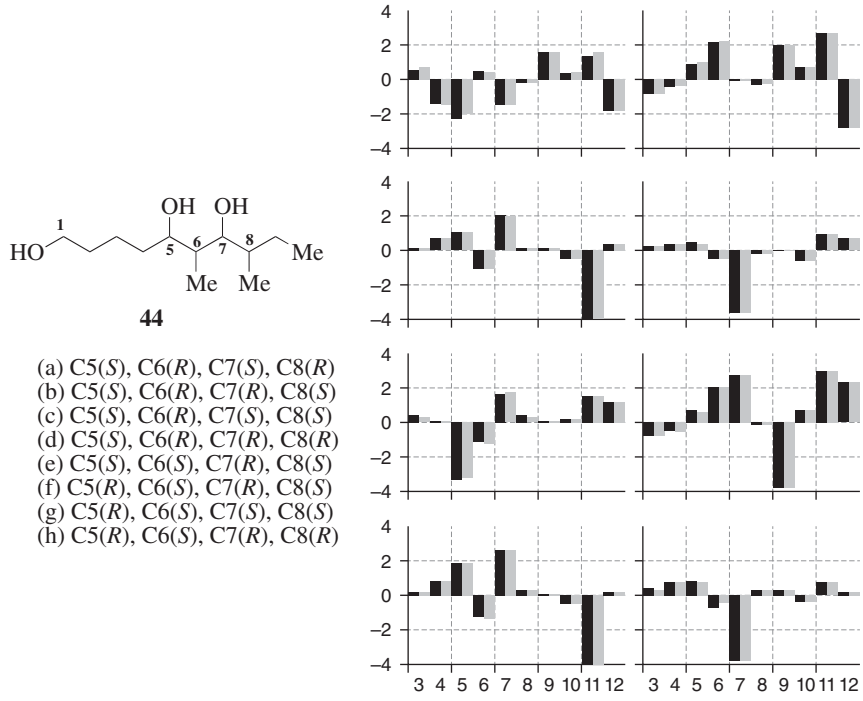
[133] LeGay, C.; Derksen, D. *Org. Biomol. Chem.* ***2013***, *11*, 3432.

[134] Kobayashi, Y.; Hayashi, N.; Tan, C.-H.; Kishi, Y. *Org. Lett.* ***2001***, *3*, 2245; Hayashi, N.; Kobayashi, Y.; Kishi, Y. *Org. Lett.* ***2001***, *3*, 2249; Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Org. Lett.* ***2001***, *3*, 2253.

[135] For another protocol, see Dambruoso, P.; Bassarello, C.; Bifulco, G.; Appendino, G.; Battaglia, A.; Fontana, G.; Gomez-Paloma, L. *Org. Lett.* ***2005***, *7*, 983.

[136] Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *J. Am. Chem. Soc.* ***2001***, *123*, 2076.

[137] Kobayashi, Y.; Hayashi, N.; Tan, C.-H.; Kishi, Y. *Org. Lett.* ***2001***, *3*, 2245.



44

(a) C5(*S*), C6(*R*), C7(*S*), C8(*R*)
(b) C5(*S*), C6(*R*), C7(*R*), C8(*S*)
(c) C5(*S*), C6(*R*), C7(*S*), C8(*S*)
(d) C5(*S*), C6(*R*), C7(*R*), C8(*R*)
(e) C5(*S*), C6(*S*), C7(*R*), C8(*S*)
(f) C5(*R*), C6(*S*), C7(*R*), C8(*S*)
(g) C5(*R*), C6(*S*), C7(*S*), C8(*S*)
(h) C5(*R*), C6(*S*), C7(*R*), C8(*R*)

FIGURE 4.3. Proton NMR analysis for assignment of stereochemistry.

A ^{1}H NMR analysis method has been developed that leads to the assignment of the stereochemistry of β-hydroxy ketones, by visual inspection of the ABX patterns for the (*R*)-methylene unit of the β-hydroxy ketones.[138] Since β-hydroxy ketones are derived from the aldol reaction (**16-34**), this method is particularly useful in organic synthesis. A method has also been developed that uses ^{13}C NMR to determine the relative stereochemistry of 2,3-dialkylpentenoic acids.[139]

4.F. THE CAUSE OF OPTICAL ACTIVITY

The question may be asked: Just why does a chiral molecule rotate the plane of polarized light? Theoretically, the answer to this question is known, and in a greatly simplified form may be explained as follows.[140]

The rotation of plane-polarized light results from the properties inherent in the interaction with the individual molecules through which it passes. Whenever any light hits any molecule in a transparent material, the light is slowed because of interactions with the

[138] Roush, W.R.; Bannister, T.D.; Wendt, M.D.; VanNieuwenhze, M.S.; Gustin, D.J.; Dilley, G.J.; Lane, G.C.; Scheidt, K.A.; Smith III, W.J. *J. Org. Chem.* ***2002***, *67*, 4284.

[139] Hong, S.-p.; McIntosh, M.C. *Tetrahedron* ***2002***, *57*, 5055.

[140] See Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 93–94, 992–999; Wheland, G.W. *Advanced Organic Chemistry*, 3rd ed., Wiley, NY, ***1960***, pp. 204–211; Caldwell, D.J.; Eyring, H. *The Theory of Optical Activity* Wiley, NY, ***1971***; Buckingham, A.D.; Stiles, P.J. *Acc. Chem. Res.* ***1974***, *7*, 258; Mason, S.F. *Q. Rev. Chem. Soc.* ***1963***, *17*, 20.

molecule. This phenomenon on a gross scale is responsible for the refraction of light, and the decrease in velocity is proportional to the refractive index of the material. The extent of interaction depends on the polarizability of the molecule. Plane-polarized light may be regarded as being made up of two kinds of circularly polarized light. Circularly polarized light has the appearance (or would have, if one could see the wave) of a helix propagating around the axis of light motion, and one kind is a left-handed helix and the other is a right-handed helix. As long as the plane-polarized light is passing through a symmetrical region, the two circularly polarized components travel at the same speed. However, a chiral molecule has a different polarizability depending on whether it is approached from the left or the right. One circularly polarized component approaches the molecule, so to speak, from the left and sees a different polarizability (hence on a gross scale, a different refractive index) than the other and is slowed to a different extent. This would seem to mean that the left- and right-handed circularly polarized components travel at different velocities, since each has been slowed to a different extent. However, it is not possible for two components of the same light to be traveling at different velocities. What actually takes place, therefore, is that the faster component "pulls" the other toward it, resulting in rotation of the plane. Empirical methods for the prediction of the sign and amount of rotation based on bond refractions and polarizabilities of groups in a molecule have been devised,[141] and have given fairly good results in many cases.

In liquids and gases, the molecules are randomly oriented. A molecule that is optically inactive because it has a plane of symmetry will very seldom be oriented so that the plane of the polarized light coincides with the plane of symmetry. When it is so oriented, that particular molecule does not rotate the plane, but all others not oriented in that manner do rotate the plane, even although the molecules are achiral. There is no net rotation because even though the molecules are present in large numbers and randomly oriented, there will always be another molecule later on in the path of the light that is oriented exactly opposite and will rotate the plane back again. Even if nearly all molecules rotate the plane individually, the total rotation is zero. For chiral molecules, however (if there is no racemic mixture), no opposite orientation is present and there is a net rotation.

An interesting phenomenon was observed when the CD (circular dichroism) of chiral molecules was measured in achiral solvents. The chiral solvent contributed as much as 10–20% to the CD intensity in some cases. Apparently, the chiral compound can induce a solvation structure that is chiral, even when the solvent molecules themselves are achiral.[142]

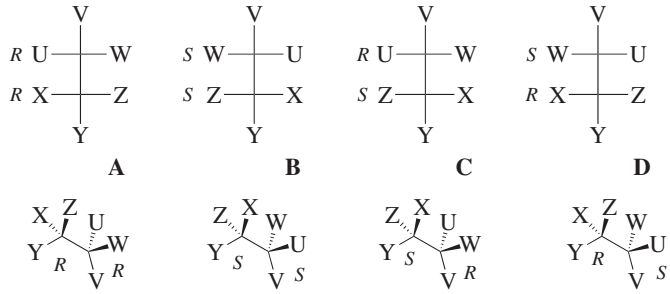
4.G. MOLECULES WITH MORE THAN ONE STEREOGENIC CENTER

When a molecule has two stereogenic centers, each has its own configuration and can be classified (*R*) or (*S*) by the Cahn-Ingold-Prelog method. There are a total of four isomers, since the first center may be (*R*) or (*S*) and so may the second. Each is drawn as both the Fischer projection and in the extended conformation. Since a molecule can have only one mirror image, only one of the other three can be the enantiomer of **A**. This is **B** [the mirror image of an (*R*) center is *always* an (*S*) center]. Both **C** and **D** are a second pair of

[141] Brewster, J.H. *Top. Stereochem.* ***1967***, *2*, 1, *J. Am. Chem. Soc.* ***1959***, *81*, 5475, 5483, 5493; Wroblewski, A.E.; Applequist, J.; Takaya, A.; Honzatko, R.; Kim, S.; Jacobson, R.A.; Reitsma, B.H.; Yeung, E.S.; Verkade, J.G. *J. Am. Chem. Soc.* ***1988***, *110*, 4144.

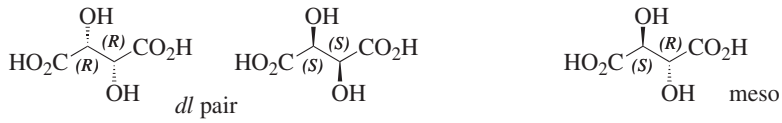
[142] Fidler, J.; Rodger, P.M.; Rodger, A. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 235.

enantiomers and the relationship of **C** and **D** to **A** and **B** is designated by the term *diastereomer*. Diastereomers may be defined as *stereoisomers that are not enantiomers (they are stereoisomers that are not mirror images, and not superimposable)*. Since **C** and **D** are enantiomers, they must have identical properties, except as noted on Sec. 4.A, and the same is true for **A** and **B**. However, the properties of **A** and **B** are not identical with those of **C** and **D**. They are different compounds, which means that they have different melting points, boiling points, solubilities, reactivity, and all other physical, chemical, and spectral properties. The properties are usually *similar*, but not *identical*. In particular, diastereomers have different specific rotations; indeed, one diastereomer may be chiral and rotate the plane of polarized light while another may be achiral and not rotate at all (an example is presented below).

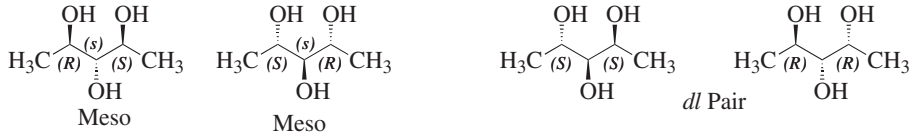


It is now possible to see why, as mentioned in Sec. 4.A, enantiomers react at different rates with other chiral molecules but at the same rate with achiral molecules. In the latter case, the activated complex formed from the (*R*) enantiomer and the other molecule is the mirror image of the activated complex formed from the (*S*) enantiomer and the other molecule. Since the two activated complexes are enantiomeric, their energies are the same and the rates of the reactions in which they are formed must be the same (see Chapter 6). However, when an (*R*) enantiomer reacts with a chiral molecule that has, say, the (*R*) configuration, the activated complex has two chiral centers with configurations (*R*) and (*R*), while the activated complex formed from the (*S*) enantiomer has the configurations (*S*) and (*R*). The two activated complexes are diastereomeric, do not have the same energies, and consequently are formed at different rates.

Although four is the maximum possible number of isomers when the compound has two stereogenic centers (chiral compounds without a stereogenic carbon, or with one stereogenic carbon and another type of stereogenic center, also follow the rules described here), some compounds have fewer. When the three groups on one stereogenic atom are the same as those on the other, one of the isomers (called a *meso* form) has a plane of symmetry, and hence is optically inactive, even though it has two stereogenic carbons. Tartaric acid is a typical case. As shown, there are only three isomers of tartaric acid: a pair of enantiomers and an inactive *meso* form. For compounds that have two stereogenic atoms, *meso forms are found only where the four groups on one of the chiral atoms are the same as those on the other chiral atom*.



In compounds with two or more stereogenic centers, the maximum number of isomers can be calculated from the formula 2^n, where n is the number of stereogenic centers. The actual number may be less than this, owing to *meso* forms,[143] but never more. An interesting case is that of 2,3,4-pentanetriol (or any similar molecule). The middle carbon is not asymmetric when the 2- and 4-carbons are both (*R*) [or both (*S*)]; labeled the *dl* pair. The compound when one of them is (*R*) and the other (*S*) is asymmetric (labeled *meso*). The middle carbon in such compounds is called a *pseudoasymmetric* carbon. In such cases, there are four isomers: two *meso* forms and one *dl* pair. Remember that the *meso* forms are superimposable on their mirror images, and that there are no other stereoisomers. Two diastereomers that have a different configuration at only one chiral center are called *epimers*.



The small letters used for the psuedoasymmetric center are assigned using established rules. An atom that is tetrahedrally substituted and bonded to four different entities, two and only two of which have opposite configurations, is stereogenic. The descriptors "*r*" and "*s*" are used to denote such centers; they are assigned in accordance with Sequence Rule 5, taking into consideration that "*R*" has precedence over "*S*" in the order of priority.[144]

1,2,3-Trichloropentane will be used as an example:

Step 1: configuration "*R*" or "*S*" is assigned to stereogenic centers C-2 and C-4.

Step 2: configuration at C-3 is assigned by applying sequence rule, "*R*" precedes "*S*", and if *R* precedes *S*, then Cl is the highest priority, followed by *R* and then *S*: C3 is *r*.

The exchange of the Cl and H atoms at C-3 of the compound on the left generates the compound on the right, and "3*r*" becomes "3*s*".

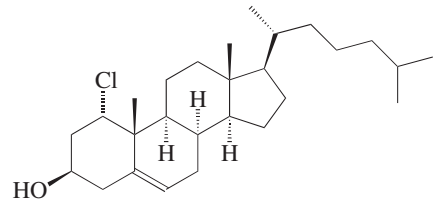
In compounds with two or more stereogenic centers, the absolute configuration must be separately determined for each center. The usual procedure is to determine the configuration at one center by the methods discussed in 4.E.ii, and then to relate the configuration at that center to the others in the molecule. One method is X-ray crystallography, which, as previously noted, cannot be used to determine the absolute configuration at any stereogenic center. This method does give *relative configurations* of all the stereogenic centers

[143] For a method of generating all stereoisomers consistent with a given empirical formula, suitable for computer use, see Nourse, J.G.; Carhart, R.E.; Smith, D.H.; Djerassi, C. *J. Am. Chem. Soc.* ***1979***, *101*, 1216; ***1980***, *102*, 6289.

[144] See http://old.iupac.org/reports/provisional/abstract04/favre_310305.html, *Preferred IUPAC Names*, Chapter 9, September 2004, p. 6.

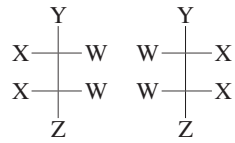
in a molecule, and if the absolute configuration of one stereogenic center is independently determined, the absolute configurations of all are then known. Other physical and chemical methods have also been used for this purpose.

How to name the different stereoisomers of a compound when there are more than two is potentially a problem.[2] Enantiomers have the same IUPAC name, being distinguished by *R* and *S* or *D* and *L* or (+) or (−). In the early days of organic chemistry, it was customary to give each pair of enantiomers a different name or at least a different prefix (such as *epi-*, *peri-*, etc.). Thus the aldohexoses are called glucose, mannose, idose, and so on, although they are all 2,3,4,5,6-pentahydroxyhexanal (in their open-chain forms). This practice was partially due to lack of knowledge about which isomers had which configurations.[145] Today it is customary to describe *each stereogenic position* separately as either (*R*) or (*S*) or, in special fields, to use other symbols. Thus, in the case of steroids, groups above the "plane" of the ring system are designated β, and those below it α. Solid lines are typically used to depict β groups and dashed lines for α groups. An example is 1α-chloro-5-cholesten-3β-ol, showing the OH group on the top side of the molecule (up) and the chlorine atom on the bottom side (down).

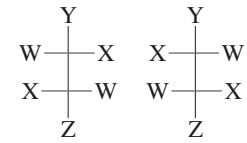


1α-Chloro-5-cholesten-3β-ol

For many open-chain compounds, prefixes are used that are derived from the names of the corresponding sugars and that describe the whole system rather than each chiral center separately. Two such common prefixes are *erythro-* and *threo-*, which are applied to systems containing two stereogenic carbons when two of the groups are the same and the third is different.[146] The *erythro* pair has the identical groups on the same side when drawn in the Fischer convention, and if Y were changed to Z, it would be *meso*. The *threo* pair has them on opposite sides, and if Y were changed to Z, it would still be a *dl* pair.



Erythro *dl* pair

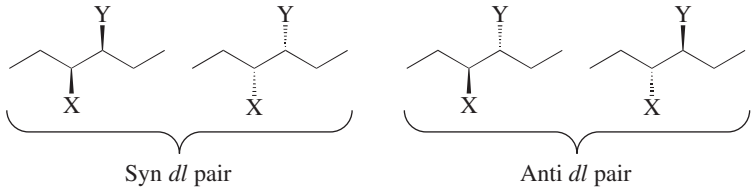


Threo *dl* pair

[145] A method has been developed for the determination of stereochemistry in six-membered chair-like rings using residual dipolar couplings. See Yan, J.; Kline, A.D.; Mo, H.; Shapiro, M.J.; Zartler, E.R. *J. Org. Chem.* ***2003***, *68*, 1786.

[146] See Carey, F.A.; Kuehne, M.E. *J. Org. Chem.* ***1982***, *47*, 3811; Boguslavskaya, L.S. *J. Org. Chem. USSR* ***1986***, *22*, 1412; Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed.* ***1982***, *21*, 654; Brewster, J.H. *J. Org. Chem.* ***1986***, *51*, 4751. See also, Tavernier, D. *J. Chem. Educ.* ***1986***, *63*, 511; Brook, M.A. *J. Chem. Educ.* ***1987***, *64*, 218.

Another system[147] for designating stereoisomers[148] uses the terms *syn* and *anti*. The "main chain" of the molecule is drawn in the common zig-zag manner. Then if two non-hydrogen substituents are on the same side of the plane defined by the main chain, the designation is *syn*; otherwise it is *anti*.



4.H. ASYMMETRIC SYNTHESIS

Organic chemists often wish to synthesize a chiral compound in the form of a single enantiomer or diastereomer, rather than as a mixture of stereoisomers.[149] There are two basic ways in which this can be done.[150] The first way, which is more common, is to begin with a single stereoisomer, and to use a synthesis that does not affect the stereogenic center (or centers). The optically active starting compound can be obtained by a previous synthesis, or by resolution of a racemic mixture (Sec. 4.I). If possible, the starting material is obtained from Nature, since many compounds, such as amino acids, sugars, and steroids, are present in Nature in the form of a single enantiomer or diastereomer. These compounds have been referred to as a *chiral pool*; that is, readily available compounds that can be used as starting materials.[151] This term is not used much now.

The other basic method is called *asymmetric synthesis*,[152] or *stereoselective synthesis*. Desymmetrization of molecules has become an important tool in asymmetric synthesis.[153]

[147] For another system, see Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed.* ***1982***, *21*, 654.

[148] Masamune, S.; Kaiho, T.; Garvey, D.S. *J. Am. Chem. Soc.* ***1982***, *104*, 5521.

[149] For a discussion of recent advances in acyclic stereocontrol, see O'Brien, A.G. *Tetrahedron* ***2011***, *67*, 9639.

[150] See Morrison, J.D.; Scott, J.W. *Asymmetric Synthesis*, Vol. 4; Academic Press, NY, ***1984***; Williams, R.M. *Synthesis of Optically Active* α*-Amino Acids*, Pergamon, Elmsford, NY, ***1989***; Crosby, J. *Tetrahedron* ***1991***, *47*, 4789; Mori, K. *Tetrahedron* ***1989***, *45*, 3233.

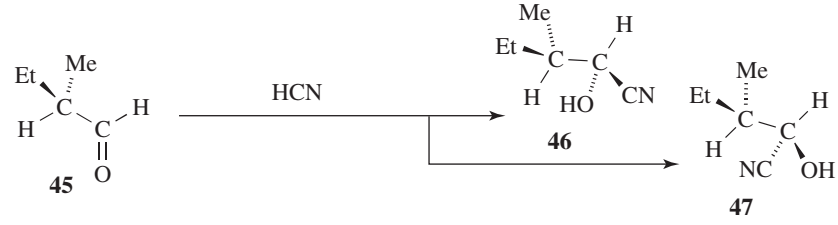
[151] See Coppola, G.M.; Schuster, H.F. *Asymmetric Synthesis*, Wiley, NY, ***1987***; Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon, Elmsford, NY, ***1983***; Hanessian, S. *Aldrichimica Acta* ***1989***, *22*, 3; Jurczak, J.; Gotebiowski, A. *Chem. Rev.* ***1989***, *89*, 149. See Alezra, V.; Kawabata, T. *Synthesis* ***2016***, *48*, 2897.

[152] See Morrison, J.D. *Asymmetric Synthesis* 5 Vols. [Vol. 4 co-edited by Scott, J.W.], Academic Press, NY, ***1983–1985***; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***; Eliel, E.L.; Otsuka, S. *Asymmetric Reactions and Processes in Chemistry,* American Chemical Society, Washington, ***1982***; Morrison, J.D.; Mosher, H.S. *Asymmetric Organic Reactions*, Prentice-Hall: Englewood Cliffs, NJ, ***1971***, paperback reprint, American Chemical Society, Washington, ***1976***. For reviews, see Ward, R.S. *Chem. Soc. Rev.* ***1990***, *19*, 1; Whitesell, J.K. *Chem. Rev.* ***1989***, *89*, 1581; Fujita, E.; Nagao, Y. *Adv. Heterocycl. Chem.* ***1989***, *45*, 1; Kochetkov, K.A.; Belikov, V.M. *Russ. Chem. Rev.* ***1987***, *56*, 1045; Oppolzer, W. *Tetrahedron* ***1987***, *43*, 1969; Seebach, D.; Imwinkelried, R.; Weber, T. *Mod. Synth. Methods*, ***1986***, *4*, 125; ApSimon, J.W.; Collier, T.L. *Tetrahedron* ***1986***, *42*, 5157; Corey, E.J.; Kürti, L. *Enantioselective Chemical Synthesis. Methods, Logic and Practice*, Direct Book Publishing, ***2010***.

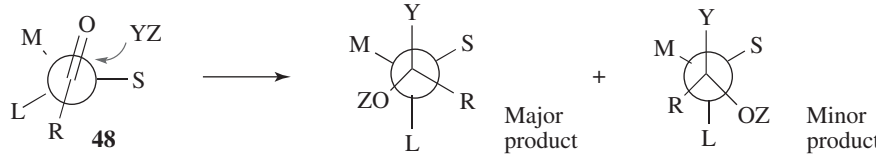
[153] For a discussion of enzymatic desymmetrization in organic synthesis, see Garcia-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* ***2011***, *111*, PR110–PR180. See Petersen, K.S. *Tetrahedron Lett.* ***2015***, *56*, 6523. For a review of recent advacnes as applied to natural product synthesis, see Wang, M.; Feng, M.; Tang, B.; Jiang, X. *Tetrahedron Lett.* ***2014***, *55*, 7147. Zeng, X.-P.; Cao, Z.-Y.; Wang, Y.-H.; Zhou, F.; Zhou, J. *Chem. Rev.* ***2016***, *116*, 7330.

As mentioned earlier, optically active materials cannot be created from inactive starting materials and conditions,[154] except in the manner previously noted.[102] However, when a new stereogenic center is created, the two possible enantiomers need not be formed in equal amounts if anything is present that is not symmetric. Asymmetric synthesis may be categorized into four headings.

1. *Active substrate*. If a new stereogenic center is created in a molecule that is already optically active, the product will generate diastereomers and the two diastereomers may not (except fortuitously) be formed in equal amounts. The reason is that the direction of attack by the reagent is determined by the groups already there. For certain additions to the carbon–oxygen double bond of ketones containing an asymmetric α carbon, *Cram's rule* predicts which of two diastereomers will predominate (diastereoselectivity).[155,156] The reaction of **45**, which has a stereogenic center at the α carbon, and HCN can generate two possible diastereomers, **46** and **47**.



If **45** is observed along its axis, it may be represented as in **48** (Sec. 4.O.i), where S, M, and L stand for small, medium, and large, respectively. The oxygen of the carbonyl orients itself between the small- and the medium-sized groups. It has been shown that n→π* interactions have a great influence over the chirality engendered by nucleophilic attack at a carbonyl.[157] The rule requires that the incoming group preferentially attacks on the side of the plane containing the small group. By this rule, it can be predicted that **47** will be formed in larger amounts than **46**.



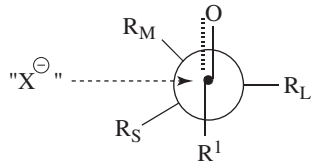
[154] For a discussion of synthesizing asymmetric quaternary centers, see Shimizu, M. *Angew. Chem. Int. Ed.* ***2011***, *50*, 5998. Also see Das, J.P.; Marck, I. *Chem. Commun.* ***2011***, *47*, 4593.

[155] Leitereg, T.J.; Cram, D.J. *J. Am. Chem. Soc.* ***1968***, *90*, 4019. For discussions, see Anh, N.T. *Top. Curr. Chem*, ***1980***, *88*, 145 (pp. 151–161); Eliel, E.L. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***, pp. 125–155. See Smith, R.J.; Trzoss, M; Bühl, M.; Bienz, S. *Eur. J. Org. Chem.* ***2002***, 2770.

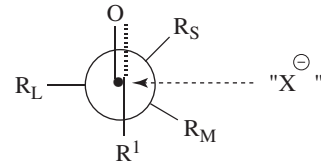
[156] See Eliel, E.L. *The Stereochemistry of Carbon Compounds*, McGraw-Hill, NY, ***1962***, pp. 68–74; Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2 (pp. 22–28); Ashby, E.C.; Laemmle, J.T. *Chem. Rev.* ***1975***, *75*, 521; Goller, E.J. *J. Chem. Educ.* ***1974***, *51*, 182; Toromanoff, E. *Top. Stereochem.* ***1967***, *2*, 157.

[157] Choudhary, A.; Newberry, R.W.; Raines, R.T. *Org. Lett.* ***2014***, *16*, 3421.

Another model uses transition state models **49** and **50** to predict diastereoselectivity in what is known as the *Felkin-Anh model*.[158] This model assumes the favored transition state will be that with the greatest separation between the incoming group and any electronegative substituent at the α carbon. The so-called *Cornforth model* has also been presented as a model for carbonyl addition to halogenated compounds,[159] and it assumes that the electron pairs on the carbonyl oxygen and on the halogen repel and assume an *anti* conformation.



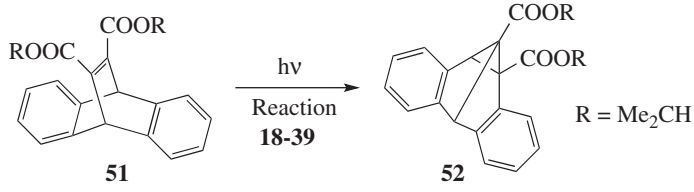
49



50

Many reactions of this type are known, and in some the extent of favoritism approaches 100% (for an example see reaction **12-12**).[160] The farther away the reaction site is from the chiral center, the less influence the latter has and the more equal the amounts of diastereomers formed. There are many examples of asymmetric induction via nucleophilic acyl addition to carbonyl compounds (**16-22** and **16-23**). Enolborane addition to α-heteroatom-substituted aldehydes has been evaluated using the Cornforth and the Felkin-Anh models.[161]

In a special case of this type of asymmetric synthesis, a compound (**51**) with achiral molecules, but whose crystals are chiral, was converted by UV light to a single enantiomer of a chiral product (**52**).[162]



51 Not chiral

52 Optically active

It is often possible to convert an achiral compound to a chiral compound by: (i) addition of a chiral group; (ii) running an asymmetric synthesis, and (iii) cleavage

[158] Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* ***1968***, 2199; Chérest, M.; Felkin, H. *Tetrahedron Lett.* ***1968***, 2205; Anh, N.T.; Eisenstein, O. *Nov. J. Chem.* ***1977***, *1*, 61. For experiments that show explanations for certain systems based on the Felkin-Anh model to be weak, see Yadav, V.K.; Gupta, A.; Balamurugan, R.; Sriramurthy, V.; Kumar, N.V. *J. Org. Chem.* ***2006***, *71*, 4178.

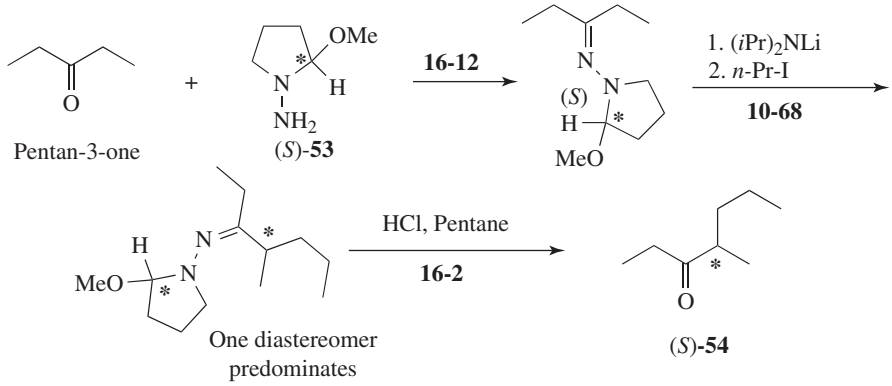
[159] Cornforth, J.W.; Cornforth, R.H.; Mathew, K.K. *J. Chem. Soc.* ***1959***, 112; Evans, D.A.; Siska, S.J.; Cee, V.J. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1761.

[160] See Eliel, E.L. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***, pp. 125–155; Eliel, E.L.; Koskimies, J.K.; Lohri, B. *J. Am. Chem. Soc.* ***1978***, *100*, 1614; Still, W.C.; McDonald, J.H. *Tetrahedron Lett.* ***1980***, *21*, 1031; Still, W.C.; Schneider, J.A. *Tetrahedron Lett.* ***1980***, *21*, 1035.

[161] Cee, V.J.; Cramer, C.J.; Evans, D.A. *J. Am. Chem. Soc.* ***2006***, *128*, 2920.

[162] Evans, S.V.; Garcia-Garibay, M.; Omkaram, N.; Scheffer, J.R.; Trotter, J.; Wireko, F. *J. Am. Chem. Soc.* ***1986***, *108*, 5648; Garcia-Garibay, M.; Scheffer, J.R.; Trotter, J.; Wireko, F. *Tetrahedron Lett.* ***1987***, *28*, 4789.

of the original chiral group. The original chiral group is called a *chiral auxiliary*, and an example is **53**. An example is conversion of the achiral pentan-2-one to the chiral 4-methyl-heptan-3-one, **54**.[163] In this case, >99% of the product was the (*S*) enantiomer. Compound **53** is an example of a *chiral auxiliary* because it is used to induce asymmetry and is then removed.



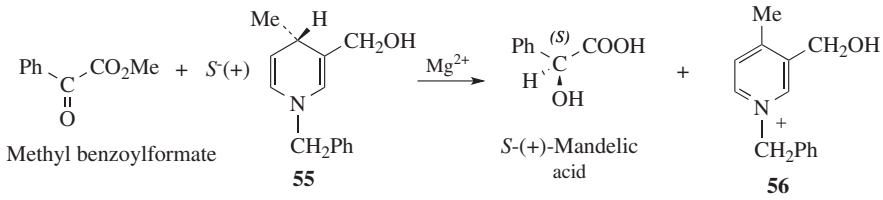
2. *Active reagent*. A pair of enantiomers can be separated by an active reagent that reacts faster with one of them than it does with the other (this is also a method of resolution). If the absolute configuration of the reagent is known, the configuration of the enantiomers can often be determined by a knowledge of the mechanism and by determining which diastereomer is preferentially formed.[164] Creation of a new stereogenic center in an inactive molecule can also be accomplished with an optically active reagent, although it is rare for 100% selectivity to be observed. An example[165,166] is the reduction of methyl benzoylformate with optically active *N*-benzyl-3-(hydroxymethyl)-4-methyl-1,4-dihydropyridine (**55**) to produce mandelic acid (after hydrolysis) that contained ~97.5% of the (*S*)-(+) isomer and 2.5% of the (*R*)-(−) isomer (for another example, see **15-11**). Note that the other product, **56**, is not chiral. Reactions like this, in which one reagent (in this case **56**) gives up its chirality to another, are called *self-immolative*.

[163] Enders, D.; Eichenauer, H.; Baus, U.; Schubert, H.; Kremer, K.A.M. *Tetrahedron* ***1984***, *40*, 1345.

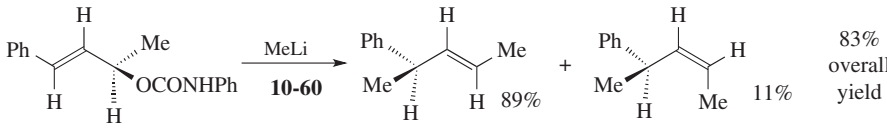
[164] See Brockmann Jr., H.; Risch, N. *Angew. Chem. Int. Ed.* ***1974***, *13*, 664; Potapov, V.M.; Gracheva, R.A.; Okulova, V.F. *J. Org. Chem. USSR* ***1989***, *25*, 311.

[165] Meyers, A.I.; Oppenlaender, T. *J. Am. Chem. Soc.* ***1986***, *108*, 1989. For reviews of asymmetric reduction, see Morrison, J.D. *Surv. Prog. Chem.* ***1966***, *3*, 147; Yamada, S.; Koga, K. *Sel. Org. Transform.* ***1970***, *1*, 1. See also, Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***.

[166] See, in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, the reviews by Halpern, J. pp. 41–69, Koenig, K.E. pp. 71–101, Harada, K. pp. 345–383; Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* ***1989***, *45*, 6901, 6902–6916; Jardine, F.H. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 751–775; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 53–87; Knowles, W.S. *Acc. Chem. Res.* ***1983***, *16*, 106; Brunner, H. *Angew. Chem. Int. Ed.* ***1983***, *22*, 897; Sathyanarayana, B.K.; Stevens, E.S. *J. Org. Chem.* ***1987***, *52*, 3170; Wroblewski, A.E.; Applequist, J.; Takaya, A.; Honzatko, R.; Kim, S.; Jacobson, R.A.; Reitsma, B.H.; Yeung, E.S.; Verkade, J.G. *J. Am. Chem. Soc.* ***1988***, *110*, 4144.



In another example, chirality is transferred from one atom to another in the same molecule.[167]



A reaction in which an inactive substrate is converted selectively to one of two enantiomers is called an *enantioselective* reaction, and the process is called *asymmetric induction*. These terms apply to reactions in this category and in categories 3 and 4. Biomimetic superhelical conducting microfibers with homochirality have been developed for enantioselective sensing.[168]

When an optically active substrate reacts with an optically active reagent to form two new stereogenic centers, it is possible for both centers to be created in the desired sense. This type of process is called *double asymmetric synthesis*[169] (for an example, see **16-34**).

3. *Optically active catalyst or solvent.*[170] Many such examples are found in the literature, among them reduction of ketones and substituted alkenes to optically active (though not optically pure) secondary alcohols and substituted alkanes by treatment with hydrogen and a chiral homogeneous hydrogenation catalyst (reactions **16-21** and **19-34**),[171] the treatment of aldehydes or ketones with organometallic compounds in the presence of a chiral catalyst (see reaction **16-22**), and the conversion of alkenes to optically active epoxides by treatment with a hydroperoxide and a chiral catalyst (see reaction **15-46**). In some instances, the ratio of enantiomers prepared in this way is 99:1 or more.[172] Other examples of the use of a chiral catalyst or solvent are the conversion of chlorofumaric acid (in the form of its di-ion) to the (−)-*threo* isomer of

[167] Goering, H.L.; Kantner, S.S.; Tseng, C.C. *J. Org. Chem.* ***1983***, *48*, 715.

[168] Zou, W.; Yan, Y.; Fang, J.; Yang, Y.; Liang, J.; Deng, K.; Yao, J.; Wei, Z. *J. Am. Chem. Soc.* ***2014***, *136*, 578.

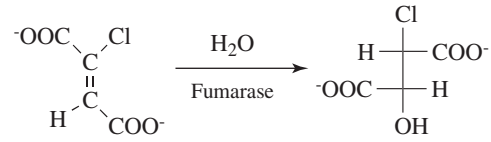
[169] For a review, see Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. *Angew. Chem. Int. Ed.* ***1985***, *24*, 1.

[170] For a monograph, see Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***. For reviews, see Tomioka, K. *Synthesis* ***1990***, 541; Consiglio, G.; Waymouth, R.M. *Chem. Rev.* ***1989***, *89*, 257; Brunner, H. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 5, Wiley, NY, ***1989***, pp. 109–146; Noyori, R.; Kitamura, M. *Mod. Synth. Methods* ***1989***, *5*, 115; Pfaltz, A. *Mod. Synth. Methods* ***1989***, *5*, 199; Brunner, H. *Synthesis* ***1988***, 645; Wynberg, H. *Top. Stereochem.* ***1986***, *16*, 87. For a discussion of stereodivergence, see Krautwald, S.; Carreira, E.M. *J. Am. Chem. Soc.* ***2017***, *139*, 5627.

[171] For reviews of these and related topics, see Zief, M.; Crane, L.J. *Chromatographic Separations*, Marcel Dekker, NY, ***1988***; Brunner, H. *J. Organomet. Chem.* ***1986***, *300*, 39; Bosnich, B.; Fryzuk, M.D. *Top. Stereochem.* ***1981***, *12*, 119.

[172] See Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***. Also see, Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, England, ***2017***, pp. 10–28.

the di-ion of chloromalic acid by treatment with H_2O and the enzyme fumarase,[173] and the preparation of optically active aldols (aldol condensation, see reaction **16-35**) by the condensation of enolate anions with optically active substrates.[174]



(-)-Threo isomer

4. *Reactions in the presence of circularly polarized light*.[175] If the light used to initiate a photochemical reaction (see Chapter 7) of achiral reagents is circularly polarized, then, in theory, a chiral product richer in one enantiomer might be obtained. However, such experiments have not proved fruitful. In certain instances, the use of left and right circularly polarized light *has* given products with opposite rotations[176] (showing that the principle is valid), but up to now the extent of favoritism has always been <1%.

4.I. METHODS OF RESOLUTION[177]

A pair of enantiomers can be separated in several ways, but conversion to diastereomers and separation of these by fractional crystallization or chromatographic methods are used most often. In this method and in some of the others, both isomers can be recovered, but in some methods it is necessary to destroy one.

1. *Conversion to diastereomers*. If the racemic mixture to be resolved contains a carboxyl group (and no strongly basic group), it is possible to form a salt with an optically active base.[178] Since the base used is, say, the (*S*) form, there will be a mixture of two salts produced having the configurations (*S*,*S*) and (*R*,*S*). Although the acids are enantiomers, the salts are diastereomers and have different properties. The property most often used for separation is differential solubility. The mixture of diastereomeric salts is allowed to crystallize from a suitable solvent. Since the solubilities

[173] Findeis, M.A.; Whitesides, G.M. *J. Org. Chem.* ***1987***, *52*, 2838; Réty, J.; Robinson, J.A. *Stereospecificity in Organic Chemistry and Enzymology*, Verlag Chemie, Deerfield Beach, FL, ***1982***. For reviews, see Klibanov, A.M. *Acc. Chem. Res.* ***1990***, *23*, 114; Jones, J.B. *Tetrahedron* ***1986***, *42*, 3351; Jones, J.B. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, pp. 309–344.

[174] Heathcock, C.H.; White, C.T. *J. Am. Chem. Soc.* ***1979***, *101*, 7076. See also, Tomooka, K.; Ezawa, T.; Inoue, H.; Uehara, K.; Igawa, K. *J. Am. Chem. Soc.* ***2011***, *133*, 1754.

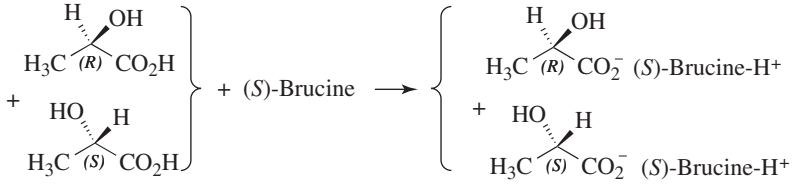
[175] For a review, See Buchardt, O. *Angew. Chem. Int. Ed.* ***1974***, *13*, 179. For a discussion, see Barron L.D. *J. Am. Chem. Soc*. ***1986***, *108*, 5539.

[176] See Bernstein, W.J.; Calvin, M.; Buchardt, O. *J. Am. Chem. Soc*. ***1973***, *95*, 527; Nicoud, J.F.; Kagan, J.F. *Isr. J. Chem.* ***1977***, *15*, 78. See also, Zandomeneghi, M.; Cavazza, M.; Pietra, F. *J. Am. Chem. Soc*. ***1984***, *106*, 7261.

[177] Faigl, F.; Fogassy, E.; Nógrádi, M.; Pálovics, E.; Schindler, J. *Tetrahedron Asymmetry* ***2008***, *19*, 519. See Wilen, S.H.; Collet, A.; Jacques, J. *Tetrahedron* ***1977***, *33*, 2725; Boyle, P.H. *Q. Rev. Chem. Soc*. ***1971***, *25*, 323; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 297–424; Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates, aand Resolutions*, Wiley, NY, ***1981***

[178] For resolutoin using quinine or Cinchona alkaloid salts, see Marzorati, L.; Fejfar, J.L.; Tormena, C.F.; Di Vitta, C. *Tetrahedron: Asymmetry* ***2012***, *23*, 748.

are different, the initial crystals formed will be richer in one diastereomer. Filtration at this point will already have achieved a partial resolution. Unfortunately, the difference in solubility is rarely if ever great enough to effect total separation with one crystallization. When fractional crystallizations must be used, the process is long and tedious. Fortunately, naturally occurring optically active bases (mostly alkaloids) are readily available. Among the most commonly used are brucine, ephedrine, strychnine, and morphine. Once the two diastereomers have been separated, it is easy to convert the salts back to the free acids and the recovered base can be used again. Catalytic methods are available, including the resolution of 2-lithio-*N*-Boc-piperidine.[179]



Most resolution of this type is done on carboxylic acids. Often, when a molecule does not contain a carboxyl group, it is converted to a carboxylic acid before resolution is attempted. Racemic compounds such as 2-aminoccylohexanol derivatives react with carboxylic acids, such as optically active mandelic acid, to give diastereomers that are separated and then converted to enantiopure compounds.[180] Racemic bases can be converted to diastereomeric salts with active acids. The principle of conversion to diastereomers is not confined to carboxylic acids, and other functional groups[181] may be coupled to an optically active reagent.[182] Alcohols[183] can be converted to diastereomeric esters, aldehydes to diastereomeric hydrazones, and so on. Amino alcohols have been resolved using boric acid and chiral binaphthols.[184] Phosphine oxides[185] and chiral calix[4]arenes[186] have been resolved. Chiral crown ethers have been used to separate mixtures of enantiomeric alkyl- and arylammonium ions, by the formation of diastereomeric complexes[187] (see also, category 3, below). Even hydrocarbons can be converted to diastereomeric inclusion

[179] Beng, T.K.; Tyree, W.S.; Parker, T.; Su, C.; Williard, P.G.; Gawley, R.E. *J. Am. Chem. Soc.* ***2012***, *134*, 16845.
[180] Schiffers, I.; Rantanen, T.; Schmidt, F.; Bergmans, W.; Zani, L.; Bolm, C. *J. Org. Chem.* ***2006***, *71*, 2320.
[181] See Boyle, P.H. *Q. Rev. Chem. Soc.* ***1971***, *25*, 323; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 322–424.
[182] For an extensive list of reagents that have been used for this purpose and of compounds resolved, see Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions*, University of Notre Dame Press, Notre Dame, IN, ***1972***.
[183] See Klyashchitskii, B.A.; Shvets, V.I. *Russ. Chem. Rev.* ***1972***, *41*, 592.
[184] Periasamy, M.; Kumar, N.S.; Sivakumar, S.; Rao, V.D.; Ramanathan, C.R.; Venkatraman, L. *J. Org. Chem.* ***2001***, *66*, 3828.
[185] Andersen, N.G.; Ramsden, P.D.; Che, D.; Parvez, M.; Keay, B.A. *J. Org. Chem.* ***2001***, *66*, 7478.
[186] Caccamese, S.; Bottino, A.; Cunsolo, F.; Parlato, S.; Neri, P. *Tetrahedron Asymmetry* ***2000***, *11*, 3103.
[187] See Davidson, R.B.; Bradshaw, J.S.; Jones, B.A.; Dalley, N.K.; Christensen, J.J.; Izatt, R.M.; Morin, F.G.; Grant, D.M. *J. Org. Chem.* ***1984***, *49*, 353.

compounds,[188] with urea. Urea is not chiral, but the cage structure is.[189] Racemic unsaturated hydrocarbons have been resolved as inclusion complex crystals with a chiral host compound derived from tartaric acid.[190] *trans*-Cyclooctene (Sec. 4.K) was resolved by conversion to a Pt complex containing an optically active amine.[191]

Fractional crystallization has always been the most common method for the separation of diastereomers. When it can be used, binary phase diagrams for the diastereomeric salts have been used to calculate the efficiency of optical resolution.[192] However, the process is tedious and the fact that it is limited to solids prompted a search for other methods. Fractional distillation has given only limited separation, but GC[193] and preparative liquid chromatography using chiral columns[194] have proved more useful. In many cases, they have supplanted fractional crystallization, especially where the quantities to be resolved are small.[195]

2. *Differential absorption*. When a racemic mixture is placed on a chromatographic column, if the column consists of chiral substances, then in principle the enantiomers should move along the column at different rates and should be separable without having to be converted to diastereomers.[195] This has been successfully accomplished with paper, column, thin-layer,[196] and gas and liquid chromatography.[197] For example, racemic mandelic acid has been almost completely resolved by column chromatography on starch.[198] Many workers have achieved separations with gas and liquid chromatography by the use of columns packed with chiral absorbents.[199] Columns packed with chiral materials are now commercially available and are capable of separating the enantiomers of certain types of compounds.[200]

[188] See Prelog, V.; Kovačević, M.; Egli, M. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1147; Worsch, D.; Vögtle, F. *Top. Curr. Chem.* ***1987***, *140*, 21; Toda, F. *Top. Curr. Chem.* ***1987***, *140*, 43; Stoddart, J.F. *Top. Stereochem.* ***1987***, *17*, 207; Arad-Yellin, R.; Green, B.S.; Knossow, M.; Tsoucaris, G. in Atwood, J.L.; Davies, J.E.D.; MacNicol, D.D. *Inclusion Compounds*, Vol. 3, Academic Press, NY, ***1984***, pp. 263–295.

[189] See Schlenk Jr., W. *Liebigs Ann. Chem.* ***1973***, 1145, 1156, 1179, 1195. See Arad-Yellin, R.; Green, B.S.; Knossow, M.; Tsoucaris, G. *J. Am. Chem. Soc.* ***1983***, *105*, 4561.

[190] Miyamoto, H.; Sakamoto, M.; Yoskioka, K.; Takaoka, R.; Toda, F. *Tetrahedron Asymmetry* ***2000***, *11*, 3045.

[191] For a review, see Tsuji, J. *Adv. Org. Chem.* ***1969***, *6*, 109, see p. 220.

[192] Amos, R.D.; Handy, N.C.; Jones, P.G.; Kirby, A.J.; Parker, J.K.; Percy, J.M.; Su, M.D. *J. Chem. Soc., Perkin Trans. 2* ***1992***, 549.

[193] See Westley, J.W.; Halpern, B.; Karger, B.L. *Anal. Chem.* ***1968***, *40*, 2046; Kawa, H.; Yamaguchi, F.; Ishikawa, N. *Chem. Lett.* ***1982***, 745.

[194] See Meyers, A.I.; Slade, J.; Smith, R.K.; Mihelich, E.D.; Hershenson, F.M.; Liang, C.D. *J. Org. Chem.* ***1979***, *44*, 2247; Goldman, M.; Kustanovich, Z.; Weinstein, S.; Tishbee, A.; Gil-Av, E. *J. Am. Chem. Soc.* ***1982***, *104*, 1093.

[195] See Lough, W.J. *Chiral Liquid Chromatography*; Blackie and Sons, London, ***1989***; Krstulović, A.M. *Chiral Separations by HPLC*, Ellis Horwood, Chichester, ***1989***; Zief, M.; Crane, L.J. *Chromatographic Separations*, Marcel Dekker, NY, ***1988***. For a review, see Karger, B.L. *Anal. Chem.* ***1967***, *39* (8), 24A.

[196] Weinstein, S. *Tetrahedron Lett.* ***1984***, *25*, 985.

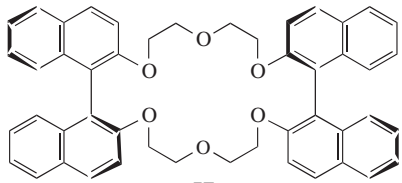
[197] See Allenmark, S.G. *Chromatographic Enantioseparation*, Ellis Horwood, Chichester, ***1988***; König, W.A. *The Practice of Enantiomer Separation by Capillary Gas Chromatography*, Hüthig, Heidelberg, ***1987***. For reviews, see Schurig, V.; Nowotny, H. *Angew. Chem. Int. Ed.* ***1990***, *29*, 939; Pirkle, W.H.; Pochapsky, T.C. *Chem. Rev.* ***1989***, *89*, 347. See also, many articles in the journal *Chirality*.

[198] Ohara, M.; Ohta, K.; Kwan, T. *Bull. Chem. Soc. Jpn.* ***1964***, *37*, 76. See also, Blaschke, G.; Donow, F. *Chem. Ber.* ***1975***, *108*, 2792; Hess, H.; Burger, G.; Musso, H. *Angew. Chem. Int. Ed.* ***1978***, *17*, 612.

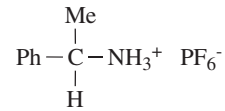
[199] See Erlandsson, P.; Marle, I.; Hansson, L.; Isaksson, R.; Pettersson, C.; Pettersson, G. *J. Am. Chem. Soc.* ***1990***, *112*, 4573.

[200] See, for example, Pirkle, W.H.; Welch, C.J. *J. Org. Chem.* ***1984***, *49*, 138.

3. *Chiral recognition*. The use of chiral hosts to form diastereomeric inclusion compounds was mentioned above. But in some cases it is possible for a host to form an inclusion compound with one enantiomer of a racemic guest, but not the other. This is called *chiral recognition*. One enantiomer fits into the chiral host cavity, the other does not. More often, both diastereomers are formed, but one forms more rapidly than the other, so that if the guest is removed it is already partially resolved (this is a form of kinetic resolution, see category 6). An example is use of the chiral crown ether **57** partially to resolve the racemic amine salt **58**.[201] When an aqueous solution of **58** was mixed with a solution of optically active **57** in chloroform, and the layers separated, the chloroform layer contained about twice as much of the complex between **57** and (*R*)-**58** as of the diastereomeric complex. Many other chiral crown ethers and cryptands have been used, as have been cyclodextrins,[202] cholic acid,[203] and other kinds of hosts.[188] Of course, enzymes are generally very good at chiral recognition, and much of the work in this area has been an attempt to mimic the action of enzymes.



57

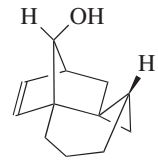


58

4. *Biochemical processes*.[204] Reactions catalyzed by enzymes can be utilized for this kind of resolution.[205] Biological molecules may react at different rates with the two enantiomers. For example, a certain bacterium may digest one enantiomer, but not the other. Pig liver esterase has been used for the selective cleavage of one enantiomeric ester.[206] This method is limited, since it is necessary to find the proper organism and since one of the enantiomers is destroyed in the process. However, when the proper organism is found, the method leads to a high extent of resolution since biological processes are usually very stereoselective. This process has been called chemoenzymatic dynamic kinetic resolution.[207]

[201] Kanoh, S.; Hongoh, Y.; Katoh, S.; Motoi, M.; Suda, H. *J. Chem. Soc., Chem. Commun.* ***1988***, 405; Bradshaw, J.S.; Huszthy, P.; McDaniel, C.W.; Zhu, C.Y.; Dalley, N.K.; Izatt, R.M.; Lifson, S. *J. Org. Chem.* ***1990***, *55*, 3129.
[202] See, for example, Hamilton, J.A.; Chen, L. *J. Am. Chem. Soc.* ***1988***, *110*, 5833.
[203] See Miyata, M.; Shibakana, M.; Takemoto, K. *J. Chem. Soc., Chem. Commun.* ***1988***, 655.
[204] For a review, see Sih, C.J.; Wu, S. *Top. Stereochem.* ***1989***, *19*, 63.
[205] See Nakamura, K.; Inoue, Y.; Ohno, A. *Tetrahedron Lett.* ***1994***, *35*, 4375; Kazlauskas, R.J. *J. Am. Chem. Soc.* ***1989***, *111*, 4953; Schwartz, A.; Madan, P.; Whitesell, J.K.; Lawrence, R.M. *Org. Synth.* ***69***, 1. For resolution with subtilisin, see Savile, C.K.; Magloire, V.P.; Kazlauskas, R.J. *J. Am. Chem. Soc.* ***2005***, *127*, 2104. For the chemoenzymatic kinetic resolution of primary amines, see Paetzold, J.; Bäckvall, J.E. *J. Am. Chem. Soc.* ***2005***, *127*, 17620.
[206] For an example, see Gais, H.-J.; Jungen, M.; Jadhav, V. *J. Org. Chem.* ***2001***, *66*, 3384.
[207] For an example of the resolution of acyloins, see Ödman, P.; Wessjohann, L.A.; Bornscheuer, U.T. *J. Org. Chem.* ***2005***, *70*, 9551.

5. *Mechanical separation*.[208] This is the method by which Pasteur proved that racemic tartaric acid was actually a mixture of (+)- and (−)-tartaric acids.[209] In the case of racemic sodium ammonium tartrate, the enantiomers crystallize separately: all the (+) molecules going into one crystal and all the (−) into another. Since the crystals too are nonsuperimposable, their appearance is not identical and a trained crystallographer can separate them with tweezers.[210] However, this is seldom a practical method, since few compounds crystallize in this manner. Even sodium ammonium tartrate does so only when it is crystallized <27 °C. A more useful variation of the method, although still not very common, is the seeding of a racemic solution with something that will cause only one enantiomer to crystallize.[211] An interesting example of the mechanical separation technique was reported in the isolation of heptahelicene (Sec. 4.C, section 7). One enantiomer of this compound, which incidentally has the extremely high rotation of $[\alpha]_D^{20} = +6200°$, spontaneously crystallizes from benzene.[212] In the case of 1,1′-binaphthyl, optically active crystals can be formed simply by heating polycrystalline racemic samples of the compound at 76–150 °C. A phase change from one crystal form to another takes place.[213] Note that 1,1′-binaphthyl is one of the few compounds that can be resolved by the Pasteur tweezer method. In some cases, resolution can be achieved by enantioselective crystallization in the presence of a chiral additive.[214] Spontaneous resolution has also been achieved by sublimation. In the case of the norborneol derivative **59**, when the racemic solid is subjected to sublimation, the (+) molecules condense into one crystal and the (−) molecules into another.[215] In this case the crystals are superimposable, unlike the situation with sodium ammonium tartrate, but the investigators were able to remove a single crystal, which proved to be optically active.



59

[208] For reviews, see Collet, A.; Brienne, M.; Jacques, J. *Chem. Rev.* ***1980***, *80*, 215; *Bull. Soc. Chim. Fr.* ***1972***, 127; ***1977***, 494. For a discussion, see Curtin, D.Y.; Paul, I.C. *Chem. Rev.* ***1981***, *81*, 525 (pp. 535–536).

[209] Besides discovering this method of resolution, Pasteur also discovered the method of conversion to diastereomers and separation by fractional crystallization and the method of biochemical separation (and, by extension, kinetic resolution).

[210] This is a case of optically active materials arising from inactive materials. However, it may be argued that an optically active investigator is required to use the tweezers.

[211] For a review of the seeding method, see Secor, R.M. *Chem. Rev.* ***1963***, *63*, 297.

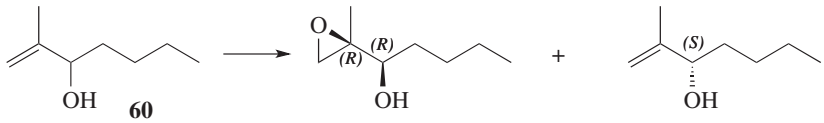
[212] Martin, R.H; Baes, M. *Tetrahedron* ***1975***, *31*, 2135. See also, Wynberg, H.; Groen, M.B. *J. Am. Chem. Soc.* ***1968***, *90*, 5339; McBride, J.M.; Carter, R.L. *Angew. Chem. Int. Ed.* ***1991***, *30*, 293.

[213] Kress, R.B.; Duesler, E.N.; Etter, M.C.; Paul, I.C.; Curtin, D.Y. *J. Am. Chem. Soc.* ***1980***, *102*, 7709. See also, Gottarelli, G.; Spada, G.P. *J. Org. Chem.* ***1991***, *56*, 2096. For a discussion and other examples, see Agranat, I.; Perlmutter-Hayman, B.; Tapuhi, Y. *Nouv. J. Chem.* ***1978***, *2*, 183.

[214] Addadi, L.; Weinstein, S.; Gati, E.; Weissbuch, I.; Lahav, M. *J. Am. Chem. Soc.* ***1982***, *104*, 4610. See also, Weissbuch, I.; Addadi, L.; Berkovitch-Yellin, Z.; Gati, E.; Weinstein, S.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* ***1983***, *105*, 6615.

[215] Paquette, L.A.; Lau, C.J. *J. Org. Chem.* ***1987***, *52*, 1634.

6. *Kinetic resolution*.[216] The literature examined for this edition has far too many literature citations for inclusion in this section. Clearly, this is an important and active area of research, and the citations listed here are meant to be illustrative and certainly not an exhaustive representation. Since enantiomers react with chiral compounds at different rates, it is sometimes possible to effect a partial separation by stopping the reaction before completion. This method is very similar to the asymmetric syntheses discussed on Sec. 4.C, category 5. A method has been developed to evaluate the enantiomeric ratio of kinetic resolution using only the extent of substrate conversion.[217] An important application of this method is the resolution of racemic alkenes by treatment with optically active diisopinocampheylborane,[218] since alkenes do not easily lend themselves to conversion to diastereomers if no other functional groups are present. Another example is the resolution of allylic alcohols, such as **60**, with one enantiomer of a chiral epoxidation agent (see **15-46**).[219] In the case of **60**, the discrimination was extreme. One enantiomer was converted to the epoxide and the other was not, the rate ratio (hence the selectivity factor) being >100. Of course, in this method only one of the enantiomers of the original racemic mixture is obtained, but there are at least two possible ways of getting the other: (i) use of the other enantiomer of the chiral reagent; (ii) conversion of the product to the starting compound by a reaction that preserves the stereochemistry.



60
Racemic

Kinetic resolution of racemic allylic acetates[220] has been accomplished via asymmetric dihydroxylation (**15-44**), and 2-oxoimidazolidine-4-carboxylates have been developed as new chiral auxiliaries for the kinetic resolution of amines.[221] A green resolution process has been reported for aliphatic secondary alcohols.[222] Kinetic resolution of allylic alcohols has been achieved by acylation catalyzed by lipase PS-30.[223] Benzotetramisole catalyzed enantioselective alcoholysis for the kinetic resolution of *N*-acyl-ß-lactams.[224] Catalytic kinetic resolution has been used, including

[216] For reviews, see Pellissier, H. *Tetrahedron* ***2008***, *64*, 1563; Ward, R.S. *Tetrahedron Asymmetry* ***1995***, *6*, 1475; Pellissier, H. *Tetrahedron* ***2003***, *59*, 8291; Pellissier, H. *Tetrahedron* ***2011***, *67*, 3769; ***2016***, *72*, 3133. For synthetic methods applied to the separation of enantiomers, see Todd, M.H. (Ed) *Separation of Enantiomers: Synthetic Methods*, Wiley-VCH, Weinheim, ***2014***.

[217] Lu, Y.; Zhao, X.; Chen, Z.-N. *Tetrahedron Asymmetry* ***1995***, *6*, 1093.

[218] Brown, H.C.; Ayyangar, N.R.; Zweifel, G. *J. Am. Chem. Soc.* ***1964***, *86*, 397.

[219] Carlier, P.R.; Mungall, W.S.; Schröder, G.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1988***, *110*, 2978; Discordia, R.P.; Dittmer, D.C. *J. Org. Chem.* ***1990***, *55*, 1414. For other examples, see Katamura, M.; Ohkuma, T.; Tokunaga, M.; Noyori, R. *Tetrahedron: Assymetry* ***1990***, *1*, 1; Hayashi, M.; Miwata, H.; Oguni, N. *J. Chem. Soc., Perkin Trans. 2* ***1991***, 1167.

[220] Lohray, B.B.; Bhushan, V. *Tetrahedron Lett.* ***1993***, *34*, 3911.

[221] Kubota, H.; Kubo, A.; Nunami, K. *Tetrahedron Lett.* ***1994***, *35*, 3107.

[222] Ren, L.; Xu, T.; He, R.; Jiang, Z.; Zhou, H.; Wei, P. *Tetrahedron: Asymmetry* ***2013***, *24*, 249.

[223] Chen, P.; Xiang, P. *Tetrahedron Lett.* ***2011***, *52*, 5758.

[224] Bumbu, V.D.; Birman, V.B. *J. Am. Chem. Soc.* ***2011***, *133*, 13902. Yang, X.; Bumbu, V.D.; Birman, V.B. *Org. Lett.* ***2011***, *13*, 4755.

a method to determine absolute configuration.[225] A green, enzymatic procedure has been reported for the resolution of chiral alcohols.[226] Carbenes have been used to catalyze the kinetic resolution of carboxylic esters.[227] Chemoenzymatic dynamic kinetic resolution has been used for several functional groups.[228] A ruthenium complex has been used for the dynamic kinetic resolution of aromatic α-hydroxy ketones.[229] Racemic secondary allyl boronates have been resolved.[230] Allylic carbonates have been resolved.[231]

7. *Deracemization*. In this type of process, one enantiomer is converted to the other, so that a racemic mixture is converted to a pure enantiomer, or to a mixture enriched in one enantiomer (*enantio-enriched*). This is not quite the same as the methods of resolution previously mentioned, although an outside optically active substance is required. To effect the deracemization two conditions are necessary: (i) the enantiomers must complex differently with the optically active substance; (ii) they must interconvert under the conditions of the experiment. When racemic thioesters were placed in solution with a specific optically active amide for 28 days, the resulting solution contained 89% of one enantiomer and 11% of the other.[232] In this case, the presence of a base (Et_3N) was necessary for the interconversion to take place. Biocatalytic deracemization processes induce deracemization of chiral secondary alcohols.[233] In a specific example, *Sphingomonas paucimobilis* NCIMB 8195 catalyzes the efficient deracemization of many secondary alcohols in up to 90% yield of the (*R*)-alcohol.[234]

[225] Wagner, A.J.; David, J.G.; Rychnovsky, S.D. *Org. Lett.* ***2011***, *13*, 4470.

[226] Wang, B.; Jiang, L.; Wang, J.; Ma, J.; Liu, M.; Yu, H. *Tetrahedron: Asymmetry* ***2011***, *22*, 980.

[227] Chen, X.; Fong, J.Z.M.; Xu, J.; Mou, C.; Lu, Y.; Yang, S.; Song, B.-A.; Chi, Y.R. *J. Am. Chem. Soc.* ***2016***, *138*, 7212

[228] Poulhès, F.; Vanthuyne, N.; Bertrand, M.P.; Gastaldi, S.; Gil, G. *J. Org. Chem.* ***2011***, *76*, 7281. Also see Sugai, T.; Ohta, H. *Tetrahedron Lett.* ***1991***, *32*, 7063; Sugai, T.; Ritzén, H.; Wong, C.H. *Tetrahedron: Asymmetry* ***1993***, *4*, 1051; Takikawa, H.; Nozawa, D.; Kay, A.; Muto, S.-E.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2467; Dietz, C.; Hart, T.K.; Nemati, R.; Nichols, F.C.; Smith, M.B. *Tetrahedron* ***2016***, *72*, 7557. Kim, S.; Choi, Y.K.; Hong, J.; Park, J.; Kim, M.-J. *Tetrahedron Lett.* ***2013***, *54*, 1185. Chen, P.; Yang, W. *Tetrahedron Lett.* ***2014***, *55*, 2290. Li, W.; Lin, Z.; Chen, L.; Tian, X.; Wang, Y.; Huang, S.-H.; Hong, R. *Tetrahedron Lett.* ***2016***, *57*, 603. Jadhav, D.D.; Patil, H.S.; Chaya, P.S.; Thulasiram, H.V. *Tetrahedron Lett.* ***2016***, *57*, 4563. Kim, H.; Choi, Y.K.; Lee, J.; Lee, E.; Park, J.; Kim, M.J. *Angew. Chem. Int. Ed.* ***2011***, *50*, 10944. Yasukawa, K.; Nakano, S.; Asano, Y. *Angew. Chem. Int. Ed.* ***2014***, *53*, 4428. Bencze, L.C.; Paizs, C.; Toşa, M.I.; Irimie, F.D. *Tetrahedron: Asymmetry* ***2011***, *22*, 675. Päiviö, M.; Perkiö, P.; Kanerva, L.T. *Tetrahedron: Asymmetry* ***2012***, *23*, 230. O'Neill, M.; Beecher, D.; Mangan, D.; Rowan, A.S.; Monte, A.; Sroka, S.; Modregger, J.; Hundle, B.; Moody, T.S. *Tetrahedron: Asymmetry* ***2012***, *23*, 583. Kumaraguru, T.; Fadnavis, N.W. *Tetrahedron: Asymmetry* ***2012***, *23*, 775. Engström, K. Vallin, M.; Syrén, P.-O.; Hult, K.; Bäckvall, J.-E. *Org. Biomol. Chem.* ***2011***, *9*, 81. For the use of an ionic liquid acylating agent, see Teixeira, R.; Lourenço, N.M.T. *Tetrahedron: Asymmetry* ***2014***, *25*, 944.

[229] Agrawal, S.; Martínez-Castro, E.; Marcos, R.; Martín-Matute, B. *Org. Lett.* ***2014***, *16*, 2256. For the oxidative resolution of α-hydroxy ketones, see Mutupandi, P.; Sekar, G. *Tetrahedron: Asymmetry* ***2011***, *22*, 512. A Ru complex was used in the kinetic resolution of a wide range of secondary alcohols: see Päiviö, M.; Mavrynsky, D.; Leino, R.; Kanerva, L.T. *Eur. J. Org. Chem.* ***2011***, 1452.

[230] Incerti-Pradillos, C.A.; Kabeshov, M.A.; Malkov, A.V. *Angew. Chem. Int. Ed.* ***2013***, *52*, 5338.

[231] Bai, D.-C.; Wang, W.Y.; Ding, C.-H.; Hou, X.-L. *Synlett.* ***2015***, *26*, 1510.

[232] Pirkle, W.H.; Reno, D.S. *J. Am. Chem. Soc.* ***1987***, *109*, 7189. For another example, see Reider, P.J.; Davis, P.; Hughes, D.L.; Grabowski, E.J.J. *J. Org. Chem.* ***1987***, *52*, 955.

[233] Stecher, H.; Faber, K. *Synthesis* ***1997***, 1.

[234] Allan, G. R.; Carnell, A. J. *J. Org. Chem.* ***2001***, *66*, 6495.

4.J. OPTICAL PURITY[235]

An attempt to resolve a racemic mixture by one of the methods described in the previous section gives either a pure compound or a new mixture. How can the purity of the two enantiomers obtained be determined? If the (+) isomer is contaminated by, say, 20% of the (−) isomer, how can this be determined? If the value of [α] for the pure material ($[\alpha]_{max}$) is known, the purity of a sample is easily determined by measuring its rotation. If $[\alpha]_{max}$ is +80° and the resolved (+) enantiomer contains 20% of the (−) isomer, [α] for the sample will be +48°.[236] *Optical purity* is defined as:

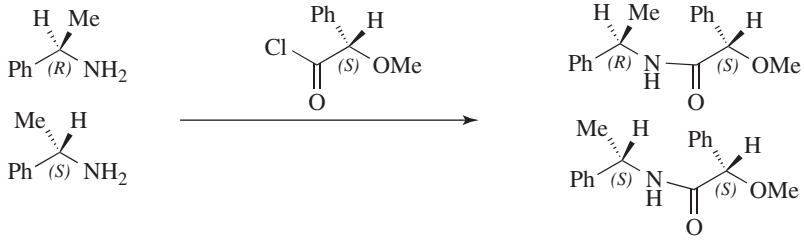
$$\text{percent optical purity} = \frac{[\alpha]_{obs}}{[\alpha]_{max}} \times 100$$

Assuming a linear relationship between [α] and concentration, which is true for most cases, the optical purity is equal to the percent excess of one enantiomer over the other:

$$\text{optical purity} = \text{percent enantiomeric excess (\%ee)}^{237} = \frac{[R] - [S]}{[R] + [S]} \times 100 = \%R - \%S$$

How is the value of $[\alpha]_{max}$ determined? It is plain that there are two related problems; namely, what are the optical purities of our two samples and what is the value of $[\alpha]_{max}$. Finding the properties of one also gives the other. Several methods for solving these problems are known.

One of these methods involves the use of NMR[238] (Sec. 4.E.ii, category 7). If there is a nonracemic mixture of two enantiomers and the proportions constitute an unknown, convert the mixture into a mixture of diastereomers with an optically pure reagent and look at the NMR spectrum of the resulting mixture, for example:



[235] For a review, see Raban, M.; Mislow, K. *Top. Stereochem.* ***1967***, *2*, 199.

[236] If a sample contains 80% (+) and 20% (–) isomer, the (–) isomer cancels an equal amount of (+) isomer and the mixture behaves as if 60% of it were (+) and the other 40% inactive. Therefore the rotation is 60% of 80° or 48°. This type of calculation, however, is not valid for cases in which [α] is dependent on concentration (Sec. 4.B); see Horeau, A. *Tetrahedron Lett.* ***1969***, 3121.

[237] For a method to measure %ee using electrooptics, see Walba, D.M.; Eshdat, L.; Korblova, E.; Shao, R.; Clark, N.A. *Angew. Chem. Int. Ed.* ***2007***, *46*, 1473. For determination via mass spectrometry, see Piovesana, S.; Samperi, R.; Laganà, A.; Bella, M. *Chem. Eur. J.* ***2013***, *19*, 11478.

[238] Raban, M.; Mislow, K. *Tetrahedron Lett.* ***1965***, 4249, ***1966***, 3961; Tokles, M.; Snyder, J.K. *Tetrahedron Lett.* ***1988***, *29*, 6063. For a review, see Yamaguchi, S. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 125–152. See also, Raban, M.; Mislow, K. *Top. Stereochem.* ***1967***, *2*, 199.

If the NMR spectrum of the starting mixture is examined, only one peak would be found (split into a doublet by the C—H) for the Me protons, since enantiomers give identical NMR spectra.[239] But the two amide products are not enantiomers and each Me gives its own doublet. From the intensity of the two peaks, the relative proportions of the two diastereomers (and hence of the original enantiomers) can be determined. Alternatively, the "unsplit" OMe peaks could have been used. This method was satisfactorily used to determine the optical purity of a sample of 1-phenylethylamine (the case shown above),[240] as well as other cases, but it is obvious that sometimes corresponding groups in diastereomeric molecules will give NMR signals that are too close together for resolution. In such cases, one may resort to the use of a different optically pure reagent. ^{13}C NMR can be used in a similar manner.[241]

It is also possible to use these spectra to determine the absolute configuration of the original enantiomers by comparing the spectra of the diastereomers with those of the original enantiomers.[242] From a series of experiments with related compounds of known configurations it can be determined in which direction one or more of the ^{1}H or ^{13}C NMR peaks are shifted by formation of the diastereomer. It is then assumed that the peaks of the enantiomers of unknown configuration will be shifted the same way.

A closely related method does not require conversion of enantiomers to diastereomers, but relies on the fact that (in principle, at least) enantiomers have different NMR spectra *in a chiral solvent*, or when mixed with a chiral molecule (in which case transient diastereomeric species may form – Sec. 4.E.ii). In such cases, the peaks may be separated enough to permit the proportions of enantiomers to be determined from their intensities.[243] Another variation, which gives better results in many cases, is to use an achiral solvent but with the addition of a *chiral lanthanide shift reagent* such as *tris*[3-trifluoroacetyl-*d*-camphorato]europium(III).[244] Lanthanide shift reagents have the property of spreading NMR peaks of compounds with which they can form coordination compounds, for example, alcohols, carbonyl compounds, and amines. Chiral lanthanide shift reagents shift the peaks of the two enantiomers of many such compounds to different extents.

Another method, involving GC,[245] is similar in principle to the NMR chiral complex method. A mixture of enantiomers whose purity is to be determined is converted by means of an optically pure reagent into a mixture of two diastereomers. These diastereomers are then separated by GC and the ratios determined from the peak areas. Once again, the ratio

[239] Though enantiomers give identical NMR spectra, the spectrum of a single enantiomer may be different from that of the racemic mixture, even in solution. See Williams, T.; Pitcher, R.G.; Bommer, P.; Gutzwiller, J.; Uskoković, M. *J. Am. Chem. Soc.* ***1969***, *91*, 1871.

[240] Raban, M.; Mislow, K. *Top. Stereochem.* ***1967***, *2*, 199 (pp. 216–218).

[241] For a method that relies on diastereomer formation without a chiral reagent, see Feringa, B.L.; Strijtveen, B.; Kellogg, R.M. *J. Org. Chem.* ***1986***, *51*, 5484. See also, Luchinat, C.; Roelens, S. *J. Am. Chem. Soc.* ***1986***, *108*, 4873.

[242] See Trost, B.M.; Belletire, J.L.; Godleski, S.; McDougal, P.G.; Balkovec, J.M.; Baldwin, J.J.; Christy, M.E.; Ponticello, G.S.; Varga, S.L.; Springer, J.P. *J. Org. Chem.* ***1986***, *51*, 2370.

[243] For reviews of NMR chiral solvating agents, see Weisman, G.R. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 153–171; Pirkle, W.H.; Hoover, D.J. *Top. Stereochem.* ***1982***, *13*, 263. Sweeting, L.M.; Anet, F.A.L. *Org. Magn. Reson.* ***1984***, *22*, 539. See also, Pirkle, W.H.; Tsipouras, A. *Tetrahedron Lett.* ***1985***, *26*, 2989; Parker, D.; Taylor, R.J. *Tetrahedron* ***1987***, *43*, 5451.

[244] Sweeting, L.M.; Crans, D.C.; Whitesides, G.M. *J. Org. Chem.* ***1987***, *52*, 2273; Morrill, T.C. *Lanthanide Shift Reagents in Stereochemical Analysis*, VCH, NY, ***1986***; Fraser, R.R. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 173–196; Sullivan, G.R. *Top. Stereochem.* ***1978***, *10*, 287.

[245] See Westley, J.W.; Halpern, B. *J. Org. Chem.* ***1968***, *33*, 3978.

of diastereomers is the same as that of the original enantiomers. High-pressure liquid chromatography (HPLC) has been used in a similar manner and has wider applicability.[246] The direct separation of enantiomers by gas or liquid chromatography on a chiral column has also been used to determine optical purity.[247]

Other methods[248] involve isotopic dilution,[249] kinetic resolution,[250] ^{13}C NMR relaxation rates of diastereomeric complexes,[251] and circular polarization of luminescence.[252]

4.K. *CIS–TRANS* ISOMERISM

Compounds in which rotation is restricted may exhibit *cis–trans* isomerism.[253] These compounds do not rotate the plane of polarized light (unless they also happen to be chiral), and the properties of the isomers are not identical. The two most important types are isomerism resulting from double bonds and isomerism resulting from rings.

4.K.i. *Cis–Trans* Isomerism Resulting from Double Bonds

In the discussion of alkene structure (Sec. 1.D) it was noted that the presence of the π bond prevents rotation around the double bond, and that the two carbon atoms of a C=C double bond and the four atoms directly attached to them are all in the same plane. In the case of a molecule WXC=CYZ, stereoisomerism exists when W ≠ X and Y ≠ Z. There are two and only two isomers (**61** and **62**), each superimposable on its mirror image unless one of the groups happens to carry a stereogenic center. Note that **61** and **62** are diastereomers, by the definition given in Sec. 4.E.i. There are two ways to name such isomers. In the older and less versatile method, one isomer is called *cis* and the other *trans*. When each carbon of the C=C unit has an *identical group* (W in **61** and **62**) but fits the substitution pattern of **61** and **62**, the *cis–trans* nomenclature system may be applied. When the two identical groups are on the same side (W and W in **61**), it is labeled *cis*. *cis*-Hex-3-ene is shown as an example. When the two identical groups are on opposite side (W and W in **62**) it is labeled *trans*. *trans*-Hex-3-ene is also shown as an example. Unfortunately, there is no obvious way to apply this method when the four groups are different.

61 **62**

[246] For a review, see Pirkle, W.H.; Finn, J. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 87–124.

[247] For reviews, see in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, the articles by Schurig, V. pp. 59–86 and Pirkle, W.H.; Finn, J. pp. 87–124.

[248] See Hill, H.W.; Zens, A.P.; Jacobus, J. *J. Am. Chem. Soc.* ***1979***, *101*, 7090; Matsumoto, M.; Yajima, H.; Endo, R. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 4139.

[249] Berson, J.A.; Ben-Efraim, D.A. *J. Am. Chem. Soc.* ***1959***, *81*, 4083; Andersen, K.K.; Gash, D.M.; Robertson, J.D. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 45–57.

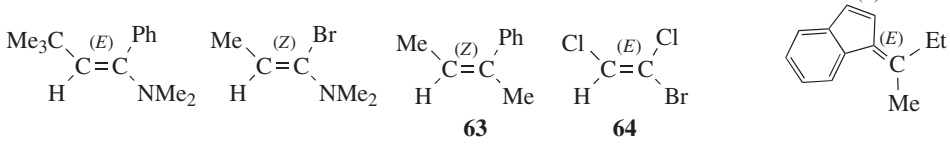
[250] Horeau, A.; Guetté, J.; Weidmann, R. *Bull. Soc. Chim. Fr.* ***1966***, 3513. For a review, see Schoofs, A.R.; Guetté, J. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 1, Academic Press, NY, ***1983***, pp. 29–44.

[251] Hofer, E.; Keuper, R. *Tetrahedron Lett.* ***1984***, *25*, 5631.

[252] Schippers, P.H.; Dekkers, H.P.J.M. *Tetrahedron* ***1982***, *38*, 2089.

[253] *Cis–trans* isomerism has also been called *geometrical isomerism*.

The newer and more widely applicable method can be applied to all cases, and is based on the Cahn-Ingold-Prelog system (Sec. 4.E.i). The two groups at each carbon of the C=C unit are ranked by the sequence rules. The isomer with the two higher-ranking groups on the same side of the double bond is called (*Z*) (for the German word *zusammen* meaning *together*). The isomer with the two higher-ranking groups on opposite sides of the double bond is called (*E*) (for *entgegen* meaning *opposite*).[254] A few examples are shown. Note that the (*Z*) isomer is not necessarily the one that would be called *cis* under the older system (e.g., **63** and **64**). Like *cis* and *trans*, (*E*) and (*Z*) are used as prefixes; for example, **64** is called (*E*)-1-bromo-1,2-dichloroethene.

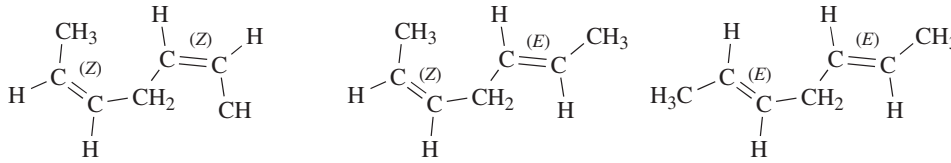


63 **64**

This type of isomerism is also possible with other double bonds, such as C=N,[255] N=N,[256] or even C=S,[257] although in these cases only two or three groups are connected to the double-bond atoms. In the case of imines, oximes, and other C=N compounds, if W = Y, **65** may be called *syn* and **66** *anti*, but (*E*) and (*Z*) are used here too.[258] In azo compounds there is no ambiguity. Compound **67** is always *syn* or (*Z*) regardless of the nature of W and Y.

65 **66** **67**

If there is more than one double bond[259] in a molecule and if W ≠ X and Y ≠ Z for each, the number of isomers in the most general case is 2^n, although this number may be decreased if some of the substituents are the same, as in the three hepta-2,5-dienes shown.



[254] For a complete description of the system, see *Pure Appl. Chem.* ***1976***, *45*, 13; *Nomenclature of Organic Chemistry*, Pergamon, Elmsford, NY, ***1979*** (the "Blue Book").

[255] See in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, the articles by McCarty, C.G. pp. 363–464 (pp. 364–408), and Wettermark, G. pp. 565–596 (pp. 574–582).

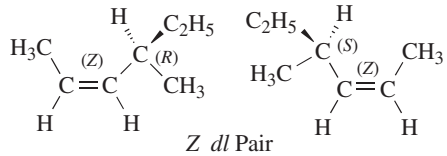
[256] Wang, Y.-N.; Bohle, D.S.; Bonifant, C.L.; Chmurny, G.N.; Collins, J.R.; Davies, K.M.; Deschamps, J.; Flippen-Anderson, J.L.; Keefer, L.K.; Klose, J.R.; Saavedra, J.E.; Waterhouse, D.J.; Ivanic, J. *J. Am. Chem. Soc.* ***2005***, *127*, 5388.

[257] King, J.F.; Durst, T. *Can. J. Chem.* ***1966***, *44*, 819.

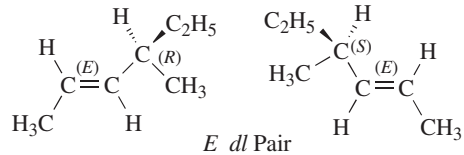
[258] A mechanism has been reported for the acid-catalyzed (*Z/E*) isomerization of imines. See Johnson, J.E.; Morales, N.M.; Gorczyca, A.M.; Dolliver, D.D.; McAllister, M.A. *J. Org. Chem.* ***2001***, *66*, 7979.

[259] This rule does not apply to allenes, which do not show *cis–trans* isomerism (Sec. 4.C, category 5).

When a molecule contains a double bond and a stereogenic carbon, there are four isomers, a *cis* pair of enantiomers and a *trans* pair, as shown for 4-methylhex-2-ene.

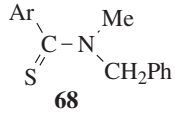


Z dl Pair

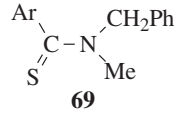


E dl Pair

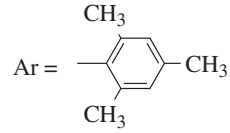
Double bonds in small rings are so constrained that they must be *cis*. From cyclopropene (a known system) to cycloheptene, double bonds in a stable ring *cannot* be *trans*. However, the cyclooctene ring is large enough to permit *trans* double bonds to exist (Sec. 4.K), and for rings larger than 10- or 11-membered, *trans* isomers are more stable[260] (see also, Sec. 4.Q.ii).



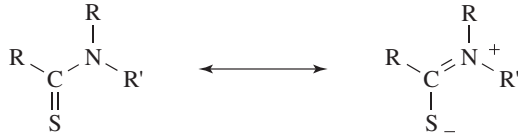
68



69



In a few cases, single-bond rotation is so slowed that *cis* and *trans* isomers can be isolated even where no double bond exists.[261] One example is *N*-methyl-*N*-benzylthiomesitylide (**68** and **69**).[262] The isomers are stable in the crystalline state but interconvert with a half-life of ~25 hours in $CDCl_3$ at 50 °C.[263] This type of isomerism is rare; it is found chiefly in certain amides and thioamides, because resonance gives the single bond some double-bond character and slows rotation.[83] (For other examples of restricted rotation about single bonds, see Sec. 4.Q.iv.)



Conversely, there are compounds in which nearly free rotation is possible around what are formally C=C double bonds. These compounds, called *push-pull* or *captodative* ethenes, have two electron-withdrawing groups on one carbon and two electron-donating groups on the other (**70**).[264] The contribution of di-ionic canonical forms, such as the one shown, decreases the double-bond character and allows easier rotation.

[260] Cope, A.C.; Moore, P.T.; Moore, W.R. *J. Am. Chem. Soc.* ***1959***, *81*, 3153.

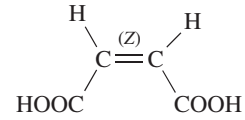
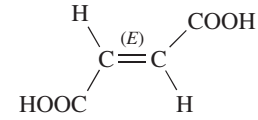
[261] Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 41–71.

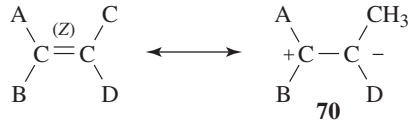
[262] Mannschreck, A. *Angew. Chem. Int. Ed.* ***1965***, *4*, 985. See also, Völter, H.; Helmchen, G. *Tetrahedron Lett.* ***1978***, 1251; Walter, W.; Hühnerfuss, H. *Tetrahedron Lett.* ***1981***, *22*, 2147.

[263] This is another example of atropisomerism (Sec. 4.C, category 5).

[264] For reviews, see Sandström, J. *Top. Stereochem.* ***1983***, *14*, 83; Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 111–125.

TABLE 4.2 Some properties of maleic and fumaric acids

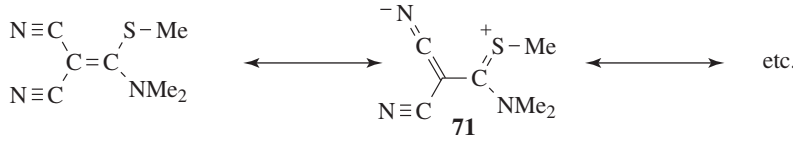
Property	**Maleic acid**	**Fumaric acid**
		
Melting point, °C	130	286
Solubility in water at 25 °C, g L^{-1}	788	7
K_1 (at 25 °C)	1.5×10^{-2}	1×10^{-3}
K_2 (at 25 °C)	2.6×10^{-7}	3×10^{-5}



70

A, B = electron- withdrawing
C, D = electron-donating

Compound **71** has a barrier to rotation of 13 kcal mol^{-1} (55 kJ mol^{-1}),[265] for example, compared to a typical value of about 62–65 kcal mol^{-1} (260–270 kJ mol^{-1}) for simple alkenes.



71

Since they are diastereomers, *cis–trans* isomers always differ in properties; the differences may range from very slight to considerable. The properties of maleic acid are so different from those of fumaric acid (Table 4.2) that it is not surprising that they have different names. Since they generally have more symmetry than *cis* isomers, *trans* isomers in most cases have higher melting points and lower solubilities in inert solvents. The *cis* isomer usually has a higher heat of combustion, which indicates a lower thermochemical stability. Other noticeably different properties are densities, acid strengths, boiling points, and various types of spectra, but the differences are too involved to be discussed here.

It is also important to note that *trans*-alkenes are often more stable than *cis*-alkenes due to diminished steric hindrance (Sec. 4.Q.iv), but this is not always the case. It is known, for example, that *cis*-1,2-difluoroethene is thermodynamically more stable than *trans*-1,2-difluoroethene. This appears to be due to delocalization of halogen lone pair electrons and an antiperiplanar effect between vicinal antiperiplanar bonds.[266]

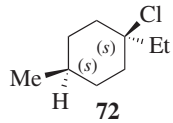
[265] Sandström, J.; Wennerbeck, I. *Acta Chem. Scand. Ser. B*, ***1978***, *32*, 421.
[266] Yamamoto, T.; Tomoda, S. *Chem. Lett.* ***1997***, 1069.

4.K.ii. *Cis–Trans* Isomerism of Monocyclic Compounds

Although rings of four carbons and larger are not generally planar (Sec. 4.O), they will be treated as such in this section, since the correct number of isomers can be determined when this is done[267] and the principles are easier to visualize (Sec. 4.O).

The presence of a ring, like that of a double bond, prevents rotation. *Cis* and *trans* isomers are possible whenever there are two carbons on a ring, each of which is substituted by two different groups. The two carbons need not be adjacent. Examples are:

In some cases, the two stereoisomers can interconvert. In *cis*- and *trans*-disubstituted cyclopropanones, for example, there is reversible interconversion that favors the more stable *trans* isomer. This fluxional isomerization occurs via ring opening to an unseen oxyallyl *valence bond* isomer.[268]



72

While *cis* and *trans* isomers are possible for rings, the restrictions are that W may equal Y and X may equal Z, but W may not equal X and Y may not equal Z. There is an important difference from the double-bond case: the substituted carbons may be stereogenic carbons. This means that there may be more than two isomers. In the most general case, where W, X, Y, and Z are all different, there are four isomers since neither the *cis* nor the *trans* isomer is superimposable on its mirror image. This is true regardless of ring size or which carbons are involved, except that in rings of even-numbered size when W, X, Y, and Z are at opposite corners. Cyclohexane derivative **72**, for example, has no stereogenic carbons because there is a plane of symmetry. Imagine a focus on the chlorine-bearing carbon, and view each "arm" of the ring as a group. There are two identical groups so the carbon will not be stereogenic. When W = Y and X = Z, the *cis* isomer is always superimposable on its mirror image and hence is a *meso* compound, while the *trans* isomer consists of a *dl* pair, except in the case noted above. Again, the *cis* isomer has a plane of symmetry while the *trans* does not.

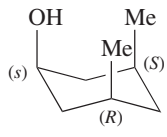
cis Meso trans *dl* Pair

Rings with more than two differently substituted carbons can be dealt with using similar principles. In some cases it is not easy to tell the number of isomers by inspection.[113] The

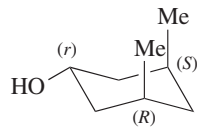
[267] See Leonard, J.E.; Hammond, G.S.; Simmons, H.E. *J. Am. Chem. Soc.* ***1975***, *97*, 5052.
[268] Sorensen, T.S.; Sun, F. *J. Chem. Soc., Perkin Trans. 2* ***1998***, 1053.

best method may be to count the number n of differently substituted carbons (these will usually be asymmetric, but not always, e.g., in **72**), and then to draw 2^n structures, crossing out those that can be superimposed on others (usually the easiest method is to look for a plane of symmetry). By this means it can be determined that for 1,2,3-cyclohexanetriol there are two *meso* compounds and a *dl* pair; and for 1,2,3,4,5,6-hexachlorocyclohexane there are seven *meso* compounds and a *dl* pair. Similar principles apply to heterocyclic rings if there are carbons (or other ring atoms) containing two different groups.

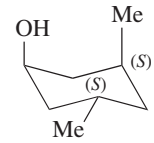
Cyclic stereoisomers containing only two differently substituted carbons are named either *cis* or *trans*, as previously indicated. The (*Z*, *E*) system is not used for cyclic compounds. However, *cis–trans* nomenclature will not suffice for compounds with more than two differently substituted atoms. For these compounds, a system is used in which the configuration of each group is given with respect to a reference group, which is chosen as the group attached to the lowest-numbered ring member bearing a substituent giving rise to *cis–trans* isomerism. The reference group is indicated by the symbol *r*. Three stereoisomers named according to this system are (3*S*,5*R*)-dimethylcyclohexan-*s*-1-ol (**73**), (3*S*,5*R*)-dimethylcyclohexan-*r*-1-ol (**74**), and (3*S*,5*S*)-dimethylcyclohexan-*s*-1-ol (**75**) (see Sec. 4G). The last example demonstrates the rule that when there are two otherwise equivalent ways of going around the ring, one chooses the path that gives the *cis* designation to the first substituent after the reference. Another example is (2*S*,4*S*)-dimethyl-(6*S*)-ethyl-1,3-dioxane (**76**).



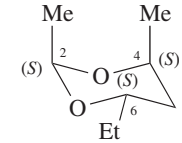
73



74



75



76

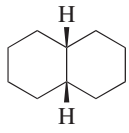
4.K.iii. *Cis–Trans* Isomerism of Fused and Bridged Ring Systems

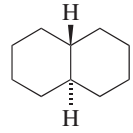
Fused bicyclic systems are those in which two rings share two and only two atoms. In such systems there is no new principle. The fusion may be *cis* or *trans*, as illustrated by *cis*- and *trans*-decalin. However, when the rings are small enough, the *trans* configuration is impossible and the junction must be *cis*. The smallest *trans* junction that has been prepared when one ring is four-membered is a four-five junction; *trans*-bicyclo[3.2.0]heptane (**77**) is known.[269] For the bicyclo[2.2.0] system (a four-four fusion), only *cis* compounds have been made. The smallest known *trans* junction when one ring is three-membered is a six-three junction (a bicyclo[4.1.0] system). An example is **78**.[270] When one ring is three-membered and the other eight-membered (an eight-three junction), the *trans*-fused isomer is more stable than the corresponding *cis*-fused isomer.[271]

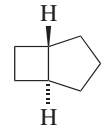
[269] Meinwald, J.; Tufariello, J.J.; Hurst, J.J. *J. Org. Chem.* ***1964***, *29*, 2914.

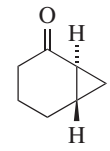
[270] Paukstelis, J.V.; Kao, J. *J. Am. Chem. Soc.* ***1972***, *94*, 4783. For references to other examples, see Dixon, D.A.; Gassman, P.G. *J. Am. Chem. Soc.* ***1988***, *110*, 2309.

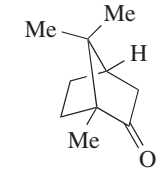
[271] Corbally, R.P.; Perkins, M.J.; Carson, A.S.; Laye, P.G.; Steele, W.V. *J. Chem. Soc., Chem. Commun.* ***1978***, 778.


cis-Decalin

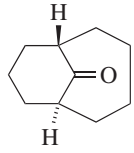

trans-Decalin

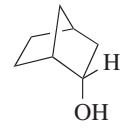

77

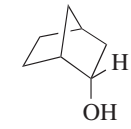

78


Camphor

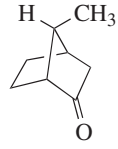
In *bridged* bicyclic ring systems, two rings share more than two atoms. In these cases there may be fewer than 2^n isomers because of the structure of the system. For example, there are only two isomers of camphor (a pair of enantiomers), although it has two stereogenic carbons. In both isomers the methyl and hydrogen are *cis*. The *trans* pair of enantiomers is impossible in this case, since the bridge *must* be *cis*. The smallest bridged system so far prepared in which the bridge is *trans* is the [4.3.1] system; the *trans* ketone **79** has been prepared.[272] In this case there are four isomers, since both the *trans* and the *cis* (which has also been prepared) are pairs of enantiomers.

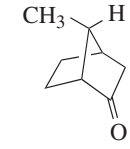

79


exo-2-Norborneol


endo-2-Norborneol

When one of the bridges contains a substituent, the question arises as to how to name the isomers involved. When the two bridges that do *not* contain the substituent are of unequal length, the rule generally followed is that the prefix *endo-* is used when the substituent is closer to the longer of the two unsubstituted bridges; the prefix *exo-* is used when the substituent is closer to the shorter bridge; for example, When the two bridges not containing the substituent are of equal length, this convention cannot be applied, but in some cases a decision can still be made; for example, if one of the two bridges contains a functional group, the *endo* isomer is the one in which the substituent is closer to the functional group.


endo-7-Methyl-2-norcamphor


exo-7-Methyl-2-norcamphor

4.L. *OUT–IN* ISOMERISM

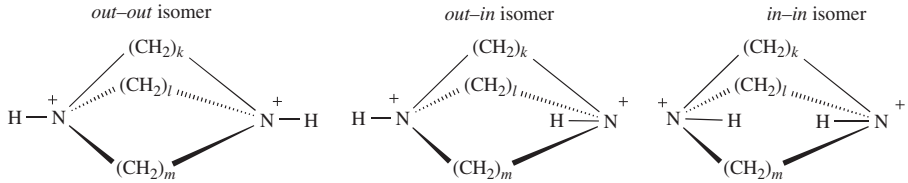
Another type of stereoisomerism, called *out–in* isomerism (or *in–out*),[273] is found in salts of tricyclic diamines with nitrogen at the bridgeheads. In medium-sized bicyclic

[272] Winkler, J.D.; Hey, J.P.; Williard, P.G. *Tetrahedron Lett.* ***1988***, *29*, 4691.
[273] See Alder, R.W. *Acc. Chem. Res.* ***1983***, *16*, 321.

ring systems, *in–out* isomerism is possible,[274] and the bridgehead nitrogen atoms adopt the arrangement that is more stable.[275] A focus on the nitrogen lone pairs reveals that 1,4-diazabicyclo[2.2.2]octane (**80**) favors the *out–out* isomer, that 1,6-diazabicyclo[4.4.4]tetradecane (**81**) the *in–in*,[276] that 1,5-diazabicyclo[3.3.3]undecane (**82**) has nearly planar nitrogen atoms,[277] and that 1,9-diazabicyclo[7.3.1]tridecane (**83**) is *in–out*.[278] One can also focus on the NH unit in the case of ammonium salts.

80 **81** **82** **83**

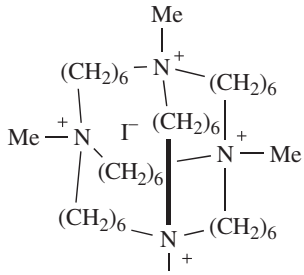
In the examples **84**–**86**, when k, l, and $m > 6$, the N—H bonds can be inside the molecular cavity or outside, giving rise to three isomers, as shown. Simmons and Park[279] isolated several such isomers with k, l, and m varying from 6 to 10. In the 9,9,9 compound, the cavity of the in-in isomer is large enough to encapsulate a chloride ion that is hydrogen bonded to the two N—H groups. The species thus formed is a cryptate, but differs from the cryptates discussed in Section 3.C.ii in that there is a negative rather than a positive ion enclosed.[280] Even smaller ones (e.g., the 4,4,4 compound) have been shown to form mono-inside-protonated ions.[281] In the compound **87**, which has four quaternary nitrogen atoms, a halide ion has been encapsulated without a hydrogen being present on a nitrogen.[282] This ion does not display *in-out* isomerism. *Out-in* and *in-in* isomers have also been prepared in analogous all-carbon tricyclic systems.[283]



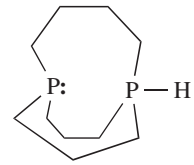
84 **85** **86**

[274] Alder, R.W.; East, S.P. *Chem. Rev.* ***1996***, *96*, 2097.
[275] Alder, R.W. *Tetrahedron* ***1990***, *46*, 683.
[276] Alder, R.W.; Orpen, A.G.; Sessions, R.B. *J. Chem. Soc., Chem. Commun.* ***1983***, 999.
[277] Alder, R.W.; Arrowsmith, R.J.; Casson, A.; Sessions, R.B.; Heilbronner, E.; Kovac, B.; Huber, H.; Taagepera, M. *J. Am. Chem. Soc.* ***1981***, *103*, 6137.
[278] Alder, R.W.; Heilbronner, E.; Honegger, E.; McEwen, A.B.; Moss, R.E.; Olefirowicz, E.; Petillo, P.A.; Sessions, R.B.; Weisman, G.R.; White, J.M.; Yang, Z.-Z. *J. Am. Chem. Soc.* ***1993***, *115*, 6580.
[279] Simmons, H.E.; Park, C.H. *J. Am. Chem. Soc.* ***1968***, *90*, 2428; Park, C.H.; Simmons, H.E. *J. Am. Chem. Soc.* ***1968***, *90*, 2429, 2431; Simmons, H.E.; Park, C.H.; Uyeda, R.T.; Habibi, M.F. *Trans. N.Y. Acad. Sci.* ***1970***, *32*, 521. See also, Dietrich, B.; Lehn, J.M.; Sauvage, J.P. *Tetrahedron* ***1973***, *29*, 1647; Dietrich, B.; Lehn, J.M.; Sauvage, J.P.; Blanzat, J. *Tetrahedron* ***1973***, *29*, 1629.
[280] See Schmidtchen, F.P.; Gleich, A.; Schummer, A. *Pure. Appl. Chem.* ***1989***, *61*, 1535; Pierre, J.; Baret, P. *Bull. Soc. Chim. Fr.* ***1983***, II-367. See also, Hosseini, M.W.; Lehn, J. *Helv. Chim. Acta* ***1988***, *71*, 749.
[281] Dietrich, B.; Lehn, J.M.; Guilhem, J.; Pascard, C. *Tetrahedron Lett.* ***1989***, *30*, 4125; Wallon, A.; Peter-Katalinić, J.; Werner, U.; Müller, W.M.; Vögtle, F. *Chem. Ber.* ***1990***, *123*, 375.
[282] Schmidtchen, F.P. *J. Am. Chem. Soc.* ***1986***, *108*, 8249; *Top. Curr. Chem.* ***1986***, *132*, 101.
[283] McMurry, J.E.; Hodge, C.N. *J. Am. Chem. Soc.* ***1984***, *106*, 6450; Winkler, J.D.; Hey, J.P.; Williard, P.G. *J. Am. Chem. Soc.* ***1986***, *108*, 6425.

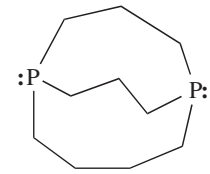
It is known that chiral phosphanes are more pyramidal and that inversion is more difficult, usually requiring temperatures well over 100 °C for racemization.[284] Alder and Read found that deprotonation of *bis*-phosphorane **88** (which is known to have an *in-out* structure with significant P—P bonding) leads to a rearrangement and the *out-out* diphosphane **89**.[285] Reprotonation gives **88**,[286] with inversion at the nonprotonated phosphorus atom occurring at room temperature.



87



88



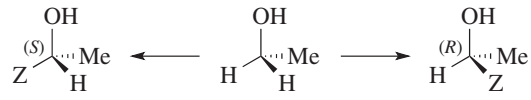
89

4.M. ENANTIOTOPIC AND DIASTEREOTOPIC ATOMS, GROUPS, AND FACES[287]

Many molecules contain atoms or groups that appear to be equivalent, but a close inspection will show them to be actually different. Two atoms can be tested to see if they are equivalent by replacing each of them in turn with some other atom or group. If the new molecules created by this process are identical, the original atoms are equivalent; otherwise they are not. There are three cases.

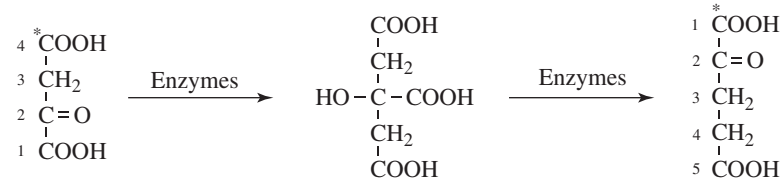
1. In the case of malonic acid $CH_2(COOH)_2$, propane CH_2Me_2, or any other molecule of the form CH_2Y_2,[288] replacing either of the CH_2 hydrogens by a group Z will give the identical compound. The two hydrogens are thus equivalent. Equivalent atoms and groups need not, of course, be located on the same carbon atom. For example, all the chlorine atoms of hexachlorobenzene are equivalent, as are the two bromine atoms of 1,3-dibromopropane.
2. In the case of ethanol, replacing one of the CH_2 hydrogens by a group Z will give one enantiomer of the compound ZCHMeOH (**90**), while replacement of the other hydrogen gives the *other* enantiomer (**91**). Since the two compounds that result upon replacement of H by Z (**90** and **91**) are not identical but enantiomeric, the hydrogens are *not* equivalent. Two atoms or groups that upon replacement with a third group give enantiomers are defined as *enantiotopic*.

[284] See Baechler, R.D.; Mislow, K. *J. Am. Chem. Soc.* ***1970***, *92*, 3090; Rauk, A.; Allen, L.C.; Mislow, K. *Angew. Chem. Int. Ed.* ***1970***, *9*, 400.
[285] Alder, R.W.; Read, D. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2879.
[286] Alder, R.W.; Ellis, D.D.; Gleiter, R.; Harris, C.J.; Lange, H.; Orpen, A.G.; Read, D.; Taylor, P.N. *J. Chem. Soc., Perkin Trans. I* ***1998***, 1657.
[287] These terms were coined by Mislow. See Eliel, E.L. *Top. Curr. Chem.* ***1982***, *105*, 1; Mislow, K.; Raban, M. *Top. Stereochem.* ***1967***, *1*, 1. See also, Jennings, W.B. *Chem. Rev.* ***1975***, *75*, 307.
[288] In the case where Y is itself a chiral group, this statement is only true when the two Y groups have the same configuration.



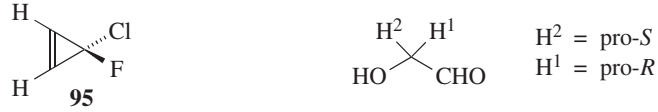
90 **91**

In any symmetrical environment the two hydrogens behave as equivalent, but in a dissymmetrical environment they may behave differently. For example, in a reaction with a chiral reagent they may be attacked at different rates. This has important consequences in enzymatic reactions,[289] since enzymes are capable of much greater discrimination than ordinary chiral reagents.



92 **93** **94**

An example is found in the Krebs cycle, in biological organisms, where oxaloacetic acid (**92**) is converted to α-oxoglutaric acid (**94**) by a sequence that includes citric acid (**93**) as an intermediate. When **92** is labeled with ^{14}C at the 4 position, the label is found only at C-1 of **94**, despite the fact that **93** is not chiral. The two CH_2COOH groups of **93** are enantiotopic and the enzyme easily discriminates between them.[290] Note that the X atoms or groups of any molecule of the form CX_2WY are always enantiotopic if neither W nor Y is chiral. However, enantiotopic atoms and groups may also be found in other molecules, for example, the hydrogen atoms in 3-fluoro-3-chlorocyclopropene (**95**). In this case, substitution of an H by a group Z makes the C-3 atom asymmetric and substitution at C-1 gives the opposite enantiomer from substitution at C-2.



95

The term *prochiral*[291] is used for a compound or group that has two enantiotopic atoms or groups, for example, CX_2WY. That atom or group X that would lead to

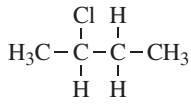
[289] For a review, see Benner, S.A.; Glasfeld, A.; Piccirilli, J.A. *Top. Stereochem.* ***1989***, *19*, 127. For a nonenzymatic example, see Job, R.C.; Bruice, T.C. *J. Am. Chem. Soc.* ***1974***, *96*, 809.

[290] The experiments were carried out by Evans Jr., E.A.; Slotin, L. *J. Biol. Chem.* ***1941***, *141*, 439; Wood, H.G.; Werkman, C.H.; Hemingway, A.; Nier, A.O. *J. Biol. Chem.* ***1942***, *142*, 31. The correct interpretation was given by Ogston, A.G. *Nature (London)* ***1948***, *162*, 963. For discussion, see Eliel, E.L. *Top. Curr. Chem.* ***1982***, *105*, 1 (pp. 5–7, 45–70).

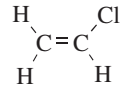
[291] Hirschmann, H.; Hanson, K.R. *Tetrahedron* ***1974***, *30*, 3649.

an (*R*) compound if preferred to the other is called *pro*-(*R*). The other is *pro*-(*S*); for example, 2-hydroxyactaldehyde.

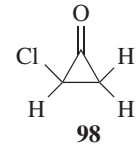
3. Where two atoms or groups in a molecule are in such positions that replacing each of them in turn by a group Z gives rise to diastereomers, the atoms or groups are called *diastereotopic*. Some examples are the CH_2 groups of 2-chlorobutane (**96**), of vinyl chloride (**97**), and of chlorocyclopropane (**98**), and the two alkenyl hydrogens of **99**. Diastereotopic atoms and groups are different in any environment, chiral or achiral. These hydrogens react at different rates with achiral reagents, but an even more important consequence is that in NMR spectra, diastereotopic hydrogens theoretically give different peaks and split each other. This is in sharp contrast to equivalent or enantiotopic hydrogens, which are indistinguishable in the NMR, except when chiral solvents are used, in which case enantiotopic (but not equivalent) protons give different peaks.[292] The term *isochronous* is used for hydrogens that are indistinguishable in the NMR.[293] In practice, the NMR signals from diastereotopic protons are often found to be indistinguishable, but this is merely because they are very close together. Theoretically they are distinct, and they have been resolved in many cases. When they appear together, it is sometimes possible to resolve them by the use of lanthanide shift reagents (Sec. 4.J) or by changing the solvent or concentration. Note that X atoms or groups CX_2WY are diastereotopic if either W or Y is chiral.



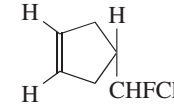
96



97



98



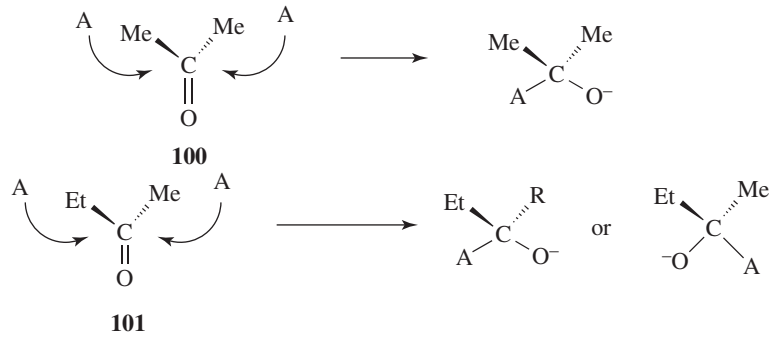
99

Just as there are enantiotopic and diastereotopic atoms and groups, *enantiotopic and diastereotopic faces* in trigonal molecules may be distinguished. Again, there are three cases.

1. In formaldehyde or acetone (**100**), attack by an achiral reagent A from either face of the molecule gives rise to the same transition state and product; the two faces are thus equivalent and there is only one product.
2. In butan-2-one (**101**) or acetaldehyde, attack by an achiral A at one face gives a chiral transition state and the enantiomeric products arise from attack at one or the other face. Such faces are *enantiotopic*. Attack at an enantiotopic face by a chiral reagent will generate another stereogenic center, which gives diastereomers that may not be formed in equal amounts.

[292] Pirkle, W.H. *J. Am. Chem. Soc.* ***1966***, *88*, 1837; Burlingame, T.G.; Pirkle, W.H. *J. Am. Chem. Soc.* ***1966***, *88*, 4294; Pirkle, W.H.; Burlingame, T.G. *Tetrahedron Lett.* ***1967***, 4039.

[293] For a review of isochronous and nonisochronous nuclei in NMR, see van Gorkom, M.; Hall, G.E. *Q. Rev. Chem. Soc.* ***1968***, *22*, 14. For a discussion, see Silverstein, R.M.; LaLonde, R.T. *J. Chem. Educ.* ***1980***, *57*, 343.



3. In a case like **102**, the two faces are obviously not equivalent and are called *diastereotopic*. Enantiotopic and diastereotopic faces can be named by an extension of the Cahn-Ingold-Prelog system (Sec. 4.E.i).[291] If the three groups as arranged by the sequence rules have the order X > Y > Z, such that the groups in this sequence are clockwise (as in **103**) that face is the *re* face (from Latin *rectus*) whereas **104** shows the *si* face (from Latin *sinister*).

Note that new terminology has been proposed.[294] The concept of sphericity is used, and the terms homospheric, enantiospheric, and hemispheric have been coined to specify the nature of an orbit (an equivalent class) assigned to a co-set representation.[295] Using these terms, prochirality can be defined: if a molecule has at least one enantiospheric orbit, the molecule is defined as being prochiral.[286]

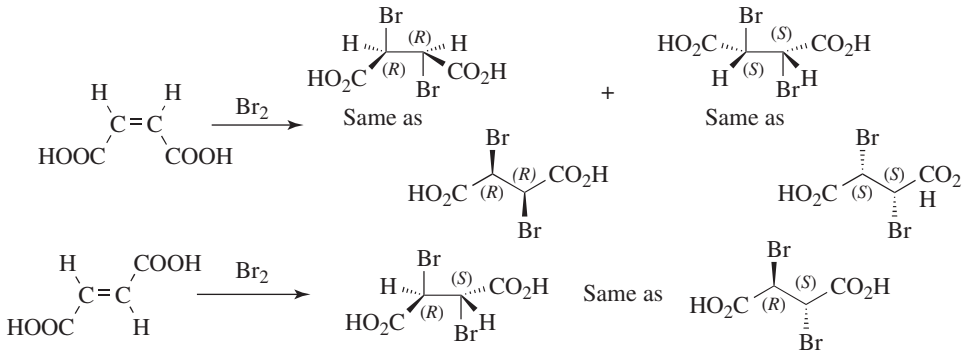
4.N. STEREOSPECIFIC AND STEREOSELECTIVE SYNTHESES

Any reaction in which only one of a set of stereoisomers is formed predominantly is called a *stereoselective* synthesis.[296] The same term is used when a mixture of two or more stereoisomers is exclusively or predominantly formed at the expense of other stereoisomers. In a *stereospecific* reaction, a given isomer leads to one product while another stereoisomer leads to the opposite product. All stereospecific reactions are necessarily stereoselective, but the converse is not true. These terms are best illustrated by examples.

Thus, if maleic acid treated with bromine gives the *dl* pair of 2,3-dibromosuccinic acid while fumaric acid gives the *meso* isomer (this is the case), the reaction is stereospecific as well as stereoselective because two opposite isomers give two opposite isomers. However,

[294] Fujita, S. *J. Org. Chem.* ***2002***, *67*, 6055.
[295] Fujita, S. *J. Am. Chem. Soc.* ***1990***, *112*, 3390.
[296] For a further discussion of these terms and of stereoselective reactions in general, see Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 835–990.

if both maleic acid and fumaric acid gave the *dl* pair or a mixture in which the *dl* pair predominated, the reaction would be stereoselective but not stereospecific. If more or less equal amounts of *dl* and *meso* forms were produced in each case, the reaction would be nonstereoselective.



A consequence of these definitions is that if a reaction is carried out on a compound that has no stereoisomers, it cannot be stereospecific, but at most can be stereoselective. For example, addition of bromine to methylacetylene could (and does) result in preferential formation of *trans*-1,2-dibromopropene, but this can be only a stereoselective, not a stereospecific, reaction. A reaction that favors one enantiomer over another is known as an enantioselective reaction, and considerable effort has been applied to reactions of this type and applications to total synthesis.[297]

4.O. CONFORMATIONAL ANALYSIS

For acyclic molecules with single covalent bonds, there is rotation about those bonds. As a practical matter, such rotation leads to different arrangements of the atoms with respect to a given bond, but all arrangements constitute the same molecule. The different arrangements for a molecule due to such rotation are called *rotamers*. In principle, there is rotation about every single bond and a near infinite number of rotamers. If two different 3D spatial arrangements of the atoms in an acyclic molecule are interconvertible merely by free rotation about bonds, they are called *conformations*.[298] If they are not interconvertible, they are called *configurations*.[299] Configurations represent *isomers* that can be separated, as previously discussed in this chapter. Conformations represent *conformers*, which are rapidly interconvertible and thus nonseparable. The terms "conformational isomer" or more

[297] Corey, E.J.; Kürti. L. *Enantioselective Chemical Synthesis. Methods, Logic and Practice*, Direct Book Publishing: Dallas, TX, ***2010***.

[298] See Bonchev, D.; Rouvray, D.H. *Chemical Topology*, Gordon and Breach, Australia, ***1999***.

[299] See Dale, J. *Stereochemistry and Conformational Analysis*, Verlag Chemie, Deerfield Beach, FL, ***1978***; Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, ***1971***; Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. *Conformational Analysis*, Wiley, NY, ***1965***; Hanack, M. *Conformation Theory*, Academic Press, NY, ***1965***. For reviews, see Dale, J. *Top. Stereochem.* ***1976***, *9*, 199; Truax, D.R.; Wieser, H. *Chem. Soc. Rev.* ***1976***, *5*, 411; Eliel, E.L. *J. Chem. Educ.* ***1975***, *52*, 762; Bastiansen, O.; Bushweller, C.H.; Gianni, M.H. in Patai, S. *The Chemistry of Functional Groups*, *Supplement E*, Wiley, NY, ***1980***, pp. 215–278.

commonly "rotamer"[300] are used to identify one of many structures that result from rotation about single covalent bonds. Typically, the conformation is the average of the collection of lower energy rotamers for an acyclic compound.

A number of methods have been used to determine conformations.[301] These include X-ray and electron diffraction, IR, Raman, UV, NMR,[302] and microwave spectra,[303] photoelectron spectroscopy,[304] supersonic molecular jet spectroscopy,[305] and optical rotatory dispersion and CD measurements.[306] Ring current NMR anisotropy has been applied to conformational analysis,[307] as has chemical shift simulation.[308] Some of these methods are useful only for solids. It must be kept in mind that the conformation of a molecule in the solid state is not necessarily the same as in solution.[309] Conformations can be *calculated* by a method called molecular mechanics (Sec. 4.P). A method was reported that characterized six-membered ring conformations as a linear combination of ideal basic conformations.[310] The term "absolute conformation" has been introduced for molecules for which one conformation is optically inactive but, by internal rotation about a C(sp^3)—C(sp^3) bond, optically active conformers are produced.[311]

Note that "free" rotation about single bonds is not possible in cyclic molecules, but rather pseudorotation that leads to different conformations. This discussion will therefore separate rotation in acyclic molecules from pseudorotation in cyclic molecules.

4.O.i. Conformation in Open-Chain Systems[312]

For any open-chain molecule with a single bond that connects two sp^3 carbon atoms, an infinite number of rotamers are possible, each of which has a certain energy associated with it,

[300] Öki, M. *The Chemistry of Rotational Isomers*, Springer-Verlag, Berlin, ***1993***.

[301] For a review, see Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. *Conformational Analysis*, Wiley, NY, ***1965***, pp. 129–188.

[302] See Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***; Marshall, J.L. *Carbon–Carbon and Carbon–Proton NMR Couplings*, VCH, NY, ***1983***. For reviews, see Anet, F.A.L.; Anet, R. in Nachod, F.C.; Zuckerman, J.J. *Determination of Organic Structures by Physical Methods*, Vol. 3, Academic Press, NY, ***1971***, pp. 343–420; Kessler, H. *Angew. Chem. Int. Ed.* ***1970***, *9*, 219; Ivanova, T.M.; Kugatova-Shemyakina, G.P. *Russ. Chem. Rev.* ***1970***, *39*, 510; See also, Whitesell, J.K.; Minton, M. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*, Chapman and Hall, NY, ***1987***.

[303] For a review see Wilson, E.B. *Chem. Soc. Rev.* ***1972***, *1*, 293.

[304] For a review, see Klessinger, M.; Rademacher, P. *Angew. Chem. Int. Ed.* ***1979***, *18*, 826.

[305] Breen, P.J.; Warren, J.A.; Bernstein, E.R.; Seeman, J.I. *J. Am. Chem. Soc.* ***1987***, *109*, 3453.

[306] See Kagan, H.B. *Determination of Configurations by Dipole Moments*, *CD*, *or ORD* (Vol. 2 of Kagan, H.B. *Stereochemistry*), Georg Thieme Publishers, Stuttgart, ***1977***; Crabbé, P. *ORD and CD in Chemistry and Biochemistry*, Academic Press, NY, ***1972***; Snatzke, G. *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Sadtler Research Laboratories, Philadelphia, ***1967***; Velluz, L.; Legrand, M.; Grosjean, M. *Optical Circular Dichroism*, Academic Press, NY, ***1965***. For reviews, see Smith, H.E. *Chem. Rev.* ***1983***, *83*, 359; Håkansson, R. in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, ***1979***, pp. 67–120; Hudec, J.; Kirk, D.N. *Tetrahedron* ***1976***, *32*, 2475; Schellman, J.A. *Chem. Rev.* ***1975***, *75*, 323.

[307] Chen, J.; Cammers-Goodwin, A. *Eur. J. Org. Chem.* ***2003***, 3861.

[308] Iwamoto, H.; Yang, Y.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* ***2001***, *42*, 49.

[309] See Kessler, H.; Zimmermann, G.; Förster, H.; Engel, J.; Oepen, G.; Sheldrick, W.S. *Angew. Chem. Int. Ed.* ***1981***, *20*, 1053.

[310] Bérces, A.; Whitfield, D.M.; Nukada, T. *Tetrahedron* ***2001***, *57*, 477.

[311] Öki, M.; Toyota, S. *Eur. J. Org. Chem.* ***2004***, 255.

[312] See Berg, U.; Sandström, J. *Adv. Phys. Org. Chem.* ***1989***, *25*, 1. Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 597–664. Also see Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 29–35.

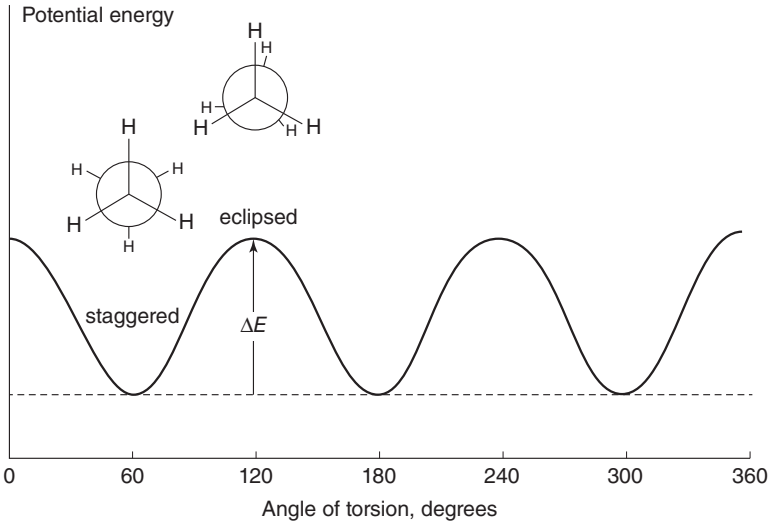
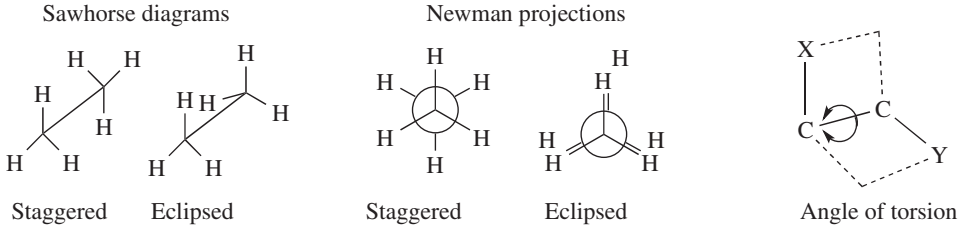


FIGURE 4.4. Conformational energy diagram for ethane.

which leads to an infinite number of conformations. As a practical matter, the number of conformations is much less. If one ignores duplications due to symmetry, the number of conformations can be *estimated* as being greater than 3^n, where n = the number of internal C—C bonds. *n*-Pentane, for example has 11, *n*-hexane 35, *n*-heptane 109, *n*-octane 347, *n*-nonane 1101, and *n*-decane 3263.[313] For ethane there are two important rotamers that are taken as the extremes, a conformation of highest potential energy (marked as "eclipsed") and one of lowest potential energy (marked as "staggered"), depicted in two ways as sawhorse diagrams or Newman projections. In *Newman projection formulas*, the observer looks at the C—C bond head on. The three lines emanating from the center of the circle represent the bonds coming from the front carbon, with respect to the observer.



The staggered conformation is the conformation of lowest potential energy for ethane. As rotation about the bond occurs, the energy gradually increases until the eclipsed conformation is reached, when the energy is at a maximum. Further rotation decreases the energy again. Figure 4.4 illustrates this. The *angle of torsion*, which is a dihedral angle, is the angle between the X—C—C and the C—C—Y planes, as shown in the diagram. For ethane the difference in energy is ~2.9 kcal mol^{-1} (12 kJ mol^{-1}).[314] This difference is called the *energy*

[313] Goto, H.; Osawa, E.; Yamato, M. *Tetrahedron* ***1993***, *49*, 387.
[314] Lide Jr., D.R. *J. Chem. Phys.* ***1958***, *29*, 1426; Weiss, S.; Leroi, G.E. *J. Chem. Phys.* ***1968***, *48*, 962; Hirota, E.; Saito, S.; Endo, Y. *J. Chem. Phys.* ***1979***, *71*, 1183.

barrier or *rotational barrier*,[315] since in free rotation about a single bond there must be enough rotational energy present to cross the barrier every time two hydrogen atoms are opposite each other. There was much speculation about the cause of the barriers and many explanations have been suggested.[316] It has been concluded from molecular-orbital calculations (Sec. 4.P) that the barrier is caused by repulsion between overlapping filled molecular orbitals.[317] The staggered conformation of ethane is lowest in energy because the orbitals of the C—H bonds in this conformation have the least amount of overlap with the C—H orbitals of the adjacent carbon.

Enough rotational energy is present at ordinary temperatures for the ethane molecule to rotate rapidly, but it spends most of its time at or near the energy minimum. Groups larger than hydrogen cause larger barriers, presumably due to steric interactions between the larger units.[318] When the barriers are large enough, as in the case of suitably substituted biphenyls (Sec. 4.C, category 5), rotation at room temperature is completely prevented, which is described as a configuration not a conformation. Even for compounds with small barriers, cooling to low temperatures may remove enough rotational energy for what would otherwise be conformational isomers to become configurational isomers.

A 1,2-disubstituted ethane ($YCH_2—CH_2Y$ or $YCH_2—CH_2X$),[319] such as *n*-butane,[320] is somewhat more complicated and there are four extremes: a fully staggered conformation, called *anti*, *trans*, or *antiperiplanar*; another staggered conformation, called *gauche* or *synclinal*; and two types of eclipsed conformations, called *synperiplanar* and *anticlinal*. An energy diagram for this system is given in Figure 4.5. Although there is constant rotation about the central bond, it is possible to estimate what percentage of the molecules are in each conformation at a given time. For example, a consideration of dipole moment and polarizability measurements led to the conclusion that for 1,2-dichloroethane in CCl_4 solution at 25 °C about 70% of the molecules are in the *anti* conformation and about 30% in the *gauche* conformation.[321] The corresponding figures for 1,2-dibromoethane are 89% *anti* and 11% *gauche*.[322] The eclipsed conformations are unpopulated and serve only as pathways from one staggered conformation to another. Solids normally consist of a single conformer.

It may be observed that the *gauche* conformation of butane (see **105**) or any other similar molecule appears to be chiral. It is not. The lack of optical activity in such compounds arises from the fact that **105** is not a static molecule, but is in dynamic equilibrium with many other conformations, including its mirror image. In effect, they interconvert too rapidly for separation.

[315] Mo, Y.; Gao, J. *Acc. Chem. Res.* ***2007***, *40*, 113.

[316] See Lowe, J.P. *Prog. Phys. Org. Chem.* ***1968***, *6*, 1; Oosterhoff, L.J. *Pure Appl. Chem.* ***1971***, *25*, 563; Wyn-Jones, E.; Pethrick, R.A. *Top. Stereochem.* ***1970***, *5*, 205; Pethrick, R.A.; Wyn-Jones, E. *Q. Rev. Chem. Soc.* ***1969***, *23*, 301; Brier, P.N. *J. Mol. Struct.* ***1970***, *6*, 23; Lowe, J.P. *Science*, ***1973***, *179*, 527.

[317] See Pitzer, R.M. *Acc. Chem. Res.* ***1983***, *16*, 207. See, however, Bader, R.F.W.; Cheeseman, J.R.; Laidig, K.E.; Wiberg, K.B.; Breneman, C. *J. Am. Chem. Soc.* ***1990***, *112*, 6530.

[318] See Bader, W.; Cortés-Guzmán, F. *Can. J. Chem.* ***2009***, *87*, 1583. See Stojanović, M.; Aleksić, J.; Baranac-Stojanović, M. *Tetrahedron.* ***2015***, *71*, 5119.

[319] See Wiberg, K.B.; Murcko, M.A. *J. Am. Chem. Soc.* ***1988***, *110*, 8029; Allinger, N.L.; Grev, R.S.; Yates, B.F.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1990***, *112*, 114.

[320] Cormanich, R.A.; Freitas, M.P. *J. Org. Chem.* ***2009***, *74*, 8384; Mo, Y. *J. Org. Chem.* ***2010***, *75*, 2733.

[321] Le Fèvre, R.J.W.; Orr, B.J. *Aust. J. Chem.* ***1964***, *17*, 1098.

[322] See Schrumpf, G. *Angew. Chem. Int. Ed.* ***1982***, *21*, 146.

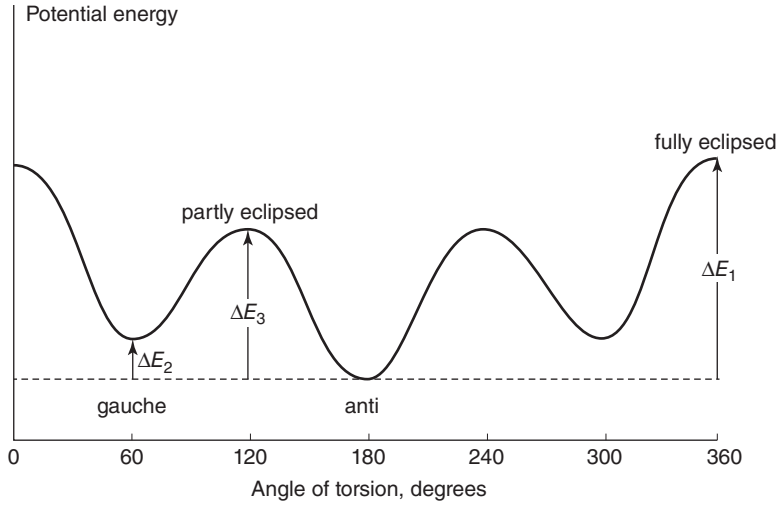
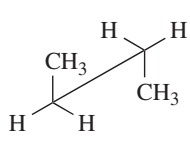
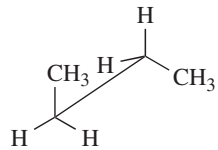


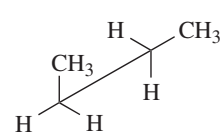
FIGURE 4.5. Conformational energy for $YCH_2—CH_2Y$ or $YCH_2—CH_2X$. For *n*-butane, $\Delta E_1 = 4$ to 6, $\Delta E_2 = 0.9$, and $\Delta E_3 = 3.4$ kcal mol^{-1} (17–25, 3.8, 14 kJ mol^{-1}, respectively).



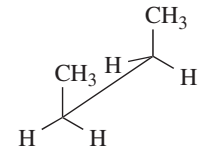
Anti, Trans, or Antiperiplanar



Anticlinal



105 Gauche or Synclinal



Synperiplanar

For butane and for most other molecules of the forms $YCH_2—CH_2Y$ and $YCH_2—CH_2X$, the *anti* conformer is the most stable, but exceptions are known. One group of exceptions consists of molecules containing small electronegative atoms, especially fluorine and oxygen. Thus 2-fluoroethanol,[323] 1,2-difluoroethane,[324] and 2-fluoroethyl trichloroacetate ($FCH_2CH_2OCOCCl_3$)[325] exist predominantly in the *gauche* form and compounds such as 2-chloroethanol and 2-bromoethanol[323] also prefer the *gauche* form. It has been proposed that the preference for the *gauche* conformation in these molecules is an example of a more general phenomenon, known as the *gauche effect*, that is, a tendency to adopt that structure that has the maximum number of *gauche* interactions between adjacent electron pairs or polar bonds.[326] It was believed that the favorable *gauche* conformation of 2-fluoroethanol was the result of intramolecular hydrogen bonding, but this explanation does not work for molecules like 2-fluoroethyl trichloroacetate and has in fact been ruled out

[323] See Davenport, D.; Schwartz, M. *J. Mol. Struct.* ***1978***, *50*, 259; Huang, J.; Hedberg, K. *J. Am. Chem. Soc.* ***1989***, *111*, 6909.

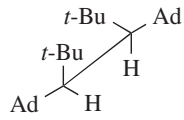
[324] See Friesen, D.; Hedberg, K. *J. Am. Chem. Soc.* ***1980***, *102*, 3987; Fernholt, L.; Kveseth, K. *Acta Chem. Scand. Ser. A* ***1980***, *34*, 163.

[325] Abraham, R.J.; Monasterios, J.R. *Org. Magn. Reson.* ***1973***, *5*, 305.

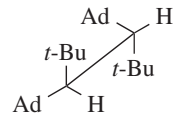
[326] See Wolfe, S. *Acc. Chem. Res.* ***1972***, *5*, 102. See also, Radom, L.; Hehre, W.J.; Pople, J.A. *J. Am. Chem. Soc.* ***1972***, *94*, 2371; Juaristi, E. *J. Chem. Educ.* ***1979***, *56*, 438.

for 2-fluoroethanol as well.[327] The effect of β-substituents in Y—C—C—OX systems where Y = F or SiR_3 has been examined and there is a small bond shortening effect on C—OX that is greatest when OX is a good leaving group. Bond lengthening was also observed with the β-silyl substituent.[328] Other exceptions are known, where small electronegative atoms are absent. For example 1,1,2,2-tetrachloroethane and 1,1,2,2-tetrabromoethane both prefer the *gauche* conformation,[329] even although 1,1,2,2-tetrafluoroethane prefers the *anti*.[330] Also, both 2,3-dimethylpentane and 3,4-dimethylhexane prefer the *gauche* conformation,[331] and 2,3-dimethylbutane shows no preference for either.[332] Furthermore, the solvent can exert a powerful effect. For example, the compound 2,3-dinitro-2,3-dimethylbutane exists entirely in the *gauche* conformation in the solid state, but in benzene, the *gauche–anti* ratio is 79:21; while in CCl_4 the *anti* form is actually favored (*gauche–anti* ratio 42:58).[333] In many cases, there are differences in the conformation of these molecules between the gas and the liquid phases (as when X = Y = OMe) because of polar interactions with the solvent.[334]

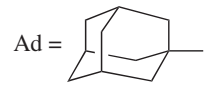
In one case, two conformational isomers of a single aliphatic hydrocarbon, 3,4-di(1-adamantyl)-2,2,5,5-tetramethylhexane, have proven stable enough for isolation at room temperature.[335] The two isomers **106** and **107** were separately crystallized, and the structures proved by X-ray crystallography. The actual dihedral angles are distorted from the 60° angles shown in the drawings, due to steric hindrance between the large adamantyl and *tert*-butyl groups.



106



107



All the conformations so far discussed have involved rotation about sp^3–sp^3 bonds. Many studies have also been made of compounds with sp^3–sp^2 bonds.[336] For example, propanal (or any similar molecule) has four extreme conformations, two of which are called *eclipsing* and the other two *bisecting*. For propanal, the eclipsing conformations have lower energy than the other two, with **108** favored over **109** by ~1 kcal mol^{-1} (4 kJ mol^{-1}).[337] As has already been pointed out (4.K.i), for a few of these compounds, rotation is slow enough

[327] Griffith, R.C.; Roberts, J.D. *Tetrahedron Lett.* ***1974***, 3499.

[328] Amos, R.D.; Handy, N.C.; Jones, P.G.; Kirby, A.J.; Parker, J.K.; Percy, J.M.; Su, M.D. *J. Chem. Soc., Perkin Trans. 2* ***1992***, 549.

[329] Kagarise, R.E. *J. Chem. Phys.* ***1956***, *24*, 300.

[330] Brown, D.E.; Beagley, B. *J. Mol. Struct.* ***1977***, *38*, 167.

[331] Ritter, W.; Hull, W.; Cantow, H. *Tetrahedron Lett.* ***1978***, 3093.

[332] Lunazzi, L.; Macciantelli, D.; Bernardi, F.; Ingold, K.U. *J. Am. Chem. Soc.* ***1977***, *99*, 4573.

[333] Tan, B.; Chia, L.H.L.; Huang, H.; Kuok, M.; Tang, S. *J. Chem. Soc., Perkin Trans. 2* ***1984***, 1407.

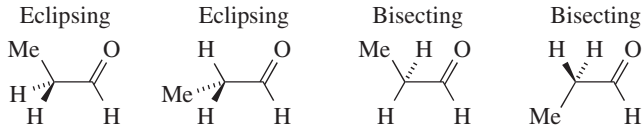
[334] Smith, G.D.; Jaffe, R.L.; Yoon, D.Y. *J. Am. Chem. Soc.* ***1995***, *117*, 530. For an analysis of *N,N*-dimethylacetamide see Mack, H.-G.; Oberhammer, H. *J. Am. Chem. Soc.* ***1997***, *119*, 3567.

[335] Flamm-ter Meer, M.A.; Beckhaus, H.-D.; Peters, K.; von Schnering, H.; Fritz, H.; Rüchardt, C. *Chem. Ber.* ***1986***, *119*, 1492; Rüchardt, C.; Beckhaus, H. *Angew. Chem. Int. Ed.* ***1985***, *24*, 529.

[336] See Sinegovskaya, L.M.; Keiko, V.V.; Trofimov, B.A. *Sulfur Rep.* ***1987***, *7*, 337 (for enol ethers and thioethers); Karabatsos, G.J.; Fenoglio, D.J. *Top. Stereochem.* ***1970***, *5*, 167; Jones, G.I.L.; Owen, N.L. *J. Mol. Struct.* ***1973***, *18*, 1 (for carboxylic esters). See also, Cossé-Barbi, A.; Massat, A.; Dubois, J.E. *Bull. Soc. Chim. Belg.* ***1985***, *94*, 919; Dorigo, A.E.; Pratt, D.W.; Houk, K.N. *J. Am. Chem. Soc.* ***1987***, *109*, 6591.

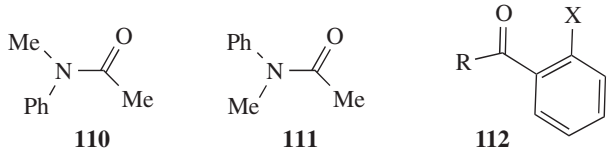
[337] Allinger, N.L.; Hickey, M.J. *J. Mol. Struct.* ***1973***, *17*, 233; Gupta, V.P. *Can. J. Chem.* ***1985***, *63*, 984.

to permit *cis–trans* isomerism, although for simple compounds rotation is rapid. The *cis* conformer of acetic acid was produced in solid Ar,[338] and it was reported that acetaldehyde has a lower rotational barrier (~1 kcal mol^{-1} or 4 kJ mol^{-1}) than ethane.[339] Calculations have examined the rotational barriers around the C—O and C—C bonds in formic acid and glycolaldedyde molecules.[340]



108 **109**

Other carbonyl compounds exhibit rotation about sp^3–sp^3 bonds, including amides.[341] In *N*-acetyl-*N*-methylaniline, the *cis* conformation (**110**) is more stable than the *trans* (**111**) by at least 3.5 kcal mol^{-1} (14.6 kJ mol^{-1}).[342] This is due to destabilization of (*S*) due to steric hindrance between two methyl groups, and to electronic repulsion between the carbonyl lone pair electrons and the phenyl π electrons in the twisted phenyl orientation.[342]



110 **111** **112**

A similar conformational analysis has been done with formamide derivatives,[343] with secondary amides,[344] and for hydroxamide acids.[345] It is known that thioformamide has a larger rotational barrier than formamide, which can be explained by a traditional picture of amide "resonance" that is more appropriate for the thioformamide than formamide itself.[346] Torsional barriers in α-keto amides have been reported,[347] and the C—N bond

[338] Macoas, E. M. S.; Khriachtchev, L.; Pettersson, M.; Fausto, R.; Rasanen, M. J. *Am. Chem. Soc.* ***2003***, *125*, 16188.
[339] Davidson, R.B.; Allen, L.C. *J. Chem. Phys.* ***1971***, *54*, 2828.
[340] Ratajczyk, T.; Pecul, M.; Sadlej, J. *Tetrahedron* ***2004***, *60*, 179.
[341] Avalos, M.; Babiano, R.; Barneto, J.L.; Bravo, J.L.; Cintas, P.; Jiménez, J.L.; Palcios, J.C. *J. Org. Chem.* ***2001***, *66*, 7275. Also see Modarresi-Alam, A.R.; Najafi, P.; Rostamizadeh, M.; Keykha, H.; Bijanzadeh, H.-R.; Kleinpeter, E. *J. Org. Chem.* ***2007***, *72*, 2208. For a discussion of possible C—H—O interactions as a determinant for conformations, see Jones, C.R.; Baruah, P.K.; Thompson, A.L.; Scheiner, S.; Smith, M.D. *J. Am. Chem. Soc.* ***2012***, *134*, 12064.
[342] Saito, S.; Toriumi, Y.; Tomioka, A.; Itai, A. *J. Org. Chem.* ***1995***, *60*, 4715.
[343] Axe, F.U.; Renugopalakrishnan, V.; Hagler, A.T. *J. Chem. Res.* ***1998***, 1. For an analysis of DMF see Wiberg, K.B.; Rablen, P.R.; Rush, D.J.; Keith, T.A. *J. Am. Chem. Soc.* ***1995***, *117*, 4261.
[344] Avalos, M.; Babiano, R.; Barneto, J.L.; Cintas, P.; Clemente, F.R.; Jiménez, J.L.; Palcios, J.C. *J. Org. Chem.* ***2003***, *68*, 1834.
[345] Kakkar, R.; Grover, R.; Chadha, P. *Org. Biomol. Chem.* ***2003***, *1*, 2200.
[346] Wiberg, K.B.; Rablen, P.R. *J. Am. Chem. Soc.* ***1995***, *117*, 2201.
[347] Bach, R.D.; Mintcheva, I.; Kronenberg, W.J.; Schlegel, H.B. *J. Org. Chem.* ***1993***, *58*, 6135.

of acetamides,[348] thioamides,[349] enamides[350] carbamates ($R_2N{-}CO_2R'$),[351] and enolate anions derived from amides[352] have been examined. It is known that substituents influence rotational barriers.[353]

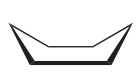
In Section 4.C, category 5, atropisomerism was possible when *ortho* substituents on biphenyl derivatives and certain other aromatic compounds prevented rotation about the C(sp^3)—C(sp^3) bond.[354] The presence of *ortho* substituents can also influence the conformation of certain groups.[355] In **112**, where R = alkyl and the carbonyl unit is planar, the *trans* C=O•••F conformer is more stable when X = F. When X = CF_3, the *cis* and *trans* are planar and the *trans* predominates.[356] When R = alkyl there is one orthogonal conformation but there are two interconverting nonplanar conformations when R = O—alkyl.[356] In 1,2-diacylbenzenes, the carbonyl units tend to adopt a twisted conformation to minimize steric interactions.[357]

4.O.ii. Conformation in Six-Membered Rings[358]

For cyclic compounds, complete rotation (360°) about a single bond is impossible. However, repulsion between atoms and groups leads to motion about each bond called *pseudorotation*. Pseudorotation leads to a variety of different conformations, depending on the size of the ring. In many such conformations the ring is said to be puckered. For cyclohexane there are two extreme conformations in which all the angles are tetrahedral (the C—C—C angles in cyclohexane are actually 111.5°).[359] These are called the *boat* and the *chair* conformations. The chair conformation is the low-energy structure that participates in a dynamic equilibrium (there are two chair conformations that are equivalent in energy for cyclohexane), and the boat form is a higher energy form[360] in equilibrium with a somewhat more stable form known as the *twist* conformation. The twist form is ~1.5 kcal mol^{-1} (6.3 kJ mol^{-1}) more stable than the boat because it has less eclipsing interactions (see below).[361] The chair form is more stable than the twist form by ~5 kcal mol^{-1} (21 kJ mol^{-1}).[362] In the vast majority of compounds containing a cyclohexane ring, the molecules exist almost entirely as

[348] Ilieva, S.; Hadjieva, B.; Galabov, B. *J. Org. Chem.* ***2002***, *67*, 6210.
[349] Wiberg, K.B.; Rush, D.J. *J. Am. Chem. Soc.* ***2001***, *123*, 2038; *J. Org. Chem.* ***2002***, *67*, 826.
[350] Rablen, P.R.; Miller, D.A.; Bullock, V.R.; Hutchinson, P.H.; Gorman, J.A. *J. Am. Chem. Soc.* ***1999***, *121*, 218.
[351] Deetz, M.J.; Forbes, C.C.; Jonas, M.; Malerich, J.P.; Smith, B.D.; Wiest, O. *J. Org. Chem.* ***2002***, *67*, 3949.
[352] Kim, Y.-J.; Streitwieser, A.; Chow, A.; Fraenkel, G. *Org. Lett.* ***1999***, *1*, 2069.
[353] Smith, B.D.; Goodenough-Lashua, D.M.; D'Souza, C.J.E.; Norton, K.J.; Schmidt, L.M.; Tung, J.C. *Tetrahedron Lett.* ***2004***, *45*, 2747.
[354] For a discussion of the role of aromatic interactions in rotational barriers, see Lima, C.F.R.A.C; Gomes, L.R.; Low, J.N.; Silva, A.M.S.; Santos, L.M.N.B.F. *J. Org. Chem.* ***2012***, *77*, 10422.
[355] For an analysis of barriers to rotation in such compounds, see Mazzanti, A.; Lunazzi, L.; Minzoni, M.; Anderson, J.E. *J. Org. Chem.* ***2006***, *71*, 5474.
[356] Abraham, R.J.; Angioloni, S.; Edgar, M.; Sancassan, F. *J. Chem. Soc., Perkin Trans. 2* ***1997***, 41.
[357] Casarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* ***1997***, *62*, 7592.
[358] See Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* ***1971***, *3*, 139; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 686–753. Also see, Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, England, ***2017***, pp. 38–53.
[359] See Geise, H.J.; Buys, H.R.; Mijlhoff, F.C. *J. Mol. Struct.* ***1971***, *9*, 447; Bastiansen, O.; Fernholt, L.; Seip, H.M.; Kambara, H.; Kuchitsu, K. *J. Mol. Struct.* ***1973***, *18*, 163.
[360] See Dunitz, J.D. *J. Chem. Educ.* ***1970***, *47*, 488.
[361] For a review of nonchair forms, see Kellie, G.M.; Riddell, F.G. *Top. Stereochem.* ***1974***, *8*, 225.
[362] Squillacote, M.; Sheridan, R.S.; Chapman, O.L.; Anet, F.A.L. *J. Am. Chem. Soc.* ***1975***, *97*, 3244.

equilibrating chair forms.[363] It is known that the boat or twist form exists transiently. In some cases, chair and twist-boat conformations have actually been observed (*cis*-1,4-di-*tert*-butylcyclohexane, for example).[364]

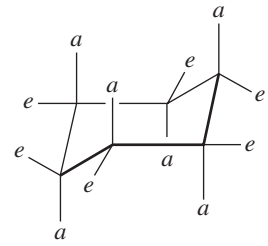


Boat

Chair

Twist

An inspection of the chair form shows that six of its bonds are directed differently from the other six. On each carbon, one bond is directed up or down and the other more or less in the "plane" of the ring. The "up" or "down" bonds are called *axial* and the others *equatorial*. The axial bonds point alternately up and down.



Axial and equatorial bonds
in chair cyclohexane

If a molecule were frozen into a chair form, there would be isomerism in monosubstituted cyclohexanes. For example, there would be an equatorial methylcyclohexane and an axial isomer. This is incorrect, however, as it has never been possible to isolate isomers of this type at room temperature.[365] In order for the two types of methylcyclohexane to be nonseparable, there must be rapid interconversion of one chair form to another (in which all axial bonds become equatorial and vice versa) and this is possible only if the boat or twist conformations are transient species. Conversion of one chair form to another requires an activation energy of about 10 kcal mol^{-1} (42 kJ mol^{-1})[366] and is very rapid at room temperature.[367] However, by working at low temperatures, Jensen and Bushweller were able to obtain the pure equatorial conformers of chlorocyclohexane and trideuteriomethoxycyclohexane as solids and in solution.[368] Equatorial chlorocyclohexane has a half-life of 22 years in solution at −160 °C. In some molecules the twist conformation is actually preferred.[369]

[363] See Wiberg, K.B.; Castejon, H.; Bailey, W.F.; Ochterski, J. *J. Org. Chem.* ***2000***, *65*, 1181.
[364] Gill, G.; Pawar, D.M.; Noe, E.A. *J. Org. Chem.* ***2005***, *70*, 10726.
[365] See Wehle, D.; Fitjer, L. *Tetrahedron Lett.* ***1986***, *27*, 5843.
[366] See Anet, F.A.L.; Bourn, A.J.R. *J. Am. Chem. Soc.* ***1967***, *89*, 760. See also, Strauss, H.L. *J. Chem. Educ.* ***1971***, *48*, 221.
[367] See Oki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 287–307; Anderson, J.E. *Top. Curr. Chem.* ***1974***, *45*, 139.
[368] See Jensen, F.R.; Bushweller, C.H. *J. Am. Chem. Soc.* ***1969***, *91*, 3223.
[369] Weiser, J.; Golan, O.; Fitjer, L.; Biali, S.E. *J. Org. Chem.* ***1996***, *61*, 8277.

TABLE 4.3 Free-energy differences between equatorial and axial substituents on a cyclohexane ring (*A* values or $A^{1,3}$-strain)[373]

Group	*A* in kcal mol^{-1}	(kJ mol^{-1})	Group	*A* in kcal mol^{-1}	(kJ mol^{-1})
H	0		N═	0.5	(2.09)
F	0.2	(0.84)	N≡	0.2	(0.84)
Cl	0.4	(1.67)	NO_2	1.1	(4.61)
Br	0.4	(1.67)	C≡	0.2	(0.84)
I	0.4	(1.67)	Aryl	3.0	(12.56)
PR_3	1.6	(6.7)	CO_2^-	2.0	(8.37)
SR	0.8	(3.35)	CHO	0.8	(3.35)
S(O)R	1.9	(7.95)	C═	1.3	(5.44)
$S(O_2)R$	2.5	(10.47)	CR_3	6.0	(25.11)
OR	0.8	(3.35)	CHR_2	2.1	(8.79)
NH_3^+	2.0	(8.37)	CH_2R	1.8	(7.54)
NR_3^+	2.1	(8.79)			
NHR	1.3	(5.44)			

Of course, in certain bicyclic compounds, the six-membered ring is forced to maintain a boat or twist conformation, as in norbornane or twistane.

Norbornane

Twistane

In mono-substituted cyclohexanes, the substituent normally prefers the equatorial position because there is an interaction between the substituent and the axial hydrogens in the axial 3 and 5 positions, but the extent of this preference depends greatly on the nature of the group.[370] Alkyl groups have a greater preference for the equatorial position than polar groups. For alkyl groups, the preference increases with size, although size seems to be unimportant for polar groups. Both the large HgBr[371] and HgCl[372] groups and the small F group have been reported to have little or no conformational preference (the HgCl group actually shows a slight preference for the axial position). Table 4.3 gives approximate values of the free energy required for various groups to go from the equatorial position to the axial (these are called *A* values),[373] although it must be kept in mind that they vary somewhat with

[370] For a study of thioether, sulfoxide and sulfone substituents, see Juaristi, E.; Labastida, V.; Antúnez, S. *J. Org. Chem.* ***2000***, *65*, 969.

[371] Jensen, F.R.; Gale, L.H. *J. Am. Chem. Soc.* ***1959***, *81*, 6337.

[372] Anet, F.A.L.; Krane, J.; Kitching, W.; Dodderel, D.; Praeger, D. *Tetrahedron Lett.* ***1974***, 3255.

[373] These values are from Corey, E.J.; Feiner, N.F. *J. Org. Chem.* ***1980***, *45*, 765. Also see Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* ***1971***, *3*, 139. Schneider, H.; Hoppen, V. *Tetrahedron Lett.* ***1974***, 579 and see Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, England, ***2017***, pp. 45–53.

physical state, temperature, and solvent.[374] Values for other groups in kcal mol^{-1} include D[375] (0.008), NH_2[376] (1.4), $CH{=}CH_2$,[377] (1.7), CH_3[378] (1.74), C_6H_{11}[379] (2.15), $SiMe_3$[380] (2.4–2.6), OMe[381] (0.75), C_6H_5[382] (2.7), and *t*-Bu[383] (4.9) (Bu = butyl).

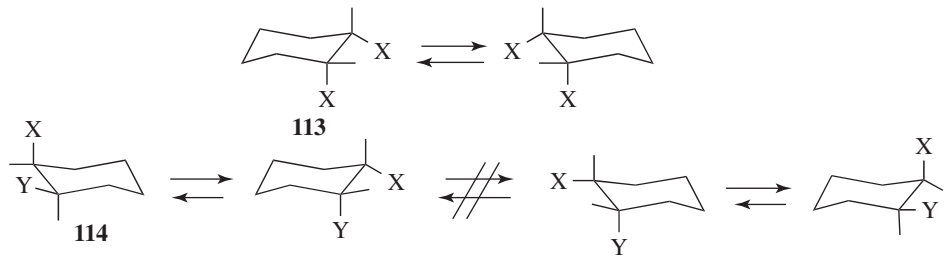
For alkyl groups in disubstituted compounds, the conformation is such that as many groups as possible adopt the equatorial position. This conformation will minimize the axial interactions (known as $A^{1,3}$-strain), and will be the lower energy conformation. The preference for one chair conformation over the other depends on the groups attached to the cyclohexane ring, and their relative positions on that ring. In a *cis* 1,2-disubstituted cyclohexane, one substituent must be axial and the other equatorial. In a *trans* 1,2 compound both may be equatorial or both axial. This is also true for 1,4-disubstituted cyclohexanes, but the reverse holds for 1,3 compounds: the *trans* isomer must have the *ae* conformation and the *cis* isomer may be *a* or *ee*. For alkyl groups, the *ee* conformation predominates over the *a* but for other groups this is not necessarily so. For example, both *trans*-1,4-dibromocyclohexane and the corresponding dichloro compound have the *ee* and *a* conformations about equally populated[384] and most *trans*-1,2-dihalocyclohexanes exist predominantly in the *a* conformation.[385] Note that in the latter case the two halogen atoms are *anti* in the *a* conformation but *gauche* in the *ee* conformation.[386]

Since compounds with alkyl equatorial substituents are generally more stable, *trans*-1,2 compounds, which can adopt the *ee* conformation, are thermodynamically more stable than their *cis*-1,2 isomers, which must exist in the *ae* conformation. For the 1,2-dimethylcyclohexanes, the difference in stability is ~2 kcal mol^{-1} (8 kJ mol^{-1}). Similarly, *trans*-1,4 and *cis*-1,3 compounds are more stable than their stereoisomers.

An interesting anomaly is all-*trans*-1,2,3,4,5,6-hexaisopropylcyclohexane, in which the six isopropyl groups prefer the axial position, although the six ethyl groups of the corresponding hexaethyl compound prefer the equatorial position.[387] The alkyl groups of these compounds can of course only be all axial or all equatorial, and it is likely that the molecule prefers the all-axial conformation because of unavoidable strain in the other conformation.

[374] Ford, R.A.; Allinger, N.L. *J. Org. Chem.* ***1970***, *35*, 3178. For a critical review of the methods used to obtain these values, see Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* ***1971***, *3*, 139.
[375] Anet, F.A.L.; O'Leary, D.J. *Tetrahedron Lett.* ***1989***, *30*, 1059.
[376] Buchanan, G.W.; Webb, V.L. *Tetrahedron Lett.* ***1983***, *24*, 4519.
[377] Eliel, E.L.; Manoharan, M. *J. Org. Chem.* ***1981***, *46*, 1959.
[378] Booth, H.; Everett, J.R. *J. Chem. Soc., Chem. Commun.* ***1976***, 278.
[379] Hirsch, J.A. *Top. Stereochem.* ***1967***, *1*, 199.
[380] Kitching, W.; Olszowy, H.A.; Drew, G.M.; Adcock, W. *J. Org. Chem.* ***1982***, *47*, 5153.
[381] Schneider, H.; Hoppen, V. *Tetrahedron Lett.* ***1974***, 579.
[382] Squillacote, M.E.; Neth, J.M. *J. Am. Chem. Soc.* ***1987***, *109*, 198. Values of 2.59–2.92 kcal mol^{-1} (10.84–12.23 kJ mol^{-1}) were determined for 4-X-C_6H_4- substituents (X = NO_2, Cl, MeO) – see Kirby, A.J.; Williams, N.H. *J. Chem. Soc., Chem. Commun.* ***1992***, 1285, 1286.
[383] Manoharan, M.; Eliel, E.L. *Tetrahedron Lett.* ***1984***, *25*, 3267.
[384] Abraham, R.J.; Rossetti, Z.L. *J. Chem. Soc., Perkin Trans. 2* ***1973***, 582. See also, Hammarström, L.; Berg, U.; Liljefors, T. *Tetrahedron Lett.* ***1987***, *28*, 4883.
[385] Abraham, M.H.; Xodo, L.E.; Cook, M.J.; Cruz, R. *J. Chem. Soc., Perkin Trans. 2* ***1982***, 1503; Samoshin, V.V.; Svyatkin, V.A.; Zefirov, N.S. *J. Org. Chem. USSR* ***1988***, *24*, 1080, and references cited therein. See Zefirov, N.S.; Samoshin, V.V.; Subbotin, O.A.; Sergeev, N.M. *J. Org. Chem. USSR* ***1981***, *17*, 1301.
[386] For a case of a preferential diaxial conformation in 1,3-isomers, see Ochiai, M.; Iwaki, S.; Ukita, T.; Matsuura, Y.; Shiro, M.; Nagao, Y. *J. Am. Chem. Soc.* ***1988***, *110*, 4606.
[387] Golan, O.; Goren, Z.; Biali, S.E. *J. Am. Chem. Soc.* ***1990***, *112*, 9300.

Incidentally, it is now apparent, at least in one case, why the correct number of stereoisomers could be predicted by assuming planar rings, even although they are not planar (Sec. 4.K.ii). In the case of both a *cis*-1,2-X,X-disubstituted and a *cis*-1,2-X,Y-disubstituted cyclohexane, the molecule is nonsuperimposable on its mirror image; neither has a plane of symmetry. However, in the former case (**113**) conversion of one chair form to the other (which of course happens rapidly) turns the molecule into its mirror image, while in the latter case (**114**) rapid interconversion does not give the mirror image but merely the conformer in which the original axial and equatorial substituents exchange places. Thus the optical inactivity of **113** is not due to a plane of symmetry, but to a rapid interconversion of the molecule and its mirror image. A similar situation holds for *cis*-1,3 compounds. However, for *cis*-1,4 isomers (both X,X and X,Y) optical inactivity arises from a plane of symmetry in both conformations. All *trans*-1,2- and *trans*-1,3-disubstituted cyclohexanes are chiral (whether X,X or X,Y), while *trans*-1,4 compounds (both X,X and X,Y) are achiral, since all conformations have a plane of symmetry. It has been shown that the equilibrium is very dependent on both the solvent and the concentration of the disubstituted cyclohexane.[388] A theoretical study of the 1,2-dihalides showed a preference for the diaxial form with X = Cl, but predicted that the energy difference between diaxial and diequatorial was small when X = F.[389]

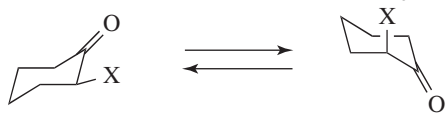


The conformation of a group can be frozen into a desired position by putting a large alkyl group into the ring (most often *tert*-butyl), which introduces significant $A^{1,3}$-strain and leads to a preference for the chair with the groups in the equatorial position.[390] It is known that silylated derivatives of *trans*-1,4- and *trans*-1,2-dihydroxycyclohexane, some monosilyloxycyclohexanes and some silylated sugars have unusually large populations of chair conformations with axial substituents.[391] Adjacent silyl groups in the 1,2-disubstituted series show a stabilizing interaction in all conformations, generally leading to unusually large axial populations.

The principles involved in the conformational analysis of six-membered rings containing one or two trigonal atoms, for example, cyclohexanone and cyclohexene, are

[388] Abraham, R.J.; Chambers, E.J.; Thomas, W.A. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 1061.
[389] Wiberg, K.B. *J. Org. Chem.* ***1999***, *64*, 6387.
[390] This idea was suggested by Winstein, S.; Holness, N.J. *J. Am. Chem. Soc.* ***1955***, *77*, 5561. See Saunders, M.; Wolfsberg, M.; Anet, F.A.L.; Kronja, O. *J. Am. Chem. Soc.* ***2007***, *129*, 10276.
[391] Marzabadi, C.H.; Anderson, J.E.; Gonzalez-Outeirino, J.; Gaffney, P.R.J.; White, C.G.H.; Tocher, D.A.; Todaro, L.J. *J. Am. Chem. Soc.* ***2003***, *125*, 15163.

TABLE 4.4 Proportion of axial conformation in 2-substituted cyclohexanones, in $CDCl_3$[396]



X	% axial conformation
F	17 ± 3
Cl	45 ± 4
Br	71 ± 4
I	88 ± 5
MeO	28 ± 4
MeS	85 ± 7
MeSe	(92)
Me_2N	44 ± 3
Me	(26)

similar.[392,393,394] The barrier to interconversion in cyclohexane has been calculated to be 8.4–12.1 kcal mol^{-1} (35.2–50.7 kJ mol^{-1}).[395] Cyclohexanone derivatives also assume a chair conformation. Substituents at C-2 can assume an axial or equatorial position depending on steric and electronic influences. The proportion of the conformation with an axial X group is shown in Table 4.4 for a variety of substituents (X) in 2-substituted cyclohexanones.[396]

4.O.iii. Conformation in Six-Membered Rings Containing Heteroatoms

In six-membered rings containing heteroatoms,[397] the basic principles are the same; that is, there are chair, twist, and boat forms, and axial and equatorial groups. The conformational

[392] See Rabideau, P.W. *The Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds*, VCH, NY, ***1989***; Vereshchagin, A.N. *Russ. Chem. Rev.* ***1983***, *52*, 1081; Johnson, F. *Chem. Rev.* ***1968***, *68*, 375. See also, Lambert, J.B.; Clikeman, R.R.; Taba, K.M.; Marko, D.E.; Bosch, R.J.; Xue, L. *Acc. Chem. Res.* ***1987***, *20*, 454.

[393] See Dale, J. *Stereochemistry and Conformational Analysis*, Verlag Chemie, Deerfield Beach, FL, ***1978***; Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, ***1971***; Eliel, E.L.; Allinger, N.L.; Angyal, S.J.; Morrison, G.A. *Conformational Analysis*, Wiley, NY, ***1965***; Dale, J. *Top. Stereochem.* ***1976***, *9*, 199; Truax, D.R.; Wieser, H. *Chem. Soc. Rev.* ***1976***, *5*, 411; Eliel, E.L. *J. Chem. Educ.* ***1975***, *52*, 762; Bushweller, C.H.; Gianni, M.H. in Patai, S. *The Chemistry of Functional Groups*, *Supplement E*, Wiley, NY, ***1980***, pp. 215–278.

[394] See Jensen, F.R.; Bushweller, C.H. *Adv. Alicyclic Chem.* ***1971***, *3*, 139; Robinson, D.L.; Theobald, D.W. *Q. Rev. Chem. Soc.* ***1967***, *21*, 314; Eliel, E.L. *Angew. Chem. Int. Ed.* ***1965***, *4*, 761; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 686–753. Also see, Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, England, ***2017***, pp. 45–53.

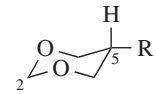
[395] Laane, J.; Choo, J. *J. Am. Chem. Soc.* ***1994***, *116*, 3889.

[396] Basso, E.A.; Kaiser, C.; Rittner, R.; Lambert, J.B. *J. Org. Chem.* ***1993***, *58*, 7865.

[397] See Glass, R.S. *Conformational Analysis of Medium-Sized Heterocycles,* VCH, NY, ***1988***; Riddell, F.G. *The Conformational Analysis of Heterocyclic Compounds*, Academic Press, NY, ***1980***; Juaristi, E. *Acc. Chem. Res.* ***1989***, *22*, 357; Crabb, T.A.; Katritzky, A.R. *Adv. Heterocycl. Chem.* ***1984***, *36*, 1; Eliel, E.L. *Angew. Chem. Int. Ed.*

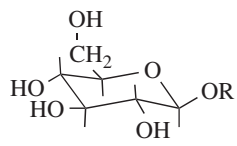
equilibrium for tetrahydropyridines, for example, has been studied.[398] In certain compounds a number of new factors enter the picture. Only two of these will be examined.[399]

1. In 5-alkyl-substituted 1,3-dioxanes, the 5-substituent has a much smaller preference for the equatorial position than in cyclohexane derivatives;[400] the $A^{1,3}$-strain is much lower. This fact indicates that the lone pairs on the oxygen atoms have a smaller steric requirement than the C—H bonds in the corresponding cyclohexane derivatives. There is some evidence of an homoanomeric interaction in these systems.[401] Similar behavior is found in the 1,3-dithianes,[402] and 2,3-disubstituted-1,4-dithianes have also been examined.[403] With certain nonalkyl substituents (e.g., F, NO_2, SOMe,[404] NMe_3^+) the axial position is actually preferred.[405]

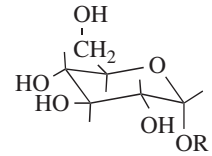


Substituted 1,3-dioxanes

2. An alkyl group located on a carbon α to a heteroatom prefers the equatorial position, which is of course the normally expected behavior, but a *polar* group in such a location prefers the *axial* position. An example of this phenomenon, known as the *anomeric effect*,[406] is the greater stability of α-glucosides (**115**) over β-glucosides (**116**).



A β-glucoside **115**



116 An α-glucoside

1972, *11*, 739; *Pure Appl. Chem.* ***1971***, *25*, 509; *Acc. Chem. Res.* ***1970***, *3*, 1; Lambert, J.B. *Acc. Chem. Res.* ***1971***, *4*, 87.

[398] Bachrach, S.M.; Liu, M. *Tetrahedron Lett.* ***1992***, *33*, 6771.

[399] These factors are discussed by Eliel, E.L. *Angew. Chem. Int. Ed.* ***1972***, *11*, 739.

[400] Riddell, F.G.; Robinson, M.J.T. *Tetrahedron* ***1967***, *23*, 3417; Eliel, E.L.; Knoeber, M.C. *J. Am. Chem. Soc.* ***1968***, *90*, 3444. See also, Eliel, E.L.; Alcudia, F. *J. Am. Chem. Soc.* ***1974***, *96*, 1939. See Cieplak, P.; Howard, A.E.; Powers, J.P.; Rychnovsky, S.D.; Kollman, P.A. *J. Org. Chem.* ***1996***, *61*, 3662 for conformational energy differences in 2,2,6-trimethyl-4-alkyl-1,3-dioxane.

[401] Cai, J.; Davies, A.G.; Schiesser, C.H. *J. Chem. Soc., Perkin Trans. 2* ***1994***, 1151.

[402] Hutchins, R.O.; Eliel, E.L. *J. Am. Chem. Soc.* ***1969***, *91*, 2703. See also, Juaristi, E.; Cuevas, G. *Tetrahedron* ***1999***, *55*, 359.

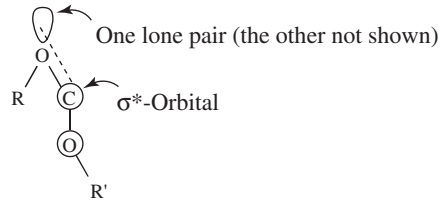
[403] Strelenko, Y.A.; Samoshin, V.V.; Troyansky, E.I.; Demchuk, D.V.; Dmitriev, D.E.; Nikishin, G.I.; Zefirov, N.S. *Tetrahedron* ***1994***, *50*, 10107.

[404] Gordillo, B.; Juaristi, E.; Matínez, R.; Toscano, R.A.; White, P.S.; Eliel, E.L. *J. Am. Chem. Soc.* ***1992***, *114*, 2157.

[405] Kaloustian, M.K.; Dennis, N.; Mager, S.; Evans, S.A.; Alcudia, F.; Eliel, E.L. *J. Am. Chem. Soc.* ***1976***, *98*, 956. See also, Eliel, E.L.; Kandasamy, D.; Sechrest, R.C. *J. Org. Chem.* ***1977***, *42*, 1533.

[406] See Kirby, A.J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer, NY, ***1983***; Szarek, W.A.; Horton, D. *Anomeric Effect*, American Chemical Society, Washington, ***1979***; Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, Pergamon, Elmsford, NY, ***1983***, pp. 4–26; Zefirov, N.S. *Tetrahedron* ***1977***, *33*, 3193; Lemieux, R.U. *Pure Appl. Chem.* ***1971***, *27*, 527. For the effect of the anomeric effect on natural bond orbital analysis, see Freitas, M.P. *Org. Biomol. Chem.* ***2013***, *11*, 2885. An S—C—P anomeric effect has been reported: see Juaristi, E.; Notario, R. *J. Org. Chem.* ***2015***, *80*, 2879.

A number of explanations have been offered for the anomeric effect.[407] The one[408] that has received the most acceptance[409] is that one of the lone pairs of the polar atom connected to the carbon (an oxygen atom in the case of **116**) can be stabilized by overlapping with an antibonding orbital of the bond between the carbon and the other polar atom, as shown:



This overlap can happen only if the two orbitals are in the positions shown. The situation can also be represented by this type of hyperconjugation (called "negative hyperconjugation," and see Sec. 2.M):

It is possible that simple repulsion between parallel dipoles in **115** also plays a part in the greater stability of **116**. It has been shown that aqueous solvation effects reduce anomeric stabilization in many systems, particularly for tetrahydropyranosyls.[410] In contrast to cyclic acetals, simple acyclic acetals rarely adopt the anomeric conformation, apparently because the eclipsed conformation better accommodates steric interactions of groups linked by relatively short carbon–oxygen bonds.[411] In all-*cis*-2,5-di-*tert*-butyl-1,4-cyclohexanediol, hydrogen bonding stabilizes the otherwise high-energy form[412] and 1,3-dioxane (**117**) exists largely as the twist conformation shown.[413] The conformational preference of 1-methyl-1-silacyclohexane (**120**) has been studied.[414] A strongly decreased activation barrier in silacyclohexane was observed, as compared to that in the parent ring, and is explained by the longer endocyclic Si—C bonds. The role of CH—O coulombic interactions has been discussed.[415]

[407] Juaristi, E.; Cuevas, G. *Tetrahedron* ***1992***, *48*, 5019.

[408] See Romers, C.; Altona, C.; Buys, H.R.; Havinga, E. *Top. Stereochem.* ***1969***, *4*, 39 (pp. 73–77); Wolfe, S.; Whangbo, M.; Mitchell, D.J. *Carbohydr. Res.* ***1979***, *69*, 1.

[409] See Praly, J.; Lemieux, R.U. *Can. J. Chem.* ***1987***, *65*, 213; Booth, H.; Khedhair, K.A.; Readshaw, S.A. *Tetrahedron* ***1987***, *43*, 4699. For evidence against it, see Box, V.G.S. *Heterocycles* ***1990***, *31*, 1157.

[410] Cramer, C.J. *J. Org. Chem.* ***1992***, *57*, 7034; Booth, H.; Dixon, J.M.; Readshaw, S.A. *Tetrahedron* ***1992***, *48*, 6151. For a discussion of solvent effects see Wang, C.; Ying, F.; Wu, W.; Mo, Y. *J. Org. Chem.* ***2014***, *79*, 1571.

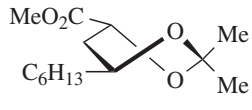
[411] Anderson, J.E. *J. Org. Chem.* ***2000***, *65*, 748.

[412] Stolow, R.D. *J. Am. Chem. Soc.* ***1964***, *86*, 2170; Stolow, R.D.; McDonagh, P.M.; Bonaventura, M.M. *J. Am. Chem. Soc.* ***1964***, *86*, 2165. Also see Fitjer, L.; Scheuermann, H.; Klages, U.; Wehle, D.; Stephenson, D.S.; Binsch, G. *Chem. Ber.* ***1986***, *119*, 1144.

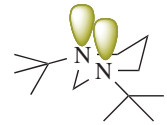
[413] Rychnovsky, S.D.; Yang, G.; Powers, J.P. *J. Org. Chem.* ***1993***, *58*, 5251.

[414] Arnason, I.; Kvaran, A.; Jonsdottir, S.; Gudnason, P.I.; Oberhammer, H. *J. Org. Chem.* ***2002***, *67*, 3827.

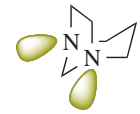
[415] Wiberg, K.B.; Lambert, K.M.; Bailey, W.F. *J. Org. Chem.* ***2015***, *80*, 7884.



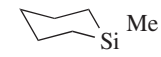
117



118



119



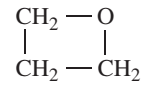
120

Second-row heteroatoms are known to show a substantial anomeric effect.[416] There appears to be evidence for a reverse anomeric effect in 2-aminotetrahydropyrans,[417] but it has been called into question whether a reverse anomeric effect exists at all.[418] In **118**, the lone pair electrons assume an axial conformation and there is an anomeric effect.[419] In **119**, however, the lone pair electron orbitals are oriented *gauche* to both the axial and equatorial α-C—H bonds and there is no anomeric effect.[419]

4.O.iv. Conformation in Other Rings[420]

Three-membered saturated rings are usually planar, but other small rings can have some flexibility. Cyclobutane[421] is not planar but exists as in **121**, with an angle between the planes of ~35°.[422] The deviation from planarity is presumably caused by relief of the strain of eclipsing bonds that would be present in the planar form (Sec. 4.Q.i).

121



Oxetane

Oxetane is closer to planarity because there is less eclipsing, with an angle between the planes of ~10°.[423] Cyclopentane might be expected to be planar, since the angles of a regular pentagon are 108°, but it is not so, also because of eclipsing effects.[424] There are two puckered conformations for cyclopentane, the *envelope* and the *half-chair*. There is little energy difference between these two forms and many five-membered ring systems have conformations somewhere in-between them.[425] Although in the envelope conformation one carbon is shown above the others, ring motions cause each of the carbons in rapid

[416] Salzner, U.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1993***, *115*, 10231; Aggarwal, V.K.; Worrall, J.M.; Adams, H.; Alexander, R.; Taylor, B.F. *J. Chem. Soc., Perkin Trans. 1* ***1997***, 21.

[417] Salzner, U.; Schleyer, P.v.R. *J. Org. Chem.* ***1994***, *59*, 2138.

[418] Perrin, C.L. *Tetrahedron* ***1995***, *51*, 11901.

[419] Anderson, J.E.; Cai, J.; Davies, A.G. *J. Chem. Soc., Perkin Trans. 2* ***1997***, 2633. For some controversy concerning the anomeric effect on a related system, see Perrin, C.L.; Armstrong, K.B.; Fabian, M.A. *J. Am. Chem. Soc.* ***1994***, *116*, 715; Salzner, U. *J. Org. Chem.* ***1995***, *60*, 986.

[420] Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 675–685 and 754–770.

[421] For reviews of the stereochemistry of four-membered rings, see Legon, A.C. *Chem. Rev.* ***1980***, *80*, 231; Moriarty, R.M. *Top. Stereochem.* ***1974***, *8*, 271; Cotton, F.A.; Frenz, B.A. *Tetrahedron* ***1974***, *30*, 1587.

[422] Miller, F.A.; Capwell, R.J.; Lord, R.C.; Rea, D.G. *Spectrochim. Acta Part A*, ***1972***, *28*, 603. However, see Margulis, T.N. *J. Am. Chem. Soc.* ***1971***, *93*, 2193.

[423] Luger, P.; Buschmann, J. *J. Am. Chem. Soc.* ***1984***, *106*, 7118.

[424] See Fuchs, B. *Top. Stereochem.* ***1978***, *10*, 1; Legon, A.C. *Chem. Rev.* ***1980***, *80*, 231.

[425] Willy, W.E.; Binsch, G.; Eliel, E.L. *J. Am. Chem. Soc.* ***1970***, *92*, 5394; Lipnick, R.L. *J. Mol. Struct.* ***1974***, *21*, 423.

succession to assume this position. The puckering rotates around the ring in what is called a *pseudorotation*[426] (Sec. 4.O.ii).

Envelope

Half-chair

In substituted cyclopentanes and five-membered rings in which at least one atom does not contain two substituents [e.g., tetrahydrofuran (THF), cyclopentanone, C_3- and C_7-monosubstituted and disubstituted hexahydroazepin-2-ones (caprolactams),[427] tetrahydrothiophene *S*-oxide[428]], one conformer may be more stable than the others. The barrier to planarity in cyclopentane has been reported to be 5.2 kcal mol^{-1} (22 kJ mol^{-1}).[429] Contrary to previous reports, there is only weak stabilization (<2 kcal mol^{-1}; <8 kJ mol^{-1}) of 3-, 4-, and 5-membered rings by *gem*-dialkoxycarbonyl substituents (e.g., COOR).[430]

Rings larger than six-membered are always puckered[431] unless they contain a large number of sp^2 atoms (see the section on strain in medium rings, Sec. 4.Q.ii). The energy and conformations of the alkane series cycloheptane to cyclodecane has been reported.[432] The conformation shown for oxacyclooctane (**122**), for example, appears to be the most abundant one.[433] The conformations of other large-ring compounds have been studied, including cycloundecane,[434] 11-membered ring lactones,[435] 10- and 11-membered ring ketones,[436] and 11- and 14-membered ring lactams.[437] Dynamic NMR was used to determine the conformation of large-ring cycloalkenes and lactones,[438] and C—H coupling constants have been used for conformational analysis.[439] Strain estimates have been made for small-ring cyclic allenes[440] and butatrienes.[441] Note that axial and equatorial hydrogens are found

[426] Poupko, R.; Luz, Z.; Zimmermann, H. *J. Am. Chem. Soc.* ***1982***, *104*, 5307; Riddell, F.G.; Cameron K.S.; Holmes, S.A.; Strange, J.H. *J. Am. Chem. Soc.* ***1997***, *119*, 7555.

[427] Matallana, A.; Kruger, A.W.; Kingsbury, C.A. *J. Org. Chem.* ***1994***, *59*, 3020.

[428] Abraham, R.J.; Pollock, L.; Sancassan, F. *J. Chem. Soc., Perkin Trans. 2* ***1994***, 2329.

[429] Carreira, L.A.; Jiang, G.J.; Person, W.B.; Willis Jr., J.N. *J. Chem. Phys.* ***1972***, *56*, 1440.

[430] Verevkin, S.P.; Kümmerlin, M.; Beckhaus, H.-D.; Galli, C.; Rüchardt, C. *Eur. J. Org. Chem.* ***1998***, 579.

[431] Arshinova, R.P. *Russ. Chem. Rev.* ***1988***, *57*, 1142; Ounsworth, J.P.; Weiler, L. *J. Chem. Educ.* ***1987***, *64*, 568; Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 307–321; Casanova, J.; Waegell, B. *Bull. Soc. Chim. Fr.* ***1975***, 911; Anet, F.A.L. *Top. Curr. Chem.* ***1974***, *45*, 169; Dunitz, J.D. *Pure Appl. Chem.* ***1971***, *25*, 495. See Glass, R.S. *Conformational Analysis of Medium-Sized Heterocycles*, VCH, NY, ***1988***.

[432] Wiberg, K.B. *J. Org. Chem* ***2003***, *68*, 9322.

[433] Meyer, W.L.; Taylor, P.W.; Reed, S.A.; Leister, M.C.; Schneider, H.-J.; Schmidt, G.; Evans, F.E.; Levine, R.A. *J. Org. Chem.* ***1992***, *57*, 291.

[434] Pawar, D.M.; Brown II, J.; Chen, K.-H.; Allinger, N.L.; Noe, E.A. *J. Org. Chem.* ***2006***, *71*, 6512.

[435] Spracklin, D.K.; Weiler, L. *J. Chem. Soc., Chem. Commun.* ***1992***, 134.

[436] Pawar, D.M.; Smith, S.V.; Moody, E.M.; Noe, E.A. *J. Am. Chem. Soc.* ***1998***, *120*, 8241.

[437] Borgen, G.; Dale, J.; Gundersen, L.-L.; Krivokapic, A.; Rise, F.; Øverås, A.T. *Acta Chem. Scand. B*, ***1998***, *52*, 1110.

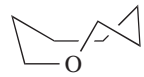
[438] Pawar, D.M.; Davids, K.L.; Brown, B.L.; Smith, S.V.; Noe, E.A. *J. Org. Chem.* ***1999***, *64*, 4580; Pawar, D.M.; Moody, E.M.; Noe, E.A. *J. Org. Chem.* ***1999***, *64*, 4586.

[439] Kleinpeter, E.; Koch, A.; Pihlaja, K. *Tetrahedron* ***2005***, *61*, 7349.

[440] Also see Patel, D.S.; Bharatam, P.V. *J. Org. Chem.* ***2011***, *76*, 2558.

[441] Daoust, K.J.; Hernandez, S.M.; Konrad, K.M.; Mackie, I.D.; Winstanley Jr., J.; Johnson, R.P. J. *Org. Chem.* ***2006***, *71*, 5708.

only in the chair conformations of six-membered rings. In rings of other sizes, the hydrogen atoms protrude at angles that generally do not lend themselves to classification in this way,[442] although in some cases the terms "pseudo-axial" and "pseudo-equatorial" have been used to classify hydrogen atoms in rings of other sizes.[443]



122

4.P. MOLECULAR MECHANICS[444]

Molecular mechanics[445] describes a molecule in terms of a collection of bonded atoms that have been distorted from some idealized geometry due to nonbonded van der Waals (steric) and Coulombic (charge–charge) interactions. This approach is fundamentally different from molecular orbital theory that is based on quantum mechanics and that make no reference whatsoever to chemical bonding. The success of molecular mechanics depends on the ability to represent molecules in terms of unique valence structures, on the notion that bond lengths and angles may be transferred from one molecule to another, and on a predictable dependence of geometrical parameters on the local atomic environment.

The molecular mechanics energy of a molecule is given as a sum of contributions arising from distortions from ideal bond distances (stretch contributions), bond angles (bend contributions) and torsion angles (torsion contributions), together with contributions from nonbonded interactions. This energy is commonly referred to as a *strain energy*, meaning that it reflects the inherent strain in a real molecule relative to a hypothetical idealized (strain-free) form.

$$\mathbf{E}^{\text{strain}} = \mathbf{E}_{\text{A}}^{\text{stretch}} + \mathbf{E}_{\text{A}}^{\text{bend}} + \mathbf{E}_{\text{A}}^{\text{torsion}} + \mathbf{E}_{\text{AB}}^{\text{non-bonded}} \tag{4-1}$$

Stretch and bend terms are most simply given in terms of quadratic (*Hooke's law*) forms:

$$\mathbf{E}^{\text{stretch}}(\text{r}) = \frac{1}{2} \quad \text{k}^{\text{stretch}} (r - r^{\text{eq}})^2 \tag{4-2}$$

$$\mathbf{E}^{\text{bend}}(\alpha) = \frac{1}{2} \quad \text{k}^{\text{bend}} (\alpha - \alpha^{\text{eq}})^2 \tag{4-3}$$

where r and α are the bond distance and angle, respectively, and r^{eq} and α^{eq} are the ideal bond length and angle, respectively.

[442] For definitions of axial, equatorial, and related terms for rings of any size, see Anet, F.A.L. *Tetrahedron Lett.* ***1990***, *31*, 2125.

[443] For a discussion of the angles of the ring positions, see Cremer, D. *Isr. J. Chem.* ***1980***, *20*, 12.

[444] Thanks to Dr. Warren Hehre, Wavefunction, Inc., Irvine, CA, personal communication. See Hehre, W.J. *A Guide to Molecular Mechanics and Quantum Chemical Calculations*, Wavefunction, Inc., Irvine, CA, ***2003***, pp. 56–57.

[445] For a review, see Rappe, A.K.; Casewit, C.J. *Molecular Mechanics Across Chemistry,* University Science Books, Sausalito, CA, ***1997***.

Torsion terms need to properly reflect the inherent periodicity of the particular bond involved in a rotation. For example, the three-fold periodicity of the carbon–carbon bond in ethane may be represented by a simple cosine form.

$$\mathbf{E}^{\text{torsion}}(\omega) = \text{k}^{\text{torsion3}}\ [1 - \cos 3\,(\omega - \omega^{\text{eq}})] \tag{4-4}$$

ω is the torsion angle, ω^{eq} is the ideal torsion angle and $\text{k}^{\text{torsion}}$ is a parameter. Torsion contributions to the strain energy will also usually need to include contributions that are one-fold and two-fold periodic. These can be represented in the same manner as the three-fold term.

$$\begin{aligned}\mathbf{E}^{\text{torsion}}(\omega) = {} & k^{\text{torsion1}}\,[1 - \cos\,(\omega - \omega^{\text{eq}})] + k^{\text{torsion2}}\,[1 - \cos 2\,(\omega - \omega^{\text{eq}})] \\ & + k^{\text{torsion3}}\,[1 - \cos 3\,(\omega - \omega^{\text{eq}})]\end{aligned} \tag{4-5}$$

Nonbonded interactions involve a sum of van der Waals (VDW) interactions and Coulombic interactions. The Coulombic term accounts for charge–charge interactions.

$$\mathbf{E}^{\text{non-bonded}}(\text{r}) = \mathbf{E}^{\text{VDW}}(\text{r}) + \mathbf{E}^{\text{Coulombic}}(\text{r}) \tag{4-6}$$

The VDW is made up of two parts, the first to account for strong repulsion on nonbonded atoms as they closely approach, and the second to account for weak long-range attraction; r is the nonbonded distance.

Molecular mechanics methods differ both in the form of the terms that make up the strain energy and in their detailed parameterization. Older methods, such as SYBYL,[446] use very simple forms and relatively few parameters, while newer methods, such as MM3,[447] MM4,[448] and MMFF,[449] use more complex forms and many more parameters. In general, the more complex the form of the strain energy terms and the more extensive the parameterization, the better will be the results. Of course, more parameters mean that more (experimental) data will be needed in their construction. Because molecular mechanics is not based on "physical fundamentals," but rather is essentially an interpolation scheme, its success depends on the availability of either experimental or high-quality theoretical data for parameterization. A corollary is that molecular mechanics would not be expected to lead to good results for "new" molecules, that is, molecules outside the range of their parameterization.

The two most important applications of molecular mechanics are geometry calculations on very large molecules, for example, on proteins, and conformational analysis on molecules for which there may be hundreds, thousands, or even tens of thousands of distinct structures. It is here that methods based on quantum mechanics are simply not (yet) practical. It should be no surprise that equilibrium geometries obtained from molecular mechanics are generally in good accord with experimental values. There are ample data with which to

[446] Clark, M.; Cramer III, R.D.; van Opdenbosch, N. *J. Computational Chem.* ***1989***, *10*, 982.
[447] Allinger, N.L.; Li, F.; Yun, Y.H. *J. Computational Chem.* ***1990***, *11*, 855, and later papers in this series.
[448] Allinger, N.L.; Chen, K.; Lii, J.-H. *J. Computational Chem.* ***1996***, *17*, 642, and later papers in this series.
[449] Halgren, T.A. *J. Computational Chem.* ***1996***, *17*, 490, and later papers in this series.

parameterize and evaluate the methods. However, because there are very few experimental data relating to the equilibrium conformations of molecules and energy differences among different conformations, molecular mechanics calculations for these quantities need to be viewed with a very critical eye. In time, high-quality data from quantum mechanics will provide the needed data and allow more careful parameterization (and assessment) than now possible.

The most important limitation of molecular mechanics is its inability to provide thermochemical data. The reason for this is that the mechanics strain energy is specific to a given molecule (it provides a measure of how much this molecule deviates from an ideal arrangement), and different molecules have different ideal arrangements. For example, acetone and methyl vinyl ether have different bonds and would be referenced to different standards. The only exception occurs for conformational energy differences or, more generally, for energy comparisons among molecules with exactly the same bonding, for example, *cis*- and *trans*-but-2-ene.

Because a molecular mechanics calculation reveals nothing about the distribution of electrons or distribution of charge in molecules, and because mechanics methods have not (yet) been parameterized to reproduce transition-state geometries, they are of limited value in describing either chemical reactivity or product selectivity. There are, however, situations where steric considerations associated with either the product or reactants are responsible for trends in reactivity and selectivity, and here molecular mechanics would be expected to be of some value.

Because of the different strengths and limitations of molecular mechanics and quantum chemical calculations, it is now common practice to combine the two, for example, to use molecular mechanics to establish conformation (or at least a set of reasonable conformations) and then to use quantum calculations to evaluate energy differences.

In practical terms, molecular mechanics calculations may easily be performed on molecules comprising several thousand atoms. Additionally, molecular mechanics calculations are sufficiently rapid to permit extensive conformational searching on molecules containing upwards of a hundred atoms. Modern graphical-based programs for desktop computers make the methods available to all chemists.

4.Q. STRAIN

Steric strain[450] exists in a molecule when bonds are forced to make abnormal angles, usually, but not always, due to repulsion of large atoms or groups attached to those bonds. This repulsion results in a higher energy than would be the case in the absence of the angle distortions. It has been shown that there is a good correlation between the ^{13}C—H coupling constants in NMR and the bond angles and bond force angles in strained organic molecules.[451] "The magnitude of a one-bond C—H coupling constant depends upon the chemical environment of the hydrogen atom and, especially, upon its stereochemical relationship to vicinal lone electron pairs. However, a lone electron pair is not essential for the observation of a stereoelectronic effect, since even cyclohexane exhibits different axial

[450] See Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, ***1978***; Wiberg, K.B. *Angew. Chem. Int. Ed.* ***1986***, *25*, 312; Greenberg, A.; Stevenson, T.A. *Mol. Struct. Energ.* ***1986***, *3*, 193; Liebman, J.F.; Greenberg, A. *Chem. Rev.* ***1976***, *76*, 311; Cremer, D.; Kraka, E. *Mol. Struct. Energ.* ***1988***, *7*, 65.
[451] Zhao, C.-Y.; Duan, W.-S.; Zhang, Y.; You, X.-Z. *J. Chem. Res. (S)* ***1998***, 156.

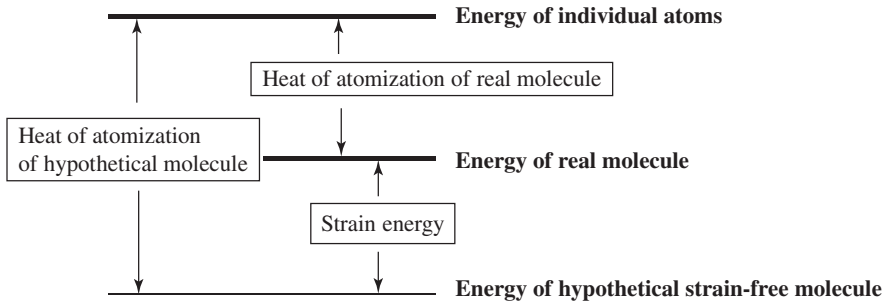


FIGURE 4.6. Strain energy calculation.

and equatorial C—H coupling constants."[452] The name "Perlin effect" has been proposed to describe such observations.[452] A reverse fluorine Perlin-like effect has been reported.[453]

There are, in general, two kinds of structural features that result in sterically caused abnormal bond angles. One of these is found in small-ring compounds, where the angles must be less than those resulting from normal orbital overlap.[454] Such strain is called *small-angle strain* or *Baeyer strain*. The other arises when nonbonded atoms are forced into close proximity by the geometry of the molecule. These are called *nonbonded interactions*. This latter type of strain is most often associated with the term steric strain.

Strained molecules possess *strain energy*. That is, their potential energies are higher than they would be if strain were absent.[455] The strain energy for a particular molecule can be estimated from heat of atomization or heat of combustion data. A strained molecule has a lower heat of atomization than it would have if it were strain-free (Figure 4.6). As in the similar case of resonance energies (Sec. 2.B), strain energies cannot be known exactly, because the energy of a real molecule can be measured, but not the energy of a hypothetical unstrained model. It is also possible to calculate strain energies by molecular mechanics, not only for real molecules, but also for those that cannot be made.[456]

4.Q.i. Strain in Small Rings

Three-membered rings have a great deal of angle strain (also called *Baeyer strain*), since 60° angles represent a large departure from the "normal" tetrahedral angles. Calculations have been interpreted to say that Baeyer strain in small-ring systems originates from a decrease in nucleus–electron attraction compared to acyclic compounds,[457] but this has been challenged in later work.[458] However, in sharp contrast to other ethers, ethylene oxide is quite reactive, the ring being opened by many reagents (Sec. 10.G.iii). Ring opening, of course, relieves

[452] Wolfe, S.; Pinto, B.M.; Varma, V.; Leung, R.Y.N. *Can. J. Chem.* ***1990***, *68*, 1051. A long-range Perlin effect has been noted for oxocane: see Berry, E.; dos Passos Gomes, G.; MacLean, A.; Martin, J.R.; Wiget, P.A. *J. Org. Chem.* ***2016***, *81*, 5740.

[453] Silla, J.M.; Freitas, M.P.; Cormanich, R.A.; Rittner, R. *J. Org. Chem.* ***2014***, *79*, 6385.

[454] Wiberg, K.B. *Accts. Chem. Res.* ***1996***, *29*, 229.

[455] For discussions, see Wiberg, K.B.; Bader, R.F.W.; Lau, C.D.H. *J. Am. Chem. Soc.* ***1987***, *109*, 985, 1001.

[456] For a review, see Rüchardt, C.; Beckhaus, K. *Angew. Chem. Int. Ed.* ***1985***, *24*, 529. See also, Burkert, U.; Allinger, N.L. *Molecular Mechanisms*, American Chemical Society, Washington, ***1982***, pp. 169–194; Allinger, N.L. *Adv. Phys. Org. Chem.* ***1976***, *13*, 1 (pp. 45–47).

[457] Barić, D.; Maksić, Z.B. *Theor. Chem. Acc.* ***2005***, 114, 222.

[458] Hohlneicher, G.; Packschies, L. *Tetrahedron Lett.* ***2007***, *48*, 6429. However, see Barić, D.; Maksić, Z.B. *Tetrahedron Lett.* ***2008***, *49*, 1428.

the strain.[459] Cyclopropane,[460] which is even more strained[461] than ethylene oxide, is also cleaved more easily than would be expected for an alkane.[462] Thus, pyrolysis at 450–500 °C converts it to propene, bromination gives 1,3-dibromopropane,[463] and it can be hydrogenated to propane (though at high pressure).[464] Other three-membered rings are similarly reactive.[465] Alkyl substituents influence the strain energy of small-ring compounds,[466] and carbonyl substitution also influences the strain energy.[467] *gem*-Dimethyl substitution, for example, "lowers the strain energy of cyclopropanes, cyclobutanes, epoxides, and dimethyldioxirane by 6–10 kcal mol^{-1} (25–42 kJ mol^{-1}) relative to an unbranched acyclic reference molecule."[466] The C—H bond dissociation energy also tends to increase ring strain in small-ring alkenes.[468] Computation of the ring strain energy of 1,1-dimethylcyclobutane, however, shows "no significant enthalpic component of the *gem*-dimethyl effect as measured by the ring strain energy."[469]

There is much evidence, chiefly derived from NMR coupling constants, that the bonding in cyclopropanes is not the same as in compounds that lack small-angle strain.[470] For a normal carbon atom, one *s* and three *p* orbitals are hybridized to give four approximately equivalent sp^3 orbitals, each containing ~25% *s* character. But for a cyclopropane carbon atom, the four hybrid orbitals are far from equivalent. The two orbitals directed to the outside bonds have more *s* character than a normal sp^3 orbital, while the two orbitals involved in ring bonding have less, because the more *p* like they are the more they resemble ordinary *p* orbitals, whose preferred bond angle is 90° rather than 109.5°. Since the small-angle strain in cyclopropanes is the difference between the preferred angle and the real angle of 60°, this additional *p* character relieves some of the strain. The external orbitals have ~33% *s* character, so that they are ~ sp^2 orbitals, while the internal orbitals have ~17% *s* character, so that they may be called ~ sp^5 orbitals.[471] Each of the three carbon–carbon bonds of cyclopropane is therefore formed by overlap of two sp^5 orbitals. Molecular-orbital calculations show that such bonds are not completely *s* in character. In normal C—C bonds, sp^3 orbitals overlap in such a way that the straight line connecting the nuclei becomes an axis about which the electron density is symmetrical. But in cyclopropane, the electron density is directed *away from* the ring.[472] Figure 4.7 shows the direction of orbital

[459] For reviews of reactions of cyclopropanes and cyclobutanes, see Trost, B.M. *Top. Curr. Chem.* ***1986***, *133*, 3; Wong, H.N.C.; Lau, C.D.H.; Tam, K. *Top. Curr. Chem.* ***1986***, *133*, 83.

[460] For a treatise, see Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, 2 pts.; Wiley, NY, ***1987***.

[461] See in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, 2 pts, Wiley, NY, ***1987***, the papers by Wiberg, K.B. pt. 1, pp. 1–26; Liebman, J.F.; Greenberg, A. pt. 2, pp. 1083–1119; Liebman, J.F.; Greenberg, A. *Chem. Rev.* ***1989***, *89*, 1225.

[462] See Wong, H.N.C.; Hon, M.; Ts, C.e.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165; Reissig, H. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, ***1987***, pp. 375–443.

[463] Ogg Jr., R.A.; Priest, W.J. *J. Am. Chem. Soc.* ***1938***, *60*, 217.

[464] Shortridge, R.W.; Craig, R.A.; Greenlee, K.W.; Derfer, J.M.; Boord, C.E. *J. Am. Chem. Soc.* ***1948***, *70*, 946.

[465] See Frey, H.M. *Adv. Phys. Org. Chem.* ***1966***, *4*, 147.

[466] Bach, R.D.; Dmitrenko, O. *J. Org. Chem.* ***2002***, *67*, 2588.

[467] Bach, R.D.; Dmitrenko, O. *J. Am. Chem. Soc.* ***2006***, *128*, 4598.

[468] Bach, R.D.; Dmitrenko, O. *J. Am. Chem. Soc.* ***2004***, *126*, 4444; Tian, Z.; Fattahi, A.; Lis, L.; Kass, S.R. *J. Am. Chem. Soc.* ***2006***, *128*, 17087.

[469] Bachrach, S.M. *J. Org. Chem.* ***2008***, *73*, *2466*. Also see Ringer, A.L.; Magers, D.H. *J. Org. Chem.* ***2007***, *72*, 2533.

[470] See Cremer, D.; Kraka, E. *J. Am. Chem. Soc.* ***1985***, *107*, 3800, 3811; Slee, T.S. *Mol. Struct. Energ.* ***1988***, *5*, 63; Casaarini, D.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* ***1997***, *62*, 7592.

[471] Randić, M.; Maksić, Z. *Theor. Chim. Acta* ***1965***, *3*, 59; Weigert, F.J.; Roberts, J.D. *J. Am. Chem. Soc.* ***1967***, *89*, 5962.

[472] Wiberg, K.B. *Accts. Chem. Res.* ***1996***, *29*, 229.

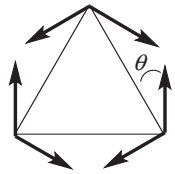
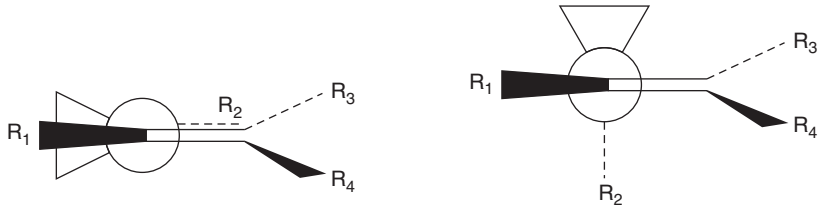


FIGURE 4.7. Orbital overlap in cyclopropane. The arrows point toward the center of electron density.



(a) (b)

FIGURE 4.8. Conformations of α-cyclopropylalkenes. Conformation (a) leads to maximum conjugation and conformation (b) to minimum conjugation.

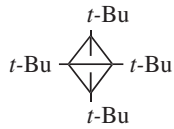
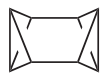
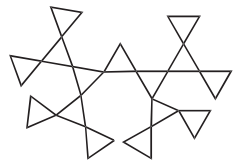
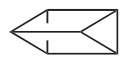
overlap.[473] For cyclopropane, the angle (marked θ) is 21°. Cyclobutane exhibits the same phenomenon but to a lesser extent, θ being 7°.[472,473] Molecular orbital calculations also show that the maximum electron densities of the C—C σ orbitals are bent away from the ring, with $\theta = 9.4°$ for cyclopropane and 3.4° for cyclobutane.[474] The bonds in cyclopropane are called *bent bonds* (sometimes, *banana bonds*), and are intermediate in character between σ and π, so that cyclopropanes behave in some respects like double-bond compounds.[475] For one thing, there is much evidence, chiefly from UV spectra,[476] that a cyclopropane ring is conjugated with an adjacent double bond. The conjugation is greatest for the conformation shown in Figure 4.8a and is least or absent for the conformation shown in Figure 4.8b since overlap of the double-bond π orbital with two of the *p*-like orbitals of the cyclopropane ring is greatest in the conformation shown in Figure 4.8a. However, the conjugation between a cyclopropane ring and a double bond is less than that between two double bonds.[477] See Section 4.O.iv for other examples of the similarities in behavior of a cyclopropane ring and a double bond.

Four-membered rings also exhibit angle strain, but much less than three-membered rings, and for that reason are less easily opened. Cyclobutane is more resistant than cyclopropane to bromination, and although it can be hydrogenated to butane, more strenuous conditions are required. Nevertheless, pyrolysis at 420 °C gives two molecules of ethene. As mentioned earlier (Sec. 4.O.iv), cyclobutane is not planar.[478]

[473] See Hoffmann, R.; Davidson, R.B. *J. Am. Chem. Soc.* ***1971***, *93*, 5699.
[474] Wiberg, K.B.; Bader, R.F.W.; Lau, C.D.H. *J. Am. Chem. Soc.* ***1987***, *109*, 985, 1001.
[475] See Tidwell, T.T. in Rappoport, Z. *The Chemistry of the Cyclopropyl Groups*, pt. 1, Wiley, NY, ***1987***, pp. 565–632; Charton, M. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, pp. 511–610, Wiley, NY, ***1970***.
[476] See Tsuji, T.; Shibata, T.; Hienuki, Y.; Nishida, S. *J. Am. Chem. Soc.* ***1978***, *100*, 1806; Drumright, R.E.; Mas, R.H.; Merola, J.S.; Tanko, J.M. *J. Org. Chem.* ***1990***, *55*, 4098.
[477] Staley, S.W. *J. Am. Chem. Soc.* ***1967***, *89*, 1532; Pews, R.G.; Ojha, N.D. *J. Am. Chem. Soc.* ***1969***, *91*, 5769. See, however, Noe, E.A.; Young, R.M. *J. Am. Chem. Soc.* ***1982***, *104*, 6218.
[478] Reissig, H.-U.; Zimmer, R. *Angew. Chem. Int. Ed.* ***2015***, *54*, 5009.

Many highly strained compounds containing small rings in fused systems have been prepared,[479] showing that organic molecules can exhibit much more strain than simple cyclopropanes or cyclobutanes.[480] Table 4.5 shows a few of these compounds.[481]

TABLE 4.5 Some strained small-ring compounds

Structural formula of compound prepared	Systematic name of ring system, if any	Common name	Reference
	Bicyclo[1.1.0]butane	Bicyclobutane	482
	$\Delta^{1,4}$-Bicyclo[2.2.0]hexene		483
	Tricyclo[1.1.0.0^{2,4}]butane	Tetrahedrane	484
	Pentacyclo [5.1.0.0^{2,4}.0^{3,5}.0^{6,8}]octane	Octabisvalene	485
	Tricyclo[1.1.1.0^{1,3}] pentane	a [1.1.1]propellane	486
	Tetradecaspiro[2.0.2.0. 0.0.0.0.2.0.2.0.0. 0.2.0.2.0.0.1.0.0.2.0.2. 0.0.0]untriacontane	[15]-triangulane	487
	Tetracyclo[2.2.0.0^{2,6}.0^{3,5}] hexane	Prismane	488

[479] See the reviews in *Chem. Rev.* ***1989***, *89*, 975, and the following: Jefford, C.W. *J. Chem. Educ.* ***1976***, *53*, 477; Seebach, D. *Angew. Chem. Int. Ed.* ***1965***, *4*, 121; Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, ***1978***, pp. 210–220; Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds*, Wiley-Interscience, NY, ***1994***, pp. 771–811.

[480] For a useful classification of strained polycyclic systems, see Gund, P.; Gund, T.M. *J. Am. Chem. Soc.* ***1981***, *103*, 4458.

[481] For a computer program that generates IUPAC names for complex bridged systems, see Rücker, G.; Rücker, C. *Chimia* ***1990***, *44*, 116.

[482] Hoz, S. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, ***1987***, pp. 1121–1192; Wiberg, K.B. *Adv. Alicyclic Chem.* ***1968***, *2*, 185. For a review of [*n*.1.1] systems, see Meinwald, J.; Meinwald, Y.C. *Adv. Alicyclic Chem.* ***1966***, *1*, 1.

[483] Casanova, J.; Bragin, J.; Cottrell, F.D. *J. Am. Chem. Soc.* ***1978***, *100*, 2264.

[484] Maier, G.; Fleischer, F. *Tetrahedron Lett.* ***1991***, *32*, 57. Also see Maier, G.; Rang, H.; Born, D. in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, ***1990***, pp. 219–259; Maier, G.; Born, D. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1050.

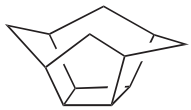
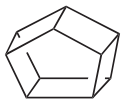
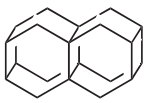
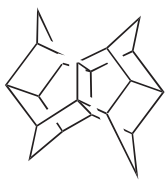
[485] Rücker, C.; Trupp, B. *J. Am. Chem. Soc.* ***1988***, *110*, 4828.

[486] Newton, M.D.; Schulman, J.M. *J. Am. Chem. Soc.* ***1972***, *94*, 767.

[487] Von Seebach, M.; Kozhushkov, S.I.; Boese, R.; Benet-Buchholz, J.; Yufit, D.S.; Howard, J.A.K.; de Meijere, A. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2495.

[488] Katz, T.J.; Acton, N. *J. Am. Chem. Soc.* ***1973***, *95*, 2738. See also, Wilzbach, K.E.; Kaplan, L. *J. Am. Chem. Soc.* ***1965***, *87*, 4004.

TABLE 4.5 (*Continued*)

Structural formula of compound prepared	Systematic name of ring system, if any	Common name	Reference
	Pentacyclo [4.2.0.0^{2,5}.0^{3,8}.0^{4,7}] octane	Cubane	489
	Pentacyclo [5.4.1.0^{3,1}.0^{5,9}.0^{8,11}] dodecane	4[Peristylane]	490
	Hexacyclo [5.3.0.0^{2,6}.0^{3,10}.0^{4,9}.0^{5,8}] decane	Pentaprismane	491
	Tricyclo[3.1.1.1^{2,4}]octane	Diasterane	492
	Hexacyclo [4.4.0.0^{2,4}.0^{3,9}.0^{5,8}.0^{7,10}] decane		493
	Nonacyclo [10.8.0^{2,11}.0^{4,9}.0^{4,19}.0^{6,17}.0^{7,16}.0^{9,14}.0^{14,19}]eicosane	A double tetraesterane	494
	Undecacyclo [9.9.0.0^{1,5}.0^{2,12}.0^{2,18}.0^{3,7}.-0^{6,10}.0^{8,12}.0^{11,15}.0^{13,17}.0^{16,20}] eicosane	Pagodane	495

Perhaps the most interesting are cubane, prismane,[496] and the substituted tetrahedrane, since preparation of these ring systems had been the object of much endeavor.

[489] Hedberg, L.; Hedberg, K.; Eaton, P.E.; Nodari, N.; Robiette, A.G. *J. Am. Chem. Soc.* ***1991***, *113*, 1514. For a review of cubanes, see Griffin, G.W.; Marchand, A.P. *Chem. Rev.* ***1989***, *89*, 997; Biegasiewicz, K.F.; Griffiths, J.R.; Savage, G.P.; Tsanaktsidis, J.; Priefer, R. *Chem. Rev.* ***2015***, *115*, 6719.

[490] Paquette, L.A.; Fischer, J.W.; Browne, A.R.; Doecke, C.W. *J. Am. Chem. Soc.* ***1985***, *105*, 686.

[491] Eaton, P.E.; Or, Y.S.; Branca, S.J.; Shankar, B.K.R. *Tetrahedron* ***1986***, *42*, 1621. See also, Dauben, W.G.; Cunningham Jr., A.F. *J. Org. Chem.* ***1983***, *48*, 2842.

[492] Otterbach, A.; Musso, H. *Angew. Chem. Int. Ed.* ***1987***, *26*, 554.

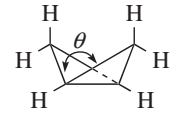
[493] Allred, E.L.; Beck, B.R. *J. Am. Chem. Soc.* ***1973***, *95*, 2393.

[494] Hoffmann, V.T.; Musso, H. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1006.

[495] Rihs, G. *Tetrahedron Lett.* ***1983***, *24*, 5857. See Mathew, T.; Keller, M.; Hunkler, D.; Prinzbach, H. *Tetrahedron Lett.* ***1996***, *37*, 4491 for the synthesis of azapagodanes (also called azadodecahedranes).

[496] Gribanova, T.N.; Minyaev, R.M.; Minkin, V.I. *Russ. J. Org. Chem.* ***2007***, *43*, 1144.

Prismane is tetracyclo[2.2.0.0^{2},^{6}.0^{3},^{5}]hexane and many derivatives are known,[497] including bis(homohexaprismane) derivatives.[498] The bicyclobutane molecule is bent, with the angle θ between the planes equal to $126 \pm 3°$.[499] The rehybridization effect, described above for cyclopropane, is even more extreme in this molecule. Calculations have shown that the central bond is essentially formed by overlap of two *p* orbitals with little or no *s* character.[487]

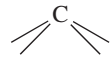


Angle between planes

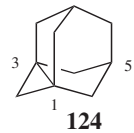
Propellanes are compounds in which two carbons, directly connected, are also connected by three other bridges.[500] [1.1.1]Propellane is in Table 4.5 and it is the smallest possible propellane,[501] and is in fact more stable than the larger [2.1.1]propellane and [2.2.1]propellane, which have been isolated only in solid matrixes at low temperature.[502] The bicyclo[1.1.1]pentanes are related to the propellanes except that the central connecting bond is missing. Several derivatives are known.[503] Spiro compounds are organic compounds in which two or three rings are linked together by one common atom, leading to a twisted structure of two or more rings (a ring system). The ring strain energy of some spiro compounds has been examined.[504] Even more complex systems are known.[505]

In certain small-ring systems, including small propellanes, the geometry of one or more carbon atoms is so constrained that all four of their valences are directed to the same side of a plane (inverted tetrahedron), as in **123**.[506] An example is 1,3-dehydroadamantane, **124** (which is also a propellane).[507] X-ray crystallography of the 5-cyano derivative of **124** shows that the four carbon valences at C-1 and C-3 are all directed "into" the molecule and none point outside.[508] Compound **124** is quite reactive; it is unstable in air, readily adds hydrogen, water, bromine, or acetic acid to the C-1–C-3 bond, and is easily polymerized. When two such atoms are connected by a bond (as in **124**), the bond is very long (the C-1–C-3 bond length in the 5-cyano derivative of **124** is 1.64 Å), as the atoms try to compensate in this way for their enforced angles. The high reactivity of the C-1–C-3 bond of **124** is not only caused by strain, but also by the fact that reagents find it easy to approach these atoms since there are no bonds (e.g., C—H bonds on C-1 or C-3) to get in the way.

[497] Gleiter, R.; Treptow, B.; Irngartinger, H.; Oeser, T. *J. Org. Chem.* ***1994***, *59*, 2787.
[498] Golobish, T.D.; Dailey, W.P. *Tetrahedron Lett.* ***1996***, *37*, 3239.
[499] Haller, I.; Srinivasan, R. *J. Chem. Phys.* ***1964***, *41*, 2745.
[500] Dilmaç, A.M.; Spuling, E.; de Meijere, A.; Bräse, S. *Angew. Chem. Int. Ed.* ***2017***, *56*, 5684.
[501] Lynch, K.M.; Dailey, W.P. *J. Org. Chem.* ***1995***, *60*, 4666. See Wiberg, K.B. *Chem. Rev.* ***1989***, *89*, 975; Ginsburg, D. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, ***1987***, pp. 1193–1221; Ginsburg, D. *Top. Curr. Chem.* ***1987***, *137*, 1. For a discussion of charge density and bonding, see Coppens, P. *Angew. Chem. Int. Ed.* ***2005***, *44*, 6810.
[502] Wiberg, K.B.; Walker, F.H.; Pratt, W.E.; Michl, J. *J. Am. Chem. Soc.* ***1983***, *105*, 3638.
[503] Della, E.W.; Taylor, D.K. *J. Org. Chem.* ***1994***, *59*, 2986.
[504] Stedjan, M.K.; Augspurger, J.D. *J. Phys. Org. Chem.* ***2015***, *28*, 298.
[505] See Kuck, D.; Krause, R.A.; Gestmann, D.; Posteher, F.; Schuster, A. *Tetrahedron* ***1998***, *54*, 5247.
[506] For a review, see Wiberg, K.B. *Acc. Chem. Res.* ***1984***, *17*, 379.
[507] Scott, W.B.; Pincock, R.E. *J. Am. Chem. Soc.* ***1973***, *95*, 2040.
[508] Gibbons, C.S.; Trotter, J. *Can. J. Chem.* ***1973***, *51*, 87.



123

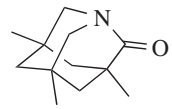


124

4.Q.ii. Strain in Other Rings[509]

In rings larger than four-membered, there is no strain due to small bond angles, but there are three other kinds of strain. In the chair form of cyclohexane, which does not exhibit any of the three kinds of strain, all six C—C bonds have the two attached carbons in the *gauche* conformation. However, in five-membered rings and in rings containing from 7 to 13 carbons any conformation in which all the ring bonds are *gauche* contains transannular interactions, that is, interactions between the substituents on C-1 and C-3 or C-1 and C-4, and so on. These interactions occur because the internal space is not large enough for all the quasi-axial hydrogen atoms to fit without coming into conflict. The molecule can adopt other conformations in which this *transannular strain* is reduced, but then some of the carbon–carbon bonds must adopt eclipsed or partially eclipsed conformations. The strain resulting from eclipsed conformations is called *Pitzer strain*. For saturated rings from 3- to 13-membered (except for the chair form of cyclohexane) there is no escape from at least one of these two types of strain. In practice, each ring adopts conformations that minimize both sorts of strain as much as possible. For cyclopentane, as seen in Sec. 4.O.iv, this means that the molecule is not planar. In rings larger than 9-membered, Pitzer strain seems to disappear, but transannular strain is still present.[510] For 9- and 10-membered rings, some of the transannular and Pitzer strain may be relieved by the adoption of a third type of strain, *large-angle strain*. Thus, C—C—C angles of 115–120° have been found in X-ray diffraction of cyclononylamine hydrobromide and 1,6-diaminocyclodecane dihydrochloride.[511]

Strain can exert other influences on molecules. 1-Aza-2-adamantanone (**125**) is an extreme case of a twisted amide.[512] The overlap of the lone pair electrons on nitrogen with the π system of the carbonyl is prevented.[512] In chemical reactions, **125** reacts more or less like a ketone, giving a *Wittig reaction* (**16-44**) and it can form a ketal (**16-6**). A twisted biadamantylidene compound has been reported.[513]



125

The amount of strain in cycloalkanes is shown in Table 4.6,[514] which lists heats of combustion per CH_2 group. As can be seen, cycloalkanes larger than 13-membered are as strain-free as cyclohexane.

[509] See Raphael, R.A. *Proc. Chem. Soc.* ***1962***, 97; Sicher, J. *Prog. Stereochem.* ***1962***, *3*, 202.
[510] Huber-Buser, E.; Dunitz, J.D. *Helv. Chim. Acta* ***1960***, *43*, 760.
[511] Dunitz, J.D.; Venkatesan, K. *Helv. Chim. Acta* ***1961***, *44*, 2033.
[512] Kirby, A.J.; Komarov, I.V.; Wothers, P.D.; Feeder, N. *Angew. Chem. Int. Ed.* ***1998***, *37*, 785. Also see Madder, R.D.; Kim, C.-Y.; Chandra, P.P.; Doyon, J.B.; Barid Jr., T.A.; Fierke, C.A.; Christianson, D.W.; Voet, J.G.; Jain, A. *J. Org. Chem.* ***2002***, *67*, 582.
[513] Okazaki, T.; Ogawa, K.; Kitagawa, T.; Takeuchi, K. *J. Org. Chem.* ***2002***, *67*, 5981.
[514] Gol'dfarb, Ya.L.; Belen'kii, L.I. *Russ. Chem. Rev.* ***1960***, *29*, 214, p. 218.

TABLE 4.6 Heats of combustion in the gas phase for cycloalkanes, per CH_2 group[514]

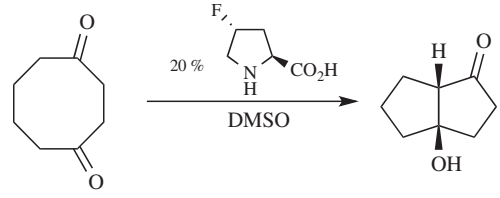
Size of ring	$-\Delta H_c$(g), kcal mol^{-1}	$-\Delta H_c$(g), kJ mol^{-1}
3	166.3	695.8
4	163.9	685.8
5	158.7	664.0
6	157,4	658.6
7	158.3	662.3
8	158.6	663.6
9	158.8	664.4
10	158.6	663.6
11	158.4	662.7
12	157.8	660.2
13	157.7	659.8
14	157.4	658.6
15	157.5	659.0
16	157.5	659.0

Reprinted with permission. Gol'dfarb, Ya.L.; Belen'kii, L.I. *Russ. Chem. Rev.* ***1960***, *29*, 214, p. 218.

Transannular interactions can exist across rings from 8- to 11-membered and even larger.[515] Such interactions can be detected by dipole and spectral measurements. For example, that the carbonyl group in **126a** is affected by the nitrogen (**126b** is probably another canonical form) has been demonstrated by photoelectron spectroscopy, which shows that the ionization potentials of the nitrogen *n* and C=O π orbitals in **126** differ from those of the two comparison molecules **127** and **128**.[516] It is significant that when **126** donates electrons to a proton, it goes to the oxygen rather than to the nitrogen.

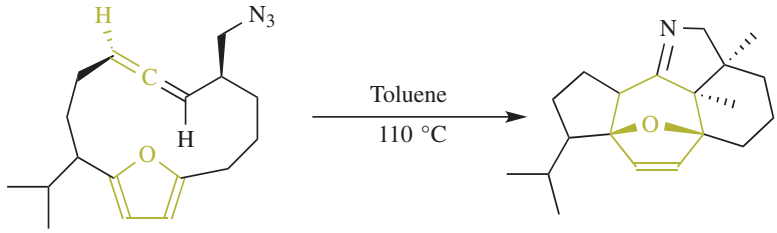
126a **126b** **127** **128**

Many examples of transannular reactions are known, including an intramolecular aldol condensation (**16-34**)[517]



and an intramolecular Diels-Alder reaction (**15-56**).[518]

[515] For a review, see Cope, A.C.; Martin, M.M.; McKervey, M.A. *Q. Rev. Chem. Soc.* ***1966***, *20*, 119.
[516] Spanka, G.; Rademacher, P. *J. Org. Chem.* ***1986***, *51*, 592. See also, Spanka, G.; Rademacher, P.; Duddeck, H. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 2119.
[517] Chandler, C.L.; List, B. *J. Am. Chem. Soc.* ***2008***, *130*, 6737.
[518] Zhurakovsky, O.; Ellis, S.R.; Thompson, A.L.; Robertson, *J. Org. Lett.* ***2017***, *19*, 2174.



In summary, saturated rings may be divided into four groups, of which the first and third are more strained than the other two.[519]

1. *Small rings* (3- and 4-membered): small-angle strain predominates.
2. *Common rings* (5-, 6-, and 7-membered): largely unstrained; the strain that is present is mostly Pitzer strain.
3. *Medium rings* (8- to 11-membered): considerable strain; Pitzer, transannular, and large-angle strain.
4. *Large rings* (12-membered and larger): little or no strain.[520]

4.Q.iii. Unsaturated Rings[521]

Double bonds can exist in rings of any size. As expected, the most highly strained are the three-membered rings such as cyclopropene. Small-angle strain, which is so important in cyclopropane, is even greater in cyclopropene[522] because the ideal angle is more distorted. In cyclopropane, the bond angle is forced to be 60°, ~50° smaller than the tetrahedral angle; but in cyclopropene, the angle, also ~60°, is now ~60° smaller than the ideal angle of 120° for an alkene. Thus, the angle of cyclopropene is ~10° more strained than in cyclopropane. However, this additional strain is offset by a decrease in strain arising from another factor. Cyclopropene, lacking two hydrogens, has none of the eclipsing strain present in cyclopropane. Cyclopropene has been prepared[523] and is stable at liquid-nitrogen temperatures, although on warming even to −80 °C it rapidly polymerizes. Many other cyclopropenes are stable at room temperature and above.[487] The highly strained benzocyclopropene,[524] in which the cyclopropene ring is fused to a benzene ring, has been prepared[525] and is stable for weeks at room temperature, although it decomposes on distillation at atmospheric pressure.

[519] See Granik, V.G. *Russ. Chem. Rev.* ***1982***, *51*, 119.

[520] An example is the calculated strain of 1.4–3.2 kcal mol^{-1} (5.9–13.4 kJ mol^{-1}) in cyclotetradecane. See Chickos, J.S.; Hesse, D.G.; Panshin, S.Y.; Rogers, D.W.; Saunders, M.; Uffer, P.M.; Liebman, J.F. *J. Org. Chem.* ***1992***, *57*, 1897.

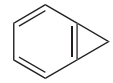
[521] For a review of strained double bonds, see Zefirov, N.S.; Sokolov, V.I. *Russ. Chem. Rev.* ***1967***, *36*, 87. For a review of double and triple bonds in rings, see Johnson, R.P. *Mol. Struct. Energ.* ***1986***, *3*, 85.

[522] See Baird, M.S. *Top. Curr. Chem.* ***1988***, *144*, 137; Halton, B.; Banwell, M.G. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, ***1987***, pp. 1223–1339; Closs, G.L. *Adv. Alicyclic Chem.* ***1966***, *1*, 53. For a discussion of the bonding and hybridization, see Allen, F.H. *Tetrahedron* ***1982***, *38*, 645.

[523] Stigliani, W.M.; Laurie, V.W.; Li, J.C. *J. Chem. Phys.* ***1975***, *62*, 1890.

[524] See Halton, B. *Chem. Rev.* ***1989***, *89*, 1161; ***1973***, *73*, 113; Billups, W.E.; Rodin, W.A.; Haley, M.M. *Tetrahedron* ***1988***, *44*, 1305; Billups, W.E. *Acc. Chem. Res.* ***1978***, *11*, 245.

[525] Vogel, E.; Grimme, W.; Korte, S. *Tetrahedron Lett.* ***1965***, 3625. Also see Müller, P.; Bernardinelli, G.; Thi, H.C.G. *Chimia* ***1988***, *42*, 261; Neidlein, R.; Christen, D.; Poignée, V.; Boese, R.; Bläser, D.; Gieren, A.; Ruiz-Pérez, C.; Hübner, T. *Angew. Chem. Int. Ed.* ***1988***, *27*, 294.



Benzocyclopropene

As previously mentioned, double bonds in relatively small rings must be *cis*. A stable *trans* double bond[526] first appears in an eight-membered ring (*trans*-cyclooctene, Sec. 4.C, category 6), although the transient existence of *trans*-cyclohexene and cycloheptene has been demonstrated.[527] Above ~11 members, the *trans* isomer is more stable than the *cis*.[260] It has proved possible to prepare compounds in which a *trans* double bond is shared by two cycloalkene rings (e.g., **129**). Such compounds have been called *[m.n]betweenanenes*, and several have been prepared with *m* and *n* values from 8 to 26.[528] The double bonds of the smaller betweenanenes, as might be expected from the fact that they are deeply buried within the bridges, are much less reactive than those of the corresponding *cis–cis* isomers.

The smallest unstrained cyclic triple bond is found in cyclononyne.[529] Cyclooctyne has been isolated,[530] but its heat of hydrogenation shows that it is considerably strained. There have been a few compounds isolated with triple bonds in seven-membered rings. 3,3,7,7-Tetramethylcycloheptyne (**130**) is known, but it dimerizes within 1 hour at room temperature,[531] but the thia derivative **131**, in which the C—S bonds are longer than the corresponding C—C bonds in **130**, is indefinitely stable even at 140 °C.[532] Cycloheptyne itself has not been isolated, although its transient existence has been shown.[533] Cyclohexyne[534] and its 3,3,6,6-tetramethyl derivative[535] have been trapped at 77 K, and in an argon matrix at 12 K, respectively, and IR spectra have been obtained. Transient six- and even five-membered rings containing triple bonds have also been demonstrated.[536] A derivative of cyclopentyne has been trapped in a matrix.[537] Although cycloheptyne and cyclohexyne have not been isolated at ambient temperatures, Pt(0) complexes of these compounds have been prepared and are stable.[538] The smallest cyclic allene[539] so far isolated is 1-*tert*-butyl-1,2-cyclooctadiene

[526] For reviews of *trans*-cycloalkenes, see Nakazaki, M.; Yamamoto, K.; Naemura, K. *Top. Curr. Chem.* ***1984***, *125*, 1; Marshall, J.A. *Acc. Chem. Res.* ***1980***, *13*, 213.

[527] Wallraff, G.M.; Michl, J. *J. Org. Chem.* ***1986***, *51*, 1794; Squillacote, M.; Bergman, A.; De Felippis, J. *Tetrahedron Lett.* ***1989***, *30*, 6805.

[528] Marshall, J.A.; Flynn, K.E. *J. Am. Chem. Soc.* ***1983***, *105*, 3360. For reviews, see Nakazaki, M.; Yamamoto, K.; Naemura, K. *Top. Curr. Chem.* ***1984***, *125*, 1; Marshall, J.A. *Acc. Chem. Res.* ***1980***, *13*, 213. For a review of these and similar compounds, see Borden, W.T. *Chem. Rev.* ***1989***, *89*, 1095.

[529] See Meier, H. *Adv. Strain Org. Chem.* ***1991***, *1*, 215; Krebs, A.; Wilke, J. *Top. Curr. Chem.* ***1983***, *109*, 189; Nakagawa, M. in Patai, S. *The Chemistry of the C≡C Triple Bond*, pt. 2, Wiley, NY, ***1978***, pp. 635–712; Krebs, A. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 987–1062. See Meier, H.; Hanold, N.; Molz, T.; Bissinger, H.J.; Kolshorn, H.; Zountsas, J. *Tetrahedron* ***1986***, *42*, 1711.

[530] Blomquist, A.T.; Liu, L.H. *J. Am. Chem. Soc.* ***1953***, *75*, 2153. See also, Bühl, H.; Gugel, H.; Kolshorn, H.; Meier, H. *Synthesis* ***1978***, 536.

[531] Schmidt, H.; Schweig, A.; Krebs, A. *Tetrahedron Lett.* ***1974***, 1471.

[532] Krebs, A.; Kimling, H. *Tetrahedron Lett.* ***1970***, 761.

[533] Bottini, A.T.; Frost II, K.A.; Anderson, B.R.; Dev, V. *Tetrahedron* ***1973***, *29*, 1975.

[534] Wentrup, C.; Blanch, R.; Briehl, H.; Gross, G. *J. Am. Chem. Soc.* ***1988***, *110*, 1874.

[535] See Sander, W.; Chapman, O.L. *Angew. Chem. Int. Ed.* ***1988***, *27*, 398.

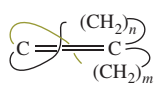
[536] See Gilbert, J.C.; Baze, M.E. *J. Am. Chem. Soc.* ***1983***, *105*, 664.

[537] Chapman, O.L.; Gano, J.; West, P.R.; Regitz, M.; Maas, G. *J. Am. Chem. Soc.* ***1981***, *103*, 7033.

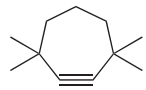
[538] Bennett, M.A.; Robertson, G.B.; Whimp, P.O.; Yoshida, T. *J. Am. Chem. Soc.* ***1971***, *93*, 3797.

[539] See Johnson, R.P. *Chem. Rev.* ***1989***, *89*, 1111; Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 38–56.

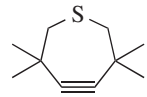
132.[540] The parent cycloocta-1,2-diene has not been isolated. It has been shown to exist as a transient species, but rapidly dimerizes.[541] Incorporation of the *tert*-butyl group apparently prevents this. The transient existence of cyclohepta-1,2-diene has also been shown,[542] and both cycloocta-1,2-diene and cyclohepta-1,2-diene have been isolated in Pt complexes.[543] Cyclohexa-1,2-diene has been trapped at low temperatures, and its structure proved by spectral studies.[544] Cyclic allenes in general are less strained than their acetylenic isomers.[545] The cyclic cumulene cyclonona-1,2,3-triene has also been synthesized and is reasonably stable in solution at room temperature in the absence of air.[546]



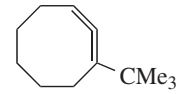
129



130



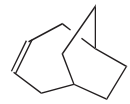
131



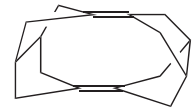
132

There are many examples of polycyclic molecules and bridged molecules that have one or more double bonds. There is flattening of the ring containing the C=C unit, and this can have a significant effect on the molecule. Norbornene (bicyclo[2.2.1]hept-2-ene; **133**) is a simple example and it has been calculated that it contains a distorted π face.[547] The double bond can appear away from the bridgehead carbon atoms, as in bicyclo[4.2.2]dec-3-ene (**134**), which flattens that part of the molecule. The C=C units in pentacyclo[8.2.1.$1^{2,5}$.$1^{4,7}$.$1^{8,11}$]hexadeca-1,7-diene (**135**) are held in a position where there is significant π–π interactions across the molecule.[548]

133



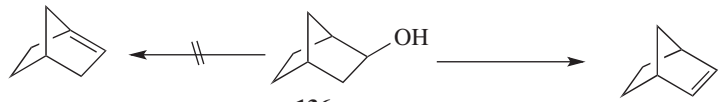
134



135

Double bonds at the bridgehead of bridged bicyclic compounds are impossible in small systems. This is the basis of *Bredt's rule*,[549] which states that elimination to give a double bond in a bridged bicyclic system (e.g., **136**) always leads away from the bridgehead. This rule no longer applies when the rings are large enough.

[540] Price, J.D.; Johnson, R.P. *Tetrahedron Lett.* ***1986***, *27*, 4679.
[541] See Marquis, E.T.; Gardner, P.D. *Tetrahedron Lett.* ***1966***, 2793.
[542] Wittig, G.; Dorsch, H.; Meske-Schüller, J. *Liebigs Ann. Chem.* ***1968***, *711*, 55.
[543] Visser, J.P.; Ramakers, J.E. *J. Chem. Soc., Chem. Commun.* ***1972***, 178.
[544] Wentrup, C.; Gross, G.; Maquestiau, A.; Flammang, R. *Angew. Chem. Int. Ed.* ***1983***, *22*, 542. 1,2,3-Cyclohexatriene has also been trapped: Shakespeare, W.C.; Johnson, R.P. *J. Am. Chem. Soc.* ***1990***, *112*, 8578.
[545] Moore, W.R.; Ward, H.R. *J. Am. Chem. Soc.* ***1963***, *85*, 86.
[546] Angus Jr., R.O.; Johnson, R.P. *J. Org. Chem.* ***1984***, *49*, 2880.
[547] Ohwada, T. *Tetrahedron* ***1993***, *49*, 7649.
[548] Lange, H.; Schäfer, W.; Gleiter, R.; Camps, P.; Vázquez, S. *J. Org. Chem.* ***1998***, *63*, 3478.
[549] See Shea, K.J. *Tetrahedron* ***1980***, *36*, 1683; Billups, W.E.; Haley, M.M.; Lee, G. *Chem. Rev.* ***1989***, *89*, 1147; Warner, P.M. *Chem. Rev.* ***1989***, *89*, 1067. Also see, Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, England, ***2017***, pp. 528–530.



136

In determining whether a bicyclic system is large enough to accommodate a bridgehead double bond, the most reliable criterion is the size of the ring in which the double bond is located.[550] Bicyclo[3.3.1]non-1-ene[551] (**137**) and bicyclo[4.2.1]non-1(8)ene[552] (**138**) are stable compounds. Both can be looked upon as derivatives of *trans*-cyclooctene, which is of course a known compound. Compound **137** has been shown to have a strain energy of the same order of magnitude as that of *trans*-cyclooctene.[553] On the other hand, in bicyclo[3.2.2]non-1-ene (**139**), the largest ring that contains the double bond is a *trans*-cycloheptene, which is as yet unknown. Compound **140** has been prepared, but dimerized before it could be isolated.[554] Even smaller systems ([3.2.1] and [2.2.2]), but with imine double bonds (**140–142**), have been obtained in matrixes at low temperatures.[555] These compounds are destroyed on warming. Compounds **140** and **141** are the first reported example of *E–Z* isomerism at a strained bridgehead double bond.[556]

137 **138** **139** **140** **141** **142**

4.Q.iv. Strain Due to Unavoidable Crowding[557]

In some molecules, large groups are so close to each other that they cannot fit into the available space in such a way that normal bond angles are maintained. It has proved possible to prepare compounds with a high degree of this type of strain. For example, success has been achieved in synthesizing benzene rings containing *ortho tert*-butyl groups. Two examples that have been prepared, of several, are 1,2,3-tri-*tert*-butyl compound **143**[558] and the 1,2,3,4-tetra-*tert*-butyl compound **144**.[559] That these molecules are strained is demonstrated by UV and IR spectra, which show that the ring is not planar in 1,2,4-tri-*tert*-butylbenzene, and by a comparison of the heats of reaction of this compound and its 1,3,5 isomer, which

[550] See Maier, W.F.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1981***, *103*, 1891.

[551] Becker, K.B. *Helv. Chim. Acta* ***1977***, *60*, 81. See Nakazaki, M.; Naemura, K.; Nakahara, S. *J. Org. Chem.* ***1979***, *44*, 2438.

[552] Carruthers, W.; Qureshi, M.I. *Chem. Commun.* ***1969***, 832; Becker, K.B. *Tetrahedron Lett.* ***1975***, 2207.

[553] Lesko, P.M.; Turner, R.B. *J. Am. Chem. Soc.* ***1968***, *90*, 6888; Burkert, U. *Chem. Ber.* ***1977***, *110*, 773.

[554] Wiseman, J.R.; Chong, J.A. *J. Am. Chem. Soc.* ***1969***, *91*, 7775.

[555] Radziszewski, J.G.; Downing, J.W.; Wentrup, C.; Kaszynski, P.; Jawdosiuk, M.; Kovacic, P.; Michl, J. *J. Am. Chem. Soc.* ***1985***, *107*, 2799.

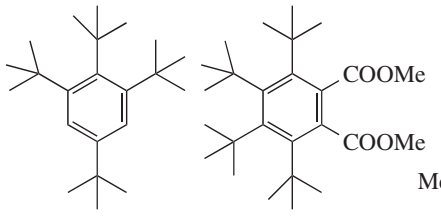
[556] Radziszewski, J.G.; Downing, J.W.; Wentrup, C.; Kaszynski, P.; Jawdosiuk, M.; Kovacic, P.; Michl, J. *J. Am. Chem. Soc.* ***1985***, *107*, 2799. See Junk, C.P.; He, Y.; Zhang, Y.; Smith, J.R.; Gleiter, R.; Kass, S.R.; Jasinski, J.P.; Lemal, D.M. *J. Org. Chem.* ***2015***, *80*, 1523.

[557] See Tidwell, T.T. *Tetrahedron* ***1978***, *34*, 1855; Mosher, H.S.; Tidwell, T.T. *J. Chem. Educ.* ***1990***, *67*, 9. For a review of van der Waals radii, see Zefirov, Yu.V.; Zorkii, P.M. *Russ. Chem. Rev.* ***1989***, *58*, 421.

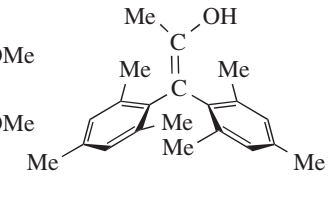
[558] Arnett, E.M.; Bollinger, J.M. *Tetrahedron Lett.* ***1964***, 3803.

[559] See Krebs, A.; Franken, E.; Müller, S. *Tetrahedron Lett.* ***1981***, *22*, 1675.

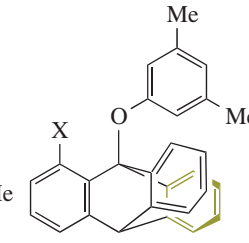
show that the 1,2,4 compound possesses ~22 kcal mol^{-1} (92 kJ mol^{-1}) more strain energy than its isomer[560] (see also **18-27**). Although $SiMe_3$ groups are larger than CMe_3 groups, it has proven possible to prepare $C_6(SiMe_3)_6$. This compound has a chair-shaped ring in the solid state, and a mixture of chair and boat forms in solution.[561] Even smaller groups can sterically interfere in ortho positions. In hexaisopropylbenzene, the six isopropyl groups are so crowded that they cannot rotate but are lined up around the benzene ring, all pointed in the same direction.[562] This compound is an example of a *geared molecule*.[563] The isopropyl groups fit into each other in the same manner as interlocked gears. Another example is **145**, which is a stable enol.[564] In this case each ring can rotate about its C—aryl bond only by forcing the other to rotate as well. In the case of triptycene derivatives such as **146**, a complete 360° rotation of the aryl group around the O—aryl bond requires the aryl group to pass over three rotational barriers; one of which is the C—X bond and other two the "top" C—H bonds of the other two rings. As expected, the C—X barrier is the highest, ranging from 10.3 kcal mol^{-1} (43.1 kJ mol^{-1}) for X = F to 17.6 kcal mol^{-1} (73.6 kJ mol^{-1}) for X = *tert*-butyl.[565]



143 **144**

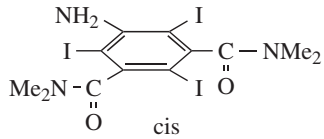


145

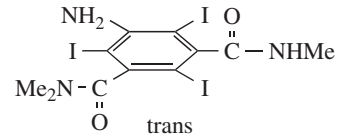


146

In another instance, it has proved possible to prepare *cis* and *trans* isomers of 5-amino-2,4,6-triiodo-*N,N,N′,N′*-tetramethylisophthalamide because there is no room for the $CONMe_2$ groups to rotate, caught as they are between two bulky iodine atoms.[566] The *trans* isomer is chiral and has been resolved, while the *cis* isomer is a *meso* form.



cis



trans

[560] Arnett, E.M.; Sanda, J.C.; Bollinger, J.M.; Barber, M. *J. Am. Chem. Soc.* ***1967***, *89*, 5389. See also, Barclay, L.R.C.; Brownstein, S.; Gabe, E.J.; Lee, F.L. *Can. J. Chem.* ***1984***, *62*, 1358.

[561] Sakurai, H.; Ebata, K.; Kabuto, C.; Sekiguchi, A. *J. Am. Chem. Soc.* ***1990***, *112*, 1799.

[562] Siegel, J.; Gutiérrez, A.; Schweizer, W.B.; Ermer, O.; Mislow, K. *J. Am. Chem. Soc.* ***1986***, *108*, 1569. Also see Kahr, B.; Biali, S.E.; Schaefer, W.; Buda, A.B.; Mislow, K. *J. Org. Chem.* ***1987***, *52*, 3713.

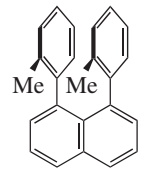
[563] See Iwamura, H.; Mislow, K. *Acc. Chem. Res.* ***1988***, *21*, 175; Mislow, K. *Chemtracts: Org. Chem.* ***1989***, *2*, 151; Berg, U.; Liljefors, T.; Roussel, C.; Sandström, J. *Acc. Chem. Res.* ***1985***, *18*, 80.

[564] Nugiel, D.A.; Biali, S.E.; Rappoport, Z. *J. Am. Chem. Soc.* ***1984***, *106*, 3357.

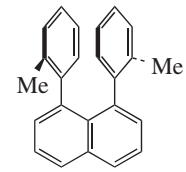
[565] Yamamoto, G.; Öki, M. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 3597. See Yamamoto, G. *Pure Appl. Chem.* ***1990***, *62*, 569; Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***, pp. 269–284.

[566] Ackerman, J.H.; Laidlaw, G.M.; Snyder, G.A. *Tetrahedron Lett.* ***1969***, 3879; Ackerman, J.H.; Laidlaw, G.M. *Tetrahedron Lett.* ***1969***, 4487. See also, Cuyegkeng, M.A.; Mannschreck, A. *Chem. Ber.* ***1987***, *120*, 803.

Another example of *cis–trans* isomerism resulting from restricted rotation about single bonds[567] is found in 1,8-di-*o*-tolylnaphthalene[568] (see also, Sec. 4.K.i).



cis



trans

There are many other cases of intramolecular crowding that result in the distortion of bond angles. Hexahelicene (Sec. 4.C, category 6) and bent benzene rings (Sec. 2.G) have been mentioned previously. The compounds tri-*tert*-butylamine and tetra-*tert*-butylmethane are as yet unknown. In the latter, there is no way for the strain to be relieved and it is questionable whether this compound can ever be made. In tri-*tert*-butylamine the crowding can be eased somewhat if the three bulky groups assume a planar instead of the normal pyramidal configuration. In tri-*tert*-butylcarbinol, co-planarity of the three *tert*-butyl groups is prevented by the presence of the OH group, and yet this compound has been prepared.[569] Tri-*tert*-butylamine should have less steric strain than tri-*tert*-butylcarbinol and it should be possible to prepare it.[570] The tetra-*tert*-butylphosphonium cation $(t\text{-Bu})_4P^+$ has been prepared.[571] Although steric effects are nonadditive in crowded molecules, a quantitative measure has been proposed by DeTar, based on molecular mechanics calculations. This is called *formal steric enthalpy* (FSE), and values have been calculated for alkanes, alkenes, alcohols, ethers, and methyl esters.[572] For example, some FSE values for alkanes are butane 0.00; 2,2,3,3-tetramethylbutane 7.27; 2,2,4,4,5-pentamethylhexane 11.30; and tri-*tert*-butylmethane 38.53.

The two carbon atoms of a C=C double bond and the four groups attached to them are normally in a plane, but if the groups are large enough, significant deviation from planarity can result.[573] The compound tetra-*tert*-butylethene (**147**) has not been prepared,[574] but the tetraaldehyde **148**, which should have about the same amount of strain, has been made. X-ray crystallography shows that **148** is twisted out of a planar shape by an angle of 28.6°.[575] Also, the C=C double bond distance is 1.357 Å, which is significantly longer than a normal C=C bond of 1.32 Å (Table 1.5). (*Z*)-1,2-Bis(*tert*-butyldimethylsilyl)-1,2-bis(trimethylsilyl)ethene (**149**) has an even greater twist, but could not be made to undergo

[567] See Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***; Förster, H.; Vögtle, F. *Angew. Chem. Int. Ed.* ***1977***, *16*, 429; Öki, M. *Angew. Chem. Int. Ed.* ***1976***, *15*, 87.

[568] Clough, R.L.; Roberts, J.D. *J. Am. Chem. Soc.* ***1976***, *98*, 1018. For a study of rotational barriers in this system, see Cosmo, R.; Sternhell, S. *Aust. J. Chem.* ***1987***, *40*, 1107.

[569] Bartlett, P.D.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1968***, *90*, 4421.

[570] See Back, T.G.; Barton, D.H.R. *J. Chem. Soc., Perkin Trans 1*, ***1977***, 924; Kopka, I.E.; Fataftah, Z.A.; Rathke, M.W. *J. Org. Chem.* ***1980***, *45*, 4616.

[571] Schmidbaur, H.; Blaschke, G.; Zimmer-Gasser, B.; Schubert, U. *Chem. Ber.* ***1980***, *113*, 1612.

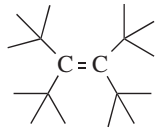
[572] DeTar, D.F.; Binzet, S.; Darba, P. *J. Org. Chem.* ***1985***, *50*, 2826, 5298, 5304.

[573] For reviews, see Luef, W.; Keese, R. *Top. Stereochem.* ***1991***, *20*, 231; Sandström, J. *Top. Stereochem.* ***1983***, *14*, 83 (pp. 160–169).

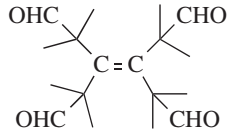
[574] For a list of crowded alkenes that have been made, see Drake, C.A.; Rabjohn, N.; Tempesta, M.S.; Taylor, R.B. *J. Org. Chem.* ***1988***, *53*, 4555. See also, Garratt, P.J.; Payne, D.; Tocher, D.A. *J. Org. Chem.* ***1990***, *55*, 1909.

[575] Krebs, A.; Nickel, W.; Tikwe, L.; Kopf, J. *Tetrahedron Lett.* ***1985***, *26*, 1639.

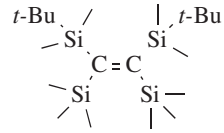
conversion to the (*E*) isomer, probably because the groups are too large to slide past each other.[576]



147

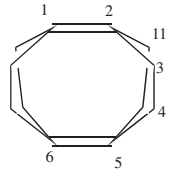


148



149

A different kind of double-bond strain is found in tricyclo[4.2.2.2^{2,5}]dodeca-1,5-diene (**150**),[577] cubene (**151**),[578] and homocub-4(5)-ene (**152**).[579] In these molecules, the four groups on the double bond are all forced to be on one side of the double-bond plane.[580] In **150**, the angle between the line C-1—C-2 (extended) and the plane defined by C-2, C-3, and C-11 is 27°. An additional source of strain in this molecule is the fact that the two double bonds are pushed into close proximity by the four bridges. In an effort to alleviate this sort of strain, the bridge bond distances (C-3—C-4) are 1.595 Å, which is considerably longer than the 1.53 Å expected for a normal sp^3–sp^3 C—C bond (Table 1.5). Compounds **151** and **152** have *not* been isolated, but have been generated as intermediates that were trapped by reaction with other compounds.[578,579]



150

151

152

[576] Sakurai, H.; Ebata, K.; Kabuto, C.; Nakadaira, Y. *Chem. Lett.* ***1987***, 301.

[577] Wiberg, K.B.; Matturo, M.G.; Okarma, P.J.; Jason, M.E. *J. Am. Chem. Soc.* ***1984***, *106*, 2194; Wiberg, K.B.; Adams, R.D.; Okarma, P.J.; Matturo, M.G.; Segmuller, B. *J. Am. Chem. Soc.* ***1984***, *106*, 2200.

[578] Eaton, P.E.; Maggini, M. *J. Am. Chem. Soc.* ***1988***, *110*, 7230.

[579] Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* ***1988***, *110*, 7229.

[580] For a review of such molecules, see Borden, W.T. *Chem. Rev.* ***1989***, *89*, 1095. See also, Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* ***1988***, *110*, 4710.

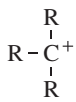
CHAPTER 5

Carbocations, Carbanions, Free Radicals, Carbenes, and Nitrenes

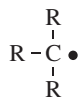
The classical, nonmetal reactive intermediates include carbocations, carbanions, radicals, or carbenes.[1] There are four types of organic species in which a carbon atom has a valence of only 2 or 3.[2] They are usually very short-lived, and most exist only as intermediates that are quickly converted to more stable molecules. However, some are more stable than others and fairly stable examples have been prepared of three of the four types. The four types of species are *carbocations* (**A**, Sec. 5.A), *carbon radicals* (**B**, Sec. 5.B), *carbanions* (**C**, Sec. 5.C), and *carbenes* (**D**, Sec. 5.D). Of the four, only carbanions have a complete octet around the carbon.

There are many other organic ions and radicals with charges and unpaired electrons on atoms other than carbon, but only *nitrenes* (**E**, Sec. 5.E), the nitrogen analogs of carbenes, will be discussed.

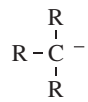
Each of these five types is discussed in a separate section, which in each case includes brief summaries of the ways in which the species form and react. These summaries are short and schematic. The generation and fate of the five types are more fully treated for the appropriate specific reactions in Part 2 of this book.



A

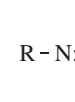


B



C

D



E

[1] Moss, R.A. *J. Org. Chem.* ***2017***, *82*, 2307; Moss, R.A. *Isr. J. Chem.* ***2016***, *56*, 9.

[2] For general references, see Isaacs, N.S. *Reactive Intermediates in Organic Chemistry*, Wiley, NY, ***1974***; McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***. Two serial publications devoted to review articles on this subject are *Reactive Intermediates* (Wiley) and *Reactive Intermediates* (Plenum).

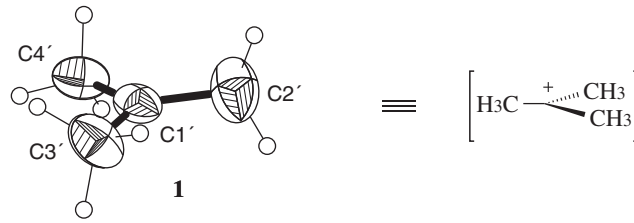
March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

5.A. CARBOCATIONS[3]

5.A.i. Nomenclature

First the nomenclature of carbocations **A** is discussed. For many years these species were called "carbonium ions," although it was suggested[4] as long ago as 1902 that this was inappropriate because "-onium" usually refers to a covalency higher than that of the neutral atom. Nevertheless, the name "carbonium ion" was well established and created few problems[5] until some years ago, when Olah and co-workers.[3,6] found evidence for another type of intermediate in which there is a positive charge at a carbon atom, but in which the formal covalency of the carbon atom is five rather than three. The simplest example is the methanonium ion CH_5^+ (see **12-01**). Olah proposed[6] that the name "carbonium ion" be henceforth reserved for pentacoordinated positive ions, and that **A** be called "carbenium ions." He also proposed the term "carbocation" to encompass both types. IUPAC has accepted these definitions.[7] For the most part, intermediates such as **A** are called *carbenium ions* or *carbocations*, but the latter term will be used more often in this book.

5.A.ii. Stability and Structure of Carbocations



1

[Reprinted with permission from Kato, T.; Reed, C.A. *Angew. Chem. Int. Ed.* ***2004****, 43*, 2908, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. Copyright © ***2004*** by Wiley-VCH Verlag]

Carbocations are intermediates in several kinds of reactions.[8] The more stable ones have been prepared in solution and in some cases even as solid salts, and X-ray crystallographic structures have been obtained in some cases.[9] The X-ray of the *tert*-butyl cation complexed with dichloromethane was reported,[10] for example, and is presented as **1** with the solvent molecules removed for clarity. The infrared spectrum of the *tert*-butyl cation

[3] See Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, 5 Vols, Wiley, NY, ***1968–1976***; Vogel, P. *Carbocation Chemistry*, Elsevier, NY, ***1985***. See Saunders, M.; Jiménez-Vázquez, H.A. *Chem. Rev.* ***1991***, *91*, 375; Arnett, E.M.; Hofelich, T.C.; Schriver, G.W. *React. Intermed. (Wiley)* ***1987***, *3*, 189. For reviews of dicarbocations, see Lammertsma, K.; Schleyer, P.v.R.; Schwarz, H. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1321. See also the series *Advances in Carbocation Chemistry*.

[4] Gomberg, M. *Ber.* ***1902***, *35*, 2397.

[5] For a history of the term "carbonium ion," see Traynham, J.G. *J. Chem. Educ.* ***1986***, *63*, 930.

[6] Olah, G.A. *CHEMTECH* ***1971***, *1*, 566; *J. Am. Chem. Soc.* ***1972***, *94*, 808.

[7] Gold, V.; Loening, K.L.; McNaught, A.D.; Sehmi, P. *Compendium of Chemical Terminology, IUPAC Recommendations*, Blackwell Scientific Publications, Oxford, ***1987***.

[8] Olah, G.A. *J. Org. Chem.* ***2001***, *66*, 5943. See Olah, G.A.; Prakash, G.K.S. (Eds), *Carbocation Chemistry*, Wiley Intersience, Hoboken, NJ, ***2004***.

[9] See Laube, T. *J. Am. Chem. Soc.* ***2004***, *126*, 10904 and references therein. For the X-ray of a vinyl carbocation see Müller, T.; Juhasz, M.; Reed, C.A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 1543.

[10] Kato, T.; Reed, C.A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 2908.

has been recorded in the gas phase.[11] An isolable dioxa-stabilized pentadienylium ion was isolated and its structure was determined by ^{1}H NMR,[12] ^{13}C NMR, mass spectrometry, and infrared.[13] A β-fluoro-substituted 4-methoxyphenethyl cation has been observed directly by laser flash photolysis.[14] In solution the carbocation may be free (this is more likely in polar solvents, in which it is solvated) or it may exist as an ion pair,[15] which means that it is closely associated with a negative ion, called a *counterion* or *gegenion*. Ion pairs are more likely in nonpolar solvents.

A carbocation is an electron-deficient species often formed by loss of a leaving group. The leaving group is referred to as being more or less electrofugal. An electrofuge is defined as a leaving group that does not retain the bonding pair of electrons from its previous bond with another species. Conversely, a nucleofuge is a leaving group that does retain the lone pair from its previous bond with another species. Electrofugality describes the effects of an atom or group in a molecule on the movement of electrons in neighboring bonds. Therefore, an electrofugic carbocation is one formed by dissociation, or loss or a leaving group (an electrofuge). Such a reaction is more closely associated with S_N1 reactions (Sec. 10-A.2). Therefore a cation can be described as an electrofuge while a nucleophile, such as the bromide ion, can be described as a nucleophile. When the leaving group is categorized as a nucleofuge, that retains the electron pair, the reaction is more closely associated with S_N2 reactions (Sec. 10.A.1). In the S_N2 reaction, the terms electrofuge and nucleofuge are likely most associated with the pentacoordinate transition state (Sec. 10.A.1). Carbocations readily react with electron-donating species called nucleophiles. It is common to describe the reactivity of carbocations in terms of their electrofugality,[16] and the reactivity of nucleophiles in terms of their nucleofugality.

Among simple alkyl carbocations[17] the order of stability is tertiary >secondary >primary. There are many known examples of rearrangements of primary or secondary carbocations to tertiary, both in solution and in the gas phase (Sec. 18.A.ii). Since simple alkyl cations are unstable in ordinary strong acid solutions, e.g., H_2SO_4, the study of these species was greatly facilitated by the discovery that many of them could be kept indefinitely as stable solutions in mixtures of fluorosulfuric acid and antimony pentafluoride. Such mixtures, usually dissolved in SO_2 or SO_2ClF, are among the strongest acidic solutions known and are often called *superacids*.[18] The original experiments involved the addition of alkyl fluorides to SbF_5.[19]

$$RF + SbF_5 \longrightarrow R^+SbF_6^-$$

[11] Douberly, G.E.; Ricks, A.M.; Ticknor, B.W.; Schleyer, P.v.R.; Duncan, M.A. *J. Am. Chem. Soc.* ***2007***, *129*, 13782.
[12] See Buntkowsky, G.; Gutmann, T. *Angew. Chem. Int. Ed.* ***2015***, *54*, 9450.
[13] Lüning, U.; Baumstark, R. *Tetrahedron Lett.* ***1993***, *34*, 5059.
[14] McClelland, R.A.; Cozens, F.L.; Steenken, S.; Amyes, T.L.; Richard, J.P. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 1717.
[15] For a treatise, see Szwarc, M. *Ions and Ion Pairs in Organic Reactions*, 2 Vols, Wiley, NY, ***1972–1974***.
[16] Schaller, H.F.; Tishkov, A.A.; Feng, X.; Mayr, H. *J. Am. Chem. Soc.* ***2008***, *130*, 3012; Horn, M.; Mayr, H. *Chemistry* ***2010***, *16*, 7478. Troshin, K.; Mayr, H. *J. Org. Chem.* ***2013***, *78*, 2649.
[17] For a review, see Olah, G.A.; Olah, J.A. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1969***, pp. 715–782. Also see Farcasiu, D.; Norton, S.H. *J. Org. Chem.* ***1997***, *62*, 5374.
[18] See Olah, G.A.; Prakash, G.K.S.; Sommer, J. in *Superacids*, Wiley, NY, ***1985***, pp. 65–175.
[19] Olah, G.A.; Baker, E.B.; Evans, J.C.; Tolgyesi, W.S.; McIntyre, J.S.; Bastien, I.J. *J. Am. Chem. Soc.* ***1964***, *86*, 1360; Kramer, G.M. *J. Am. Chem. Soc.* ***1969***, *91*, 4819.

Subsequently, it was found that the same carbocations could also be generated from alcohols in superacid-SO_2 at −60 °C[20] and from alkenes by the addition of a proton from superacid or HF–SbF_5 in SO_2 or SO_2ClF at low temperatures.[21] Even alkanes give carbocations in superacid by loss of H^-. For example,[22] 2-methylpropane gives the *tert*-butyl cation.

$$Me_3CH \xrightarrow{FSO_3H-SbF_6} Me_3C^+SbF_5FSO_3^- + H_2$$

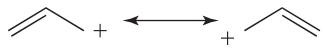
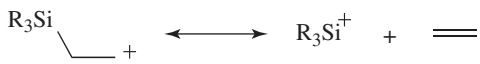
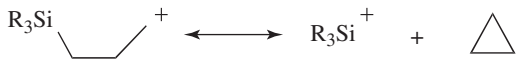
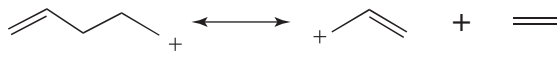
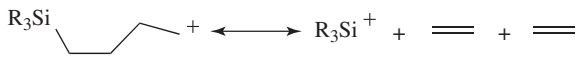
No matter how they are generated, study of the simple alkyl carbocations has provided dramatic evidence for the stability order.[23] Both propyl fluorides gave the isopropyl cation; all four butyl fluorides[24] gave the *tert*-butyl cation, and all seven of the pentyl fluorides examined gave the *tert*-pentyl cation. *n*-Butane, in superacid, gave only the *tert*-butyl cation. To date no primary cation has survived long enough for detection. Neither methyl fluoride nor ethyl fluoride gave the corresponding carbocations when treated with SbF_5. At low temperatures, methyl fluoride gave chiefly the methylated sulfur dioxide salt $(CH_3OSO)^+SbF_6^-$,[25] while ethyl fluoride rapidly formed the *tert*-butyl and *tert*-hexyl cations by addition of the initially formed ethyl cation to ethyne molecules also formed.[26] At room temperature, methyl fluoride also gave the *tert*-butyl cation.[27] In accord with the stability order, hydride ion is abstracted from alkanes by superacid most readily from tertiary positions and least readily from primary positions.

$$\underset{\mathbf{2}}{(CD_3)_3C^+} + (CH_3)_3CH \rightleftharpoons \underset{\mathbf{3}}{(CH_3)_3C^+} + (CD_3)_3CH \quad K_{298} + 1.97 \pm 0.20$$

The stability order can be explained by the polar effect and by hyperconjugation (Sec. 2.M). In the polar effect, nonconjugated substituents exert an influence on stability through bonds (inductive effect) or through space (field effect). Since a tertiary carbocation has more carbon substituents on the positively charged carbon, relative to a primary, there is a greater polar effect that leads to great stability. In the hyperconjugation explanation,[28] a primary carbocation is compared with a tertiary, and "*the hyperconjugation concept arises from model-building procedures* (Sec. 2.M). In general, this means that the model must be corrected by including some delocalization in order to get a good enough description."[29] Evidence used to support the hyperconjugation explanation is that the equilibrium constant for this reaction involving **2** and **3** is 1.97, showing that **3** is more stable than **2**.[30] Due to a β secondary isotope effect, there is less hyperconjugation in **2** than in **3** (see Sec. 6.J.vii for

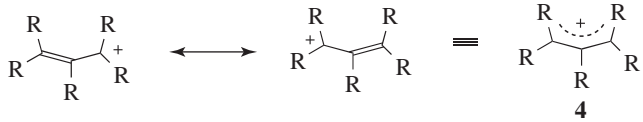
[20] Olah, G.A.; Sommer, J.; Namanworth, E. *J. Am. Chem. Soc.* ***1967***, *89*, 3576.
[21] Olah, G.A.; Halpern, Y. *J. Org. Chem.* ***1971***, *36*, 2354. See also Herlem, M. *Pure Appl. Chem.* ***1977***, *49*, 107.
[22] Olah, G.A.; Lukas, J. *J. Am. Chem. Soc.* ***1967***, *89*, 4739.
[23] See Amyes, T.L.; Stevens, I.W.; Richard, J.P. *J. Org. Chem.* ***1993***, *58*, 6057 for a recent study.
[24] See Saunders, M.; Hagen, E.L.; Rosenfeld, J. *J. Am. Chem. Soc.* ***1968***, *90*, 6882; Saunders, M.; Cox, D.; Lloyd, J.R. *J. Am. Chem. Soc.* ***1979***, *101*, 6656; Myhre, P.C.; Yannoni, C.S. *J. Am. Chem. Soc.* ***1981***, *103*, 230.
[25] Olah, G.A.; Donovan, D.J. *J. Am. Chem. Soc.* ***1978***, *100*, 5163.
[26] Olah, G.A.; Olah, J.A. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1969***, p. 722.
[27] Bacon, J.; Gillespie, R.J. *J. Am. Chem. Soc.* ***1971***, *91*, 6914.
[28] See Radom, L.; Poppinger, D.; Haddon, R.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 2303–2426.
[29] Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry*, 3rd ed., HarperCollins, NY, ***1987***, p. 68.
[30] Meot-Ner, M. *J. Am. Chem. Soc.* ***1987***, *109*, 7947.

TABLE 5.1 Structural types of delocalization[28]

Valence structures	Abbreviation	Name
	ππ	simple conjugation
	σπ	hyperconjugation
	πσ	homoconjugation
	σσ	homohyperconjugation
	σπ/ππ	hyperconjugation/ conjugation
	σπ/σπ	double hyperconjugation

Reprinted with permission from Radom, L.; Poppinger, D.; Haddon, R.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 2303–2426, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. Copyright © ***1976*** by Wiley-VCH Verlag.

isotope effects).[31] The field-effect explanation is that the electron-donating effect of alkyl groups increases the electron density at the charge-bearing carbon, reducing the net charge on the carbon, and in effect spreading the charge over the α carbons. It is a general rule that the more concentrated any charge is, the less stable the species bearing it will be. There are several structural types of delocalization, as summarized in Table 5.1.[32]

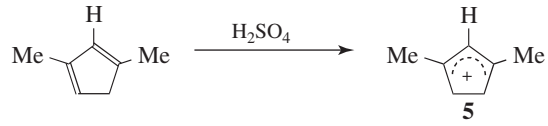


4

The most stable of the simple alkyl cations is the *tert*-butyl cation. Even the relatively stable *tert*-pentyl and *tert*-hexyl cations fragment at higher temperatures to produce the *tert*-butyl cation, as do all other alkyl cations with four or more carbons so far studied.[33] Methane,[34] ethane, and propane, in superacid, also yield *tert*-butyl cations as the main product (see **12-20**). Even paraffin wax and polyethylene give the *tert*-butyl cation. Solid salts of *tert*-butyl and *tert*-pentyl cations, e.g., Me_3C^+ SbF_6^-, have been prepared from superacid solutions and are stable below −20 °C.[35]

[31] If only the field effect were operating, **2** would be more stable than **3**, since D is electron-donating with respect to H (Sec. 1.J), assuming that the field effect of D could be felt two bonds away.
[32] Lambert, J.B.; Ciro, S.M. *J. Org. Chem.* ***1996***, *61*, 1940.
[33] Olah, G.A.; Lukas, J. *J. Am. Chem. Soc.* ***1967***, *89*, 4739; Olah, G.A.; Olah, J.A. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1969***, pp. 750–764.
[34] Olah, G.A.; Klopman, G.; Schlosberg, R.H. *J. Am. Chem. Soc.* ***1969***, *91*, 3261. See also Hogeveen, H.; Gaasbeek, C.J. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 319.
[35] Olah, G.A.; Svoboda, J.J.; Ku, A.T. *Synthesis* ***1973***, 492.

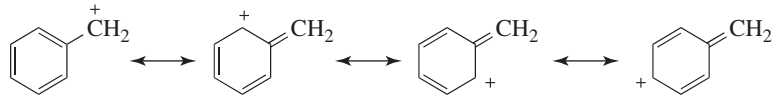
In carbocations where the positive carbon is in conjugation with a double bond, as in allylic cations (the allyl cation is **4**, R=H), the stability is greater because of increased delocalization due to resonance[36] where the positive charge is spread over several atoms instead of being concentrated on one (see the molecular orbital picture of **4** in Sec. 2.C, category 2). Each of the terminal atoms in **4** has a charge of about $\frac{1}{2}$ (the charge is exactly $\frac{1}{2}$ if all of the R groups are the same). Stable cyclic and acyclic allylic-type carbocations[37] have been prepared by dissolving conjugated dienes in concentrated sulfuric acid; the cyclopentadienyl cation, **5**, is an example.[38]



5

Stable allylic carbocations have also been obtained by the reaction between alkyl halides, alcohols, or alkenes (by hydride extraction) and SbF_5 in SO_2 or SO_2ClF.[39] *bis*-Allylic cations[40] are more stable than the simple allylic type, and some of these have been prepared in concentrated sulfuric acid.[41] Arenium ions (Sec. 11.A.i) are familiar examples of this type. Propargyl cations ($RC{\equiv}CC^+R_2$) have also been prepared.[42]

Canonical forms can be drawn for benzylic carbocations, as shown,[43] and they are similar to those shown above for allylic cations.



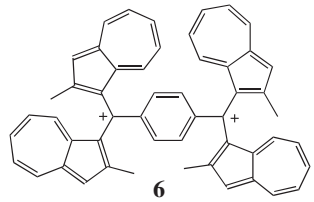
A number of benzylic carbocations have been obtained in solution as SbF_6^- salts.[44] Diarylmethyl and triarylmethyl cations are even more stable because more canonical forms are possible (i.e., there is more extensive delocalization, hence greater stability). Chlorotriphenylmethane ionizes in polar solvents to give the stable triphenylmethyl cation (trityl cation; see **18** below), for example,

$$Ph_3CC1 \rightleftharpoons Ph_3C^+ + C1^-$$

because the solvent does not react with the ion, whereas water does react with the ion. In liquid SO_2, for example, the ion remains stable for many years. Both triphenylmethyl and diphenylmethyl cations have been isolated as solid salts[45] and, in fact, $Ph_3C^+\ BF_4^-$

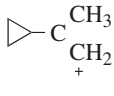
[36] See Mo, Y. *J. Org. Chem.* ***2004***, *69*, 5563 and references cited therein.
[37] For reviews, see Deno, N.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 783–806; Richey Jr., H.G. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 39–114.
[38] Deno, N.C.; Richey Jr., H.G.; Friedman, N.; Hodge, J.D.; Houser, J.J.; Pittman Jr., C.U. *J. Am. Chem. Soc.* ***1963***, *85*, 2991.
[39] Olah, G.A.; Spear, R.J. *J. Am. Chem. Soc.* ***1975***, *97*, 1539 and references cited therein.
[40] For a review of divinylmethyl and trivinylmethyl cations, see Sorensen, T.S. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 807–835.
[41] Deno, N.C.; Pittman Jr., C.U. *J. Am. Chem. Soc.* ***1964***, *86*, 1871.
[42] Olah, G.A.; Spear, R.J.; Westerman, P.W.; Denis, J. *J. Am. Chem. Soc.* ***1974***, *96*, 5855.
[43] For a review of benzylic, diarylmethyl, and triarymethyl cations, see Freedman, H.H. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1971***, pp. 1501–1578.
[44] Olah, G.A.; Porter, R.D.; Jeuell, C.L.; White, A.M. *J. Am. Chem. Soc.* ***1972***, *94*, 2044.
[45] Volz, H.; Schnell, H.W. *Angew. Chem. Int. Ed.* ***1965***, *4*, 873.

and related salts are available commercially. Arylmethyl cations are further stabilized if they have electron-donating substituents in ortho or para positions.[46] Dications[47] and trications are also possible, including the particularly stable dication (**6**), where each positively charged benzylic carbon is stabilized by two azulene rings.[48] A related trication is known where two azulene rings stabilize each benzylic cationic center.[49]

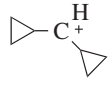


6

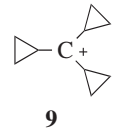
Cyclopropylmethyl carbocations[50] are even more stable than benzylic carbocations. Carbocations **7**, **8**, and similar ions have been prepared by dissolution of the alcohols in FSO_3H–SO_2–SbF_5,[51] and **9** has been prepared from the corresponding alcohol in 96% sulfuric acid.[52] This special stability, which increases with each additional cyclopropyl group, is a result of conjugation between the bent orbitals of the cyclopropyl rings (Sec. 4.Q.i) and the vacant *p* orbital of the cationic carbon (see **10**). NMR and other studies have shown that the vacant *p* orbital lies parallel to the C-2,C-3 bond of the cyclopropane ring and not perpendicular to it.[53] In this respect the geometry is similar to that of a cyclopropane ring conjugated with a double bond (Sec. 4.Q.i). Cyclopropylmethyl cations are further discussed in Sec. 10.C.i, category 4. The stabilizing effect just discussed is unique to cyclopropyl groups. Cyclobutyl and larger cyclic groups are about as effective at stabilizing a carbocation as ordinary alkyl groups.[54]



7



8



9

10

Another structural feature that increases carbocation stability is the presence, adjacent to the cationic center, of a heteroatom bearing an unshared pair,[55] e.g., oxygen,[56]

[46] Deno, N.C.; Schriesheim, A. *J. Am. Chem. Soc.* ***1955***, *77*, 3051.

[47] Prakash, G.K.S. *Pure Appl. Chem.* ***1998***, *70*, 2001. Also see Do, C.; Hatfield, J.; Patel, S.; Vasude, D.; Tirla, van C.; Mills, N.S. *J. Org. Chem.* ***2011***, *76*, 181. Mistry, D.; Powles, N.; Page, M.I. *J. Org. Chem.* ***2013***, *78*, 10732.

[48] Ito, S.; Morita, N.; Asao, T. *Tetrahedron Lett.* ***1992***, *33*, 3773.

[49] Ito, S.; Morita, N.; Asao, T. *Tetrahedron Lett.* ***1994***, *35*, 751.

[50] For reviews, see in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***; Richey Jr., H.G. pp. 1201–294; Wiberg, K.B.; Hess Jr., B.A.; Ashe III, A.H. pp. 1295–1345.

[51] Pittman Jr., C.U.; Olah, G.A. *J. Am. Chem. Soc.* ***1965***, *87*, 2998; Deno, N.C.; Liu, J.S.; Turner, J.O.; Lincoln, D.N.; Fruit Jr., R.E. *J. Am. Chem. Soc.* ***1965***, *87*, 3000.

[52] Deno, N.C.; Richey Jr., H.G.; Liu, J.S.; Hodge, J.D.; Houser, H.J.; Wisotsky, M.J. *J. Am. Chem. Soc.* ***1962***, *84*, 2016.

[53] Childs, R.F.; Kostyk, M.D.; Lock, C.J.L.; Mahendran, M. *J. Am. Chem. Soc.* ***1990***, *112*, 8912.

[54] Sorensen, T.S.; Miller, I.J.; Ranganayakulu, K. *Aust. J. Chem.* ***1973***, *26*, 311.

[55] See Hevesi, L. *Bull. Soc. Chim. Fr.* ***1990***, 697; Olah, G.A.; Liang, G.; Mo, Y.M. *J. Org. Chem.* ***1974***, *39*, 2394; Rabinovitz, M.; Bruck, D. *Tetrahedron Lett.* ***1971***, 245.

[56] For a review of ions of the form $R2C^+$–OR', see Rakhmankulov, D.L.; Akhmatdinov, R.T.; Kantor, E.A. *Russ. Chem. Rev.* ***1984***, *53*, 888. For a review of ions of the form $R'C^+(OR)2$ and $C^+(OR)3$, see Pindur, U.; Müller, J.; Flo, C.; Witzel, H. *Chem. Soc. Rev.* ***1987***, *16*, 75.

nitrogen,[57] or halogen.[58] Such ions are stabilized by resonance, as with the oxocarbenium ion $R_2C{=}O^+Me$).

This methoxymethyl cation can be obtained as a stable solid, $MeOCH_2^+\ SbF_6^-$.[59] Carbocations containing either α-, β-, or γ-silicon atoms are also stabilized[60] relative to similar ions without the silicon atom. γ-Silyl cyclobutylcarbocations are known.[61] In superacid solution, ions such as CX_3^+ (X═Cl, Br, I) have been prepared.[62] Vinyl-stabilized halonium ions are also known.[63] Imidazolium cations show very good alkaline stability.[64]

Simple acyl cations RCO^+ have been prepared[65] in solution and the solid state.[66] The acetyl cation CH_3CO^+ is about as stable as the *tert*-butyl cation (see Table 5.1). The 2,4,6-trimethylbenzoyl and 2,3,4,5,6-pentamethylbenzoyl cations are especially stable (for steric reasons) and are easily formed in 96% H_2SO_4.[67] These ions, often referred to as *acylium ions*, are stabilized by a canonical form containing a triple bond (**12**), although the positive charge is principally located on the carbon,[68] so that **11** contributes more than **12**.

11 **12**

The stabilities of many other stable carbocations can also be attributed to resonance. Among these are the tropylium, cyclopropenium,[69] and other aromatic cations discussed in Chapter 2. Where resonance stability is completely lacking, as in the phenyl ($C_6H_5^+$) or

[57] For a review of such ions where nitrogen is the heteroatom, see Scott, F.L.; Butler, R.N. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1974***, pp. 1643–1696.

[58] See Allen, A.D.; Tidwell, T.T. *Adv. Carbocation Chem.* ***1989***, *1*, 1. See also Teberekidis, V.I.; Sigalas, M.P. *Tetrahedron* ***2003***, *59*, 4749.

[59] Olah, G.A.; Svoboda, J.J. *Synthesis* ***1973***, 52.

[60] See Emblidge, R.W.; Salvador, L.A.; Liu, X.; So, J.-H.; Chelius, E.C. *Acc. Chem. Res.* **1999**, 32, 183. See also Lambert, J.B.; Chelius, E.C. *J. Am. Chem. Soc.* ***1990***, *112*, 8120.

[61] Creary, X.; Kochly, E.D. *J. Org. Chem.* ***2009***, *74*, 9044.

[62] Olah, G.A.; Heiliger, L.; Prakash, G.K.S. *J. Am. Chem. Soc.* ***1989***, *111*, 8020.

[63] Haubenstock, H.; Sauers, R.R. *Tetrahedron* ***2004***, *60*, 1191.

[64] Hugar, K.M.; Kostalik IV, H.A.; Coates, G.W. *J. Am. Chem. Soc.* ***2015***, *137*, 8730.

[65] See Al-Talib, M.; Tashtoush, H. *Org. Prep. Proced. Int.* ***1990***, *22*, 1; Olah, G.A.; Germain, A.; White, A.M. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 2049–2133; Lindner, E. *Angew. Chem. Int. Ed.* ***1970***, *9*, 114.

[66] See Olah, G.A.; Dunne, K.; Mo, Y.K.; Szilagyi, P. *J. Am. Chem. Soc.* ***1972***, *94*, 4200; Olah, G.A.; Svoboda, J.J. *Synthesis* ***1972***, 306.

[67] Hammett, L.P.; Deyrup, A.J. *J. Am. Chem. Soc.* ***1933***, *55*, 1900; Newman, M.S.; Deno, N.C. *J. Am. Chem. Soc.* ***1951***, *73*, 3651.

[68] Le Carpentier, J.; Weiss, R. *Acta Crystallogr. Sect. B* ***1972***, 1430. See also Olah, G.A.; Westerman, P.W. *J. Am. Chem. Soc.* ***1973***, *95*, 3706.

[69] See Komatsu, K.; Kitagawa, T. *Chem. Rev.* ***2003***, *103*, 1371. Also see Gilbertson, R.D.; Weakley, T.J.R.; Haley, M.M. *J. Org. Chem.* ***2000***, *65*, 1422.

vinyl cations,[70] the ion, if formed at all, is usually very short-lived.[71] Neither vinyl[72] nor phenyl cation has as yet been prepared as a stable species in solution.[73] However, stable alkenyl carbocations have been generated on Zeolite Y,[74] and the phenyl cation has been observed in cryogenic argon matrices.[75]

Various quantitative methods have been developed to express the relative stabilities of carbocations.[76] One of the most common of these, although useful only for relatively stable carbocations that are formed by ionization of alcohols in acidic solutions, is based on the equation[77]

$$H_R = \mathrm{pK}_{R+} - \log \frac{C_{R+}}{C_{\mathrm{ROH}}}$$

where $\mathrm{p}K_{\mathrm{R}+}$ is the pK value for the reaction

$$\mathrm{R}^+ + 2\mathrm{H_2O} \rightleftharpoons \mathrm{ROH} + \mathrm{H_3O}^+$$

and is a measure of the stability of the carbocation. The H_{R} parameter is an easily obtainable measurement of the stability of a solvent (Sec. 8.C) and approaches pH at low concentrations of acid. In order to obtain $\mathrm{p}K_{\mathrm{R}+}$ for a cation R^+, one dissolves the alcohol ROH in an acidic solution of known H_{R}. The concentration of R^+ and ROH are obtained, generally from spectra, and $\mathrm{p}K_{\mathrm{R}+}$ is easily calculated.[78] A measure of carbocation stability that applies to less stable ions is the dissociation energy $D(\mathrm{R}^+\!-\!\mathrm{H}^-)$ for the cleavage reaction

$$\mathrm{R}\!-\!\mathrm{H} \rightarrow \mathrm{R}^+ + \mathrm{H}^-$$

[70] See Gronheid, R.; Lodder, G.; Okuyama, T. *J. Org. Chem.* ***2002***, *67*, 693. Vinyl carbocations are sluggish electrophiles: see Byrne, P.A.; Kobayashi, S.; Würthwein, E.-U.; Ammer, J.; Mayr, H. *J. Am. Chem. Soc.* ***2017***, *139*, 1499. For a discussion of aryl substituted vinyl cations, see Müller, T.; Margraf, D.; Syha, Y. *J. Am. Chem. Soc.* ***2005***, *127*, *10852*.

[71] For a review of destabilized carbocations, see Tidwell, T.T. *Angew. Chem. Int. Ed.* ***1984***, *23*, 20.

[72] See Abram, T.S.; Watts, W.E. *J. Chem. Soc., Chem. Commun.* ***1974***, 857; Siehl, H.; Carnahan Jr., J.C.; Eckes, L.; Hanack, M. *Angew. Chem. Int. Ed.* ***1974***, *13*, 675. Also see Franke, W.; Schwarz, H.; Stahl, D. *J. Org. Chem.* ***1980***, *45*, 3493. See also Siehl, H.; Koch, E. *J. Org. Chem.* ***1984***, *49*, 575.

[73] See Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*, Academic Press, NY, 1979; Hanack, M. *Pure Appl. Chem.* ***1984***, *56*, 1819, *Acc. Chem. Res.* ***1976***, *9*, 364; Ambroz, H.B.; Kemp, T.J. *Chem. Soc. Rev.* ***1979***, *8*, 353; Richey Jr., H.G.; Richey, J.M. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 899–957; Richey Jr., H.G. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 42–49; Stang, P.J. *Prog. Phys. Org. Chem.* ***1973***, *10*, 205. See also Charton, M. *Mol. Struct. Energ.* ***1987***, *4*, 271. For a computational study, see Glaser, R.; Horan, C.J.; Lewis, M.; Zollinger, H. *J. Org. Chem.* ***1999***, *64*, 902.

[74] Yang, S.; Kondo, J.N.; Domen, K. *Chem. Commun.* ***2001***, 2008.

[75] Winkler, M.; Sander, W. *J. Org. Chem.* ***2006***, *71*, 6357.

[76] For reviews, see Bagno, A.; Scorrano, G.; More O'Ferrall, R.A. *Rev. Chem. Intermed.* ***1987***, *7*, 313; Bethell, D.; Gold, V. *Carbonium Ions*, Academic Press, NY, ***1967***, pp. 59–87.

[77] Deno, N.C.; Berkheimer, H.E.; Evans, W.L.; Peterson, H.J. *J. Am. Chem. Soc.* ***1959***, *81*, 2344.

[78] For a list of stabilities of 39 typical carbocations, see Arnett, E.M.; Hofelich, T.C. *J. Am. Chem. Soc.* ***1983***, *105*, 2889. See also Schade, C.; Mayr, H.; Arnett, E.M. *J. Am. Chem. Soc.* ***1988***, *110*, 567; Schade, C.; Mayr, H. *Tetrahedron* ***1988***, *44*, 5761.

TABLE 5.2 R—H → $R^+ + H^-$ dissociation energies in the gas phase

	$D(R^+—H^-)$		
Ion	kcal mol^{-1}	kJ mol^{-1}	Ref.
CH_3^+	314.6	1316	79
$C_2H_5^+$	276.7	1158	80
$(CH_3)_2CH^+$	249.2	1043	80
$(CH_3)_3C^+$	231.9	970.3	80
$C_6H_5^+$	294	1230	81
$H_2C{=}CH^+$	287	1200	82,83
$H_2C{=}CH{-}CH_2^+$	256	1070	83
cyclopentyl	246	1030	83
$C_6H_5CH_2^+$	238	996	83
CH_3CHO	230	962	83

which can be obtained from photoelectron spectroscopy (Sec. 1.E) and other measurements.[84] Some values of $D(R^+—H^-)$ are shown in Table 5.2.[85] Within a given class of ion, e.g. primary, secondary, allylic, aryl, etc., $D(R^+—H^-)$ has been shown to be a linear function of the logarithm of the number of atoms in R^+, with larger ions being more stable.[81]

Since the central carbon of tricoordinated carbocations has only three bonds and no other valence electrons, the bonds are sp^2 and should be planar.[80] Raman, IR, and NMR spectroscopic data on simple alkyl cations show this to be so.[83] In methylcycohexyl cations there are two chair conformations where the carbon bearing the positive charge is planar (**13** and **14**), and there is evidence that **14** is more stable due to a difference in hyperconjugation.[86] Arenonium ions (**15**) are also known, and are relatively stable.[87] Other evidence is that carbocations are difficult to form at bridgehead atoms in [2.2.1] systems,[88] where they cannot be planar (Sec. 10.A.ii).[89] Bridgehead carbocations are known, however, as in [2.1.1]hexanes[90] and cubyl carbocations.[91] Larger bridgehead ions can exist. For example,

[79] Schultz, J.C.; Houle, F.A.; Beauchamp, J.L. *J. Am. Chem. Soc.* ***1984***, *106*, 3917.

[80] See Schleyer, P.v.R. in Chiurdoglu, G. *Conformational Analysis*, Academic Press, NY, ***1971***, pp. 241; Hehre, W.J. *Acc. Chem. Res.* ***1975***, *8*, 369; Freedman, H.H. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions,* Vol. 4, Wiley, NY, ***1974***, pp. 1561–574.

[81] Lossing. F.P.; Holmes, J.L. *J. Am. Chem. Soc.* ***1984***, *106*, 6917.

[82] Vinyl cations are generated by photolysis of vinyl iodonium salts. See Slegt, M.; Gronheid, R.; van der Vlugt, D.; Ochiai, M.; Okuyama, T.; Zuilhof, H.; Overkleeft, H.S.; Lodder, G. *J. Org. Chem.* ***2006***, *71*, 2227.

[83] Olah, G.A.; DeMember, J.R.; Commeyras, A.; Bribes, J.L. *J. Am. Chem. Soc.* ***1971***, *93*, 459; Yannoni, C.S.; Kendrick, R.D.; Myhre, P.C.; Bebout, D.C.; Petersen, B.L. *J. Am. Chem. Soc.* ***1989***, *111*, 6440.

[84] For a study of alkane dications, see Rasul, G.; Surya Prakash, G.K.; Olah, G.A. *J. Org. Chem.* ***2013***, *78*, 1747.

[85] Hammett, L.P.; Deyrup, A.J. *J. Am. Chem. Soc.* ***1933***, *55*, 1900; Newman, M.S.; Deno, N.C. *J. Am. Chem. Soc.* ***1951***, *73*, 3651; Boer, F.P. *J. Am. Chem. Soc.* ***1968***, *90*, 6706; Le Carpentier, J.; Weiss, R. *Acta Crystallogr. Sect. B* ***1972***, 1430. See also Arnett, E.M.; Petro, C. *J. Am. Chem. Soc.* ***1978***, *100*, 5408; Arnett, E.M.; Pienta, N.J. *J. Am. Chem. Soc.* ***1980***, *102*, 3329.

[86] Rauk, A.; Sorensen, T.S.; Maerker, C.; de M. Carneiro, J.W.; Sieber, S.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1996***, *118*, 3761.

[87] Lawlor, D.A.; More O'Ferrall, R.A.; Rao, S.N. *J. Am. Chem. Soc.* ***2008***, *130*, 17997.

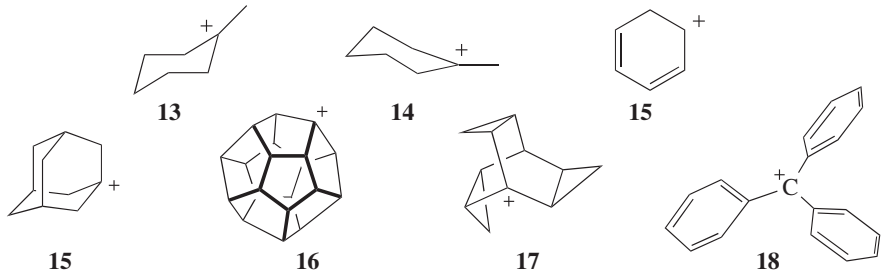
[88] For a review of bridgehead carbocations, see Fort Jr., R.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1974***, pp. 1783–1835.

[89] Della, E.W.; Schiesser, C.H. *J. Chem. Soc., Chem. Commun.* ***1994***, 417.

[90] Åhman, J.; Somfai, P.; Tanner, D. *J. Chem. Soc., Chem. Commun.* ***1994***, 2785.

[91] Della, E.W.; Head, N.J.; Janowski, W.K.; Schiesser, C.H. *J. Org. Chem.* ***1993***, *58*, 7876.

the adamantyl cation (**15**) has been synthesized, as the SF_6^- salt.[92] The relative stability of 1-adamantyl cations is influenced by the number and nature of substituents. For example, the stability of the 1-adamantyl cation increases with the number of isopropyl substituents at C3, C5 and C7.[93] Among other bridgehead carbocations that have been prepared in superacid solution at −78 °C are the dodecahydryl cation (**16**)[94] and the 1-trishomobarrelyl cation (**17**).[95] In the latter case the instability of the bridgehead position is balanced by the extra stability gained from the conjugation with the three cyclopropyl groups.



Triarylmethyl cations, such as the triphenylmethyl carbocation (**18**),[96] are propeller shaped, although the central carbon and the three ring carbons connected to it are in a plane:[97] The three benzene rings cannot be all in the same plane due to steric hindrance, although increased resonance energy would be gained if they could.

An important tool for the investigation of carbocation structure is measurement of the ^{13}C NMR chemical shift of the carbon atom bearing the positive charge.[98] This shift approximately correlates with electron density on the carbon. The ^{13}C chemical shifts for a number of ions are given in Table 5.3.[99] As shown in the table, the substitution of an ethyl for a methyl or a methyl for a hydrogen atom causes a downfield shift, indicating that the central carbon becomes somewhat more positive. On the other hand, the presence of hydroxy or phenyl groups decreases the positive character of the central carbon. The ^{13}C chemical shifts are not always in exact order of carbocation stabilities as determined in other ways. Thus the chemical shift shows that the triphenylmethyl cation has a more positive central carbon than diphenylmethyl cation, although the former is more stable. Also, the 2-cyclopropylpropyl and 2-phenylpropyl cations have shifts of −86.8 and −61.1, respectively, although we have seen that according to other criteria a cyclopropyl group is better

[92] Olah, G.A.; Prakash, G.K.S.; Shih, J.G.; Krishnamurthy, V.V.; Mateescu, G.D.; Liang, G.; Sipos, G.; Buss, V.; Gund, T.M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1985***, *107*, 2764. See also Kruppa, G.H.; Beauchamp, J.L. *J. Am. Chem. Soc.* ***1986***, *108*, 2162; Laube, T. *Angew. Chem. Int. Ed.* ***1986***, *25*, 349.

[93] Takeuchi, K.; Okazaki, T.; Kitagawa, T.; Ushino, T.; Ueda, K.; Endo, T.; Notario, R. *J. Org. Chem.* ***2001***, *66*, 2034.

[94] Olah, G.A.; Prakash, G.K.S.; Fessner, W.; Kobayashi, T.; Paquette, L.A. *J. Am. Chem. Soc.* ***1988***, *110*, 8599.

[95] de Meijere, A.; Schallner, O. *Angew. Chem. Int. Ed.* ***1973***, *12*, 399.

[96] See Sundaralingam, M.; Chwang, A.K. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 2427–2476.

[97] Schuster, I.I.; Colter, A.K.; Kurland, R.J. *J. Am. Chem. Soc.* ***1968***, *90*, 4679.

[98] For reviews of the NMR spectra of carbocations, see Young, R.N. *Prog. Nucl. Magn. Reson. Spectrosc.* ***1979***, *12*, 261; Farnum, D.G. *Adv. Phys. Org. Chem.* ***1975***, *11*, 123.

[99] Olah, G.A.; White, A.M. *J. Am. Chem. Soc.* ***1968***, *90*, 1884; ***1969***, *91*, 5801. For ^{13}C NMR data for additional ions, see Olah, G.A.; Donovan, D.J. *J. Am. Chem. Soc.* ***1977***, *99*, 5026; Olah, G.A.; Prakash, G.K.S.; Liang, G. *J. Org. Chem.* ***1977***, *42*, 2666.

TABLE 5.3 ^{13}C NMR chemical shift values, in parts per million from $^{13}CS_2$, for the charged carbon atom of some carbocations in $SO_2ClF—SbF_5$, $SO_2—FSO_3H—SbF_6$, or $SO_2—SbF_5$[99]

Ion	Chemical shift	Temperature, °C
Et_2MeC^+	−139.4	−20
Me_2EtC^+	−139.2	−60
Me_3C^+	−135.4	−20
Me_2CH^+	−125.0	−20
Me_2(cyclopropyl)C^+	−86.8	−60
$PhMe_2C^+$	−61.1	−60
Me_2COH^+	−55.7	−50
$PhMeCH^+$	−40[96]	
Ph_3C^+	−18.1	−60
Ph_2CH^+	−5.6	−60
$MeC(OH)_2^+$	−1.6	−30
$HC(OH)_2^+$	+17.0	−30
$C(OH)_3^+$	+28.0	−50

Reprinted with permission from Olah, G.A.; White, A.M. *J. Am. Chem. Soc.* ***1968***, *90*, 1884. Copyright 1968 American Chemical Society. Reprinted with permission from Olah, G.A.; White, A.M. *J. Am. Chem. Soc.* ***1969***, *91*, 5801. Copyright 1969 American Chemical Society.

than a phenyl group at stabilizing a carbocation.[100] The reasons for this discrepancy are not fully understood.[93,101]

Nonclassical carbocations are discussed in Sec. 10.C.i.

5.A.iii. The Generation And Fate Of Carbocations

A number of methods are available to generate carbocations, stable or unstable.

1. A direct ionization, in which a leaving group attached to a carbon atom leaves with its pair of electrons, as in solvolysis reactions of alkyl halides (Sec. 10.G.i) or sulfonate esters (**10-04**):

$$R - X \longrightarrow R^+ + X^- \qquad \text{(may be revrsible)}$$

2. Ionization after an initial reaction that converts one functional group into a leaving group, as in protonation of an alcohol to give an oxonium ion (ROH_2^+) or conversion of a primary amine to a diazonium salt, both of which ionize to the corresponding carbocation:

$$R - OH \xrightarrow{H^+} R - \overset{+}{O}H_2 \longrightarrow R^+ + H_2O \qquad \text{(may be reversible)}$$

$$R - NH_2 \xrightarrow{HONO} R - N_2 \longrightarrow R^+ + N_2$$

Oxonium ions are also generated by protonation of ethers,[102] including epoxides.[103] However, these ions do not always lead to carbocations via ionization, but often

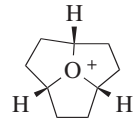
[100] Olah, G.A.; Porter, R.D.; Kelly, D.P. *J. Am. Chem. Soc.* ***1971***, *93*, 464.

[101] See Brown, H.C.; Peters, E.N. *J. Am. Chem. Soc.* ***1977***, *99*, 1712; Kitching, W.; Adcock, W.; Aldous, G. *J. Org. Chem.* ***1979***, *44*, 2652. See also Larsen, J.W. *J. Am. Chem. Soc.* ***1978***, *100*, 330.

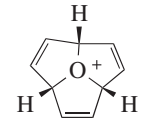
[102] Peterson, P.E.; Slama, F.J. *J. Am. Chem. Soc.* ***1968***, *90*, 6516.

[103] Carlier, P.R.; Deora, N.; Crawford, T.D. *J. Org. Chem.* ***2006***, *71*, 1592.

undergo substitution reactions (see Chapter 10). Oxatriquinane, **19**, is a fused, tricyclic alkyl oxonium ion that is remarkably stable. Oxonium ion **19** has been heated to reflux in water, can be chromatographed, and does not react with alcohols or alkyl thiols.[104] The X-ray crystal structure shows longer C—O bond distances and more acute C—O—C bond angles than any reported alkyloxonium salt. Oxatriquinene **20** has also been synthesized.

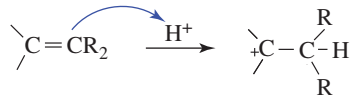


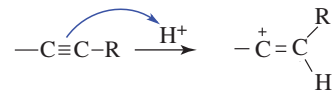
19



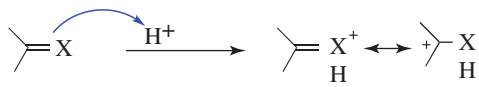
20

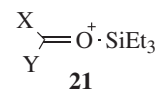
3. A proton or other positive species adds to one atom of an alkene or alkyne, leaving the adjacent carbon atom with a positive charge (see Chapters 11 and 15).





4. A proton or other positive species adds to one atom of an C=X bond, where X=O, S, N in most cases, leaving the adjacent carbon atom with a positive charge (see Chapter 16). When X=O, S this ion is a resonance-stabilized oxocarbenium ion (X=O) or thiacarbenium ion (X=S), as shown. When X=NR, protonation leads to an iminium ion (X=N), with the charge localized on the nitrogen. A silylated carboxonium ion such as **21** has been reported.[105]





21

When formed by any of the processes 1–3, carbocations are most often short-lived transient species and react further without being isolated. Oxocarbenium ions are more stable and may be longer lived, but even oxocarbenium ions are transient intermediates. The intrinsic barriers to formation and reaction of carbocations have been studied.[106]

There are two principal pathways by which carbocations react to give stable products that are effectively the reverse of the last two pathways just described.

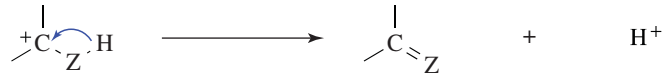
1. *A carbocation may combine with a species possessing an electron pair* (essentially a Lewis acid–base reaction, see Chapter 8). This reaction occurs by an atom or group donating electrons to the positive carbon of the carbocation. The atom or group, Y^-, that donates the electrons to carbon is called a *nucleophile* (see Chapter 10):

$$R^+ + Y^- \longrightarrow R\text{–}Y$$

[104] Mascal, M.; Hafezi, N.; Meher N.K.; Fettinger, J.C. *J. Am. Chem. Soc.* ***2008***, *130*, 13532.
[105] Prakash, G.K.S.; Bae, C.; Rasul, G.; Olah, G.A. *J. Org. Chem.* ***2002***, *67*, 1297.
[106] Richard, J.P.; Amyes, T.L.; Williams, K.B. *Pure. Appl. Chem.* ***1998***, *70*, 2007.

Any reasonable nucleophile will react with the carbocation, but the nucleophile may also be a neutral species with an electron pair to donate, in which case, of course, the immediate product must bear a positive charge (see Chapters 10, 13, 15, and 16). These reactions are very fast. A recent study measured k_s (the rate constant for reaction of a simple tertiary carbocation) to be 3.5×10^{12} s^{-1}.[107]

2. *The carbocation may have a proton* (or much less often, another positive ion) *removed* from the adjacent atom (see Chapters 11 and 17):



Carbocations can also adopt two other pathways that lead not to stable products, but to other carbocations:

3. *Rearrangement.* an alkyl or aryl group or a hydrogen atom (sometimes another group) migrates with its electron pair to the positive center, leaving another positive charge behind (see Chapter 18):

A novel rearrangement has been observed. The 2-methyl-2-butyl-1-^{13}C cation (^{13}C-labeled *tert*-amyl cation) shows an interchange of the inside and outside carbons with a barrier of 19.5 kcal mol^{-1} (81.6 kJ mol^{-1}) (± 2 kcal mol^{-1}; 8.4 kJ mol^{-1}.[108] Another unusual migratory process has been observed for the nonamethylcyclopentyl cation, in which "four methyl groups undergo rapid circumambulatory migration with a barrier < 2 kcal mol^{-1} (8.4 kJ mol^{-1}) while five methyl groups are fixed to ring carbons, and the process that equalizes the two sets of methyls has a barrier of 7.0 kcal mol^{-1} (29.3 kJ mol^{-1})."[109]

4. *Addition*. A carbocation may add to a double bond, generating a positive charge at a new position (see Chapters 11 and 15). This means that the π bond donates two electrons to a positive atom, generating positive charge on the carbon as shown:

22

Whether formed by pathway 3 or 4, the new carbocation normally reacts further in an effort to stabilize itself, usually by pathway 1 or 2. However, **22** can add to another alkene molecule, and this product can add to still another, etc. This is one of the mechanisms for vinyl polymerization.

[107] Toteva, M.M.; Richard, J.P. *J. Am. Chem. Soc.* ***1996***, *118*, 11434.
[108] Vrcek, V.; Saunders, M.; Kronja, O. *J. Am. Chem. Soc.* ***2004***, *126*, 13703.
[109] Kronja, O.; Kohli, T.-P.; Mayr, H.; Saunders, M. *J. Am. Chem. Soc.* ***2000***, *122*, 8067.

5.B. CARBANIONS

5.B.i. Stability and Structure[110]

Formally, a carbanion is a trivalent carbon atom with an unshared electron pair and a formal charge of −1. In fact, there are few carbanions that do not have an anion-stabilizing group attached to the carbon atom. Stabilization may be by resonance delocalization or by orbital participation of an atom with *d* orbitals or orbitals associated with a metal.

By definition, every carbanion possesses an unshared pair of electrons and is formally a base. When a carbanion donates an electron to a proton, it is converted to its conjugate acid (an acid–base reaction, see Chapter 8). If the carbanion $R_3C:^-$ were available, reaction with an acid generates the conjugate acid, $R_3C{-}H$, an alkane. The stability of the carbanion is directly related to the strength of the conjugate acid. The weaker that conjugate acid, the greater the base strength of the carbanion, and the lower the stability of the carbanion.[111] Stability here is judged by diminished reactivity (lower electron-donating ability) with a proton; the greater the stability, the lower the electron-donating ability (lower reactivity) for reaction of the carbanion with a proton (any acid that is sufficiently strong), and hence the longer lived the carbanion. Thus the determination of the order of stability of a series of carbanions is equivalent to a determination of the inverse order of strengths of the conjugate acids, and one can obtain information about relative carbanion stability from a table of acid strengths like Table 8.1. The cyclopropenyl anion has been discussed.[112]

While formation of simple carbanions such as CH_3^- is rare, formation of a C–metal bond often generates a molecule such as $R_3C{-}M$ (M = a metal atom) that has a polarized bond in which the carbon is electron rich (δ^-). An organic molecule that contains a C–metal bond is called an *organometallic compound*. Organometallic compounds where the metal is Mg, Li, or other metals are carbanion surrogates, and in much of their chemistry react as if they were carbanions (see reactions **12-22** to **12-37**). Many such compounds are known, and organometallic chemistry is a very large area, occupying a borderline region between organic and inorganic chemistry. This section will discuss carbanions with little reference to a metal. Section 5.B.ii will discuss the structures of organometallic compounds, which are often carbanion surrogates.

Carbanions are very strong bases, and the conjugate acids of simple unsubstituted carbanions are very weak acids, with very few exceptions. Unfortunately, it is not easy to measure acid strengths of very weak acids. There is little doubt that carbanions are very unstable in solution, and in contrast to the situation with carbocations, efforts to prepare solutions in which carbanions such as ethyl or isopropyl exist in a relatively free state have not yet been successful. Nor has it been possible to form these carbanions in the gas phase. Indeed, there is evidence that simple carbanions such as ethyl and isopropyl are unstable,

[110] See Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pts. A, B, and C; Elsevier, NY, ***1980***, ***1984***, ***1987***; Bates, R.B.; Ogle, C.A. *Carbanion Chemistry*, Springer, NY, ***1983***; Stowell, J.C. *Carbanions in Organic Synthesis*, Wiley, NY, ***1979***; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***; Staley, S.W. *React. Intermed. (Wiley)* ***1985***, *3*, 19; Staley, S.W.; Dustman, C.K. *React. Intermed. (Wiley)* ***1981***, *2*, 15. For reviews of NMR spectra of carbanions, see Young, R.N. *Prog. Nucl. Magn. Reson. Spectrosc.* ***1979***, *12*, 261. For a review of dicarbanions, see Thompson, C.M.; Green, D.L.C. *Tetrahedron* ***1991***, *47*, 4223.

[111] See Reutov, O.A.; Beletskaya, I.P.; Butin, K.P. *CH-Acids*, Pergamon, Elmsford, NY, ***1978***; Fischer, H.; Rewicki, D. *Prog. Org. Chem.* ***1968***, *7*, 116.

[112] Kass, S.R. *J. Org. Chem.* ***2013***, *78*, 7370.

losing an electron, which converts them to radicals.[113] Nevertheless, there have been several approaches to the problem. Applequist and O'Brien[114] studied the position of equilibrium for the reaction:

$$RLi + R'I \rightleftharpoons RI + R'Li$$

This reaction was done in ether or an ether–pentane mixture. The reasoning in these experiments was that the R group that forms the more stable carbanion would be more likely to be bonded to lithium than to iodine. Carbanion stability was found to be in the order: vinyl > phenyl > cyclopropyl > ethyl > *n*-propyl > isobutyl > neopentyl > cyclobutyl > cyclopentyl.

In a somewhat similar approach, Dessy and co-workers[115] treated a number of alkylmagnesium compounds with a number of alkylmercury compounds in THF, setting up the equilibrium:

$$R_2Mg + R'_2Hg \rightleftharpoons R_2Hg + R_2Mg$$

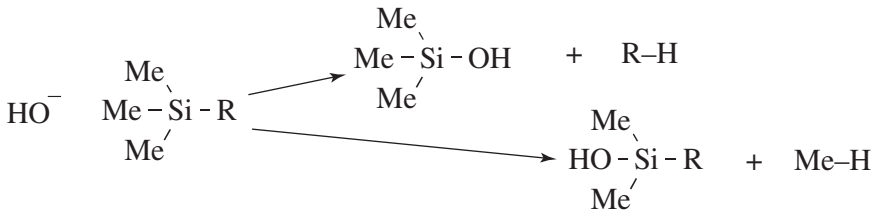
where the group of greater carbanion stability is linked to magnesium. The carbanion stability determined this way was phenyl > vinyl > cyclopropyl > methyl > ethyl > isopropyl.

The two stability orders are in fairly good agreement, and they show that stability of simple carbanions decreases in the order methyl > primary > secondary. It was not possible to determine the position of *tert*-butyl by the experiments reported by Dessy and co-workers, but there seems little doubt that it is still less stable. This stability order can be interpreted as solely a consequence of the field effect since resonance is absent. The electron-donating alkyl groups of isopropyl result in a greater negative charge density at the central carbon atom (compared with methyl), thus decreasing its stability. The results of Applequist and O'Brien[114] show that ß branching also decreases carbanion stability. Cyclopropyl occupies an apparently anomalous position, but this is probably due to the large amount of *s* character in the carbanionic carbon (Sec. 5.B.i, category 2). Strongly electron-withdrawing groups such as trifluoromethylsulfonyl provide exceptional stability to carbanions.[116]

A different approach to the problem of hydrocarbon acidity, and hence carbanion stability, is that of Shatenshtein and co-workers, who treated hydrocarbons with deuterated potassium amide and measured the rates of hydrogen exchange.[117] The experiments did not measure *thermodynamic* acidity, since rates were measured, not positions of equilibria. They measured *kinetic* acidity, i.e., which compounds gave up protons most rapidly (see Sec. 6.F for the distinction between thermodynamic and kinetic control of product). Measurements of rates of hydrogen exchange enable one to compare acidities of a series of acids against a given base even where the positions of the equilibria cannot be measured because they lie too far to the side of the starting materials, i.e., where the acids are too weak to be converted to their conjugate bases in measurable amounts. Although the correlation between thermodynamic acidity and kinetic acidity is far from perfect,[118] the results of the

[113] See Graul, S.T.; Squires, R.R. *J. Am. Chem. Soc.* ***1988***, *110*, 607.
[114] Applequist, D.E.; O'Brien, D.F. *J. Am. Chem. Soc.* ***1963***, *85*, 743.
[115] Dessy, R.E.; Kitching, W.; Psarras, T.; Salinger, R.; Chen, A.; Chivers, T. *J. Am. Chem. Soc.* ***1966***, *88*, 460.
[116] Terrier, F.; Magnier, E.; Kizilian, E.; Wakselman, C.; Buncel, E. *J. Am. Chem. Soc.* ***2005***, *127*, 5563.
[117] For reviews, see Jones, J.R. *Surv. Prog. Chem.* ***1973***, *6*, 83; Shatenshtein, A.I.; Shapiro, I.O. *Russ. Chem. Rev.* ***1968***, *37*, 845.
[118] See Bordwell, F.G.; Matthews, W.S.; Vanier, N.R. *J. Am. Chem. Soc.* ***1975***, *97*, 442.

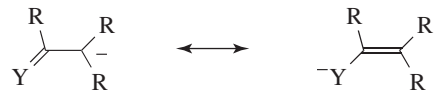
rate measurements, too, indicated that the order of carbanion stability is methyl > primary > secondary > tertiary.[117]



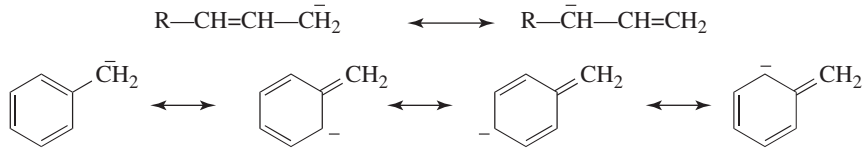
Experiments described above were done in solution, and experiments in the gas phase gave different results. In reactions of $^{-}$OH with alkyltrimethylsilanes it is possible to cleave either R or Me. Since the R or Me come off as a carbanion or incipient carbanion, the product ratio RH:MeH can be used to establish the relative stabilities of various R groups. From these experiments a stability order of neopentyl > cyclopropyl > *tert*-butyl > *n*-propyl > methyl > isopropyl > ethyl was found.[119] On the other hand, in a different kind of gas-phase experiment, Graul and Squires were able to observe CH_3^- ions, but not the ethyl, isopropyl, or *tert*-butyl ions.[120]

As mentioned above, carbanion-stabilizing groups can increase the stability of carbanions, which influences their ease of formation. Six structural features that lead to improved stability are listed:

1. *Conjugation of the unshared pair with an unsaturated bond.*



In cases where a double or triple bond is located α to the carbanionic carbon, the ion is stabilized by resonance in which the unshared pair overlaps with the π electrons of the double bond. This factor is responsible for the stability of the allylic[121] and benzylic[122] types of carbanions:



Diphenylmethyl and triphenylmethyl anions are still more stable due to extensive delocalization into the benzene rings, and can be kept in solution indefinitely if water is rigidly excluded.[123] X-ray crystallographic structures have been obtained

[119] DePuy, C.H.; Gronert, S.; Barlow, S.E.; Bierbaum, V.M.; Damrauer, R. *J. Am. Chem. Soc.* ***1989***, *111*, 1968. The same order (for *t*-Bu, Me, *i*-Pr, and Et) was found in gas-phase cleavages of alkoxides (**12-41**): Tumas, W.; Foster, R.F.; Brauman, J.I. *J. Am. Chem. Soc.* ***1984***, *106*, 4053.

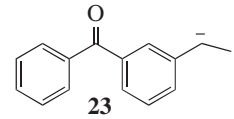
[120] Graul, S.T.; Squires, R.R. *J. Am. Chem. Soc.* ***1988***, *110*, 607.

[121] Richey Jr., H.G. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 67–77.

[122] See Bockrath, B.; Dorfman, L.M. *J. Am. Chem. Soc.* ***1974***, *96*, 5708.

[123] See Buncel, E.; Menon, B. in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pts. A, B, and C, Elsevier, NY, ***1980***, ***1984***, ***1987***, pp. 97–124.

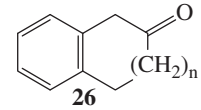
for Ph_2CH^- and Ph_3C^- enclosed in crown ethers.[124] Carbanion **23** has a lifetime of several minutes (hours in a freezer at −20 °C) in dry THF.[125] Condensed aromatic rings fused to a cyclopentadienyl anion are known to stabilize the carbanion.[126]



23

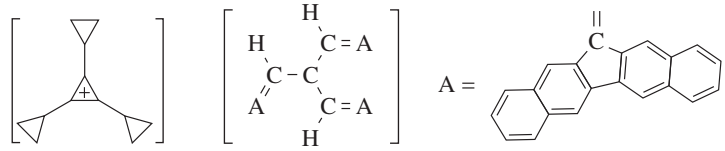
Where the carbanionic carbon is conjugated with a carbon–oxygen or carbon–nitrogen multiple bond (Y=O or N), the stability of the ion is greater than that of the triarylmethyl anions, since these electronegative atoms are better capable of bearing a negative charge than carbon. However, it is questionable whether ions of this type should be called a carbanion at all, since in the case of enolate ions, for example, **25** contributes more to the hybrid than **24** although such ions react more often at the carbon than at the oxygen. In benzylic enolate anions such as **26**, the conformation of the enolate can be coplanar with the aromatic ring or bent out of plane if the strain is too great.[127] Enolate ions can also be maintained in solution in many cases, at least for minutes or hours at lower temperatures. In the case of carbanions at a carbon α to a nitrile, the "enolate" resonance form would be a ketene imine nitranion, but the existence of this species has been called into question.[128] A nitro group is particularly effective in stabilizing a negative charge on an adjacent carbon, and the anions of simple nitro alkanes can exist in water. Thus pK_a for nitromethane is 10.2. Dinitromethane is even more acidic (pK_a = 3.6). In contrast to the stability of cyclopropylmethyl cations (Sec. 5.A.ii), the cyclopropyl group exerts only a weak stabilizing effect on an adjacent carbanionic carbon.[129]

24 **25**



26 n = 0, 1, 2

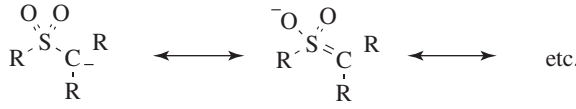
By combining a very stable carbanion with a very stable carbocation, Okamoto and co-workers were able to isolate the salt **27**, as well as several similar salts, as stable solids. These are salts that consist entirely of carbon and hydrogen atoms.[130]



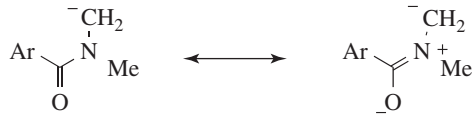
27

[124] Olmstead, M.M.; Power, P.P. *J. Am. Chem. Soc.* ***1985***, *107*, 2174.
[125] Laferriere, M.; Sanrame, C.N.; Scaiano, J.C. *Org. Lett.* ***2004***, *6*, 873.
[126] Kinoshita, T.; Fujita, M.; Kaneko, H.; Takeuchi, K-i.; Yoshizawa, K.; Yamabe, T. *Bull. Chem. Soc. Jpn.* ***1998***, *71*, 1145.
[127] Eldin, S.; Whalen, D.L.; Pollack, R.M. *J. Org. Chem.* ***1993***, *58*, 3490.
[128] Abbotto, A.; Bradamante, S.; Pagani, G.A. *J. Org. Chem.* ***1993***, *58*, 449.
[129] Perkins, M.J.; Peynircioglu, N.B. *Tetrahedron* ***1985***, *41*, 225.
[130] Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Kinoshita, T.; Aonuma, S.; Nagai, M.; Miyabo, A. *J. Org. Chem.* ***1990***, *55*, 996. See also Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Miyabo, A. *J. Chem. Soc., Chem. Commun.* ***1988***, 923.

2. *Carbanions increase in stability with an increase in the amount of* s *character at the carbanionic carbon*. Thus the order of stability is $RC{\equiv}C^- > R_2C{=}CH^- \approx Ar^- > R_3C{-}CH_2{}^-$. Acetylene, where the carbon is *sp* hybridized with 50% *s* character, is much more acidic than ethylene[131] (sp^2, 33% *s*), which in turn is more acidic than ethane, with 25% *s* character. Increased *s* character means that the electrons are closer to the nucleus and hence of lower energy. As previously mentioned, cyclopropyl carbanions are more stable than methyl, owing to the larger amount of *s* character as a result of strain (Sec. 4.Q.i).
3. *Stabilization by sulfur*[132] *or phosphorus*. Attachment to the carbanionic carbon of a sulfur or phosphorus atom causes an increase in carbanion stability, although the reasons for this are in dispute. One theory is that there is overlap of the unshared pair with an empty *d* orbital[133] ($p\pi$–$d\pi$ bonding, Sec. 2.H). For example, a carbanion containing the SO_2R group would be written:

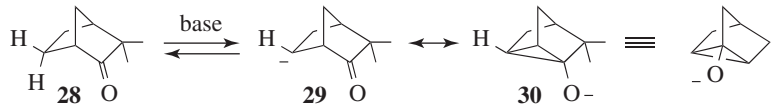


However, there is evidence against *d*-orbital overlap; and the stabilizing effects have been attributed to other causes.[134] In the case of a PhS substituent, carbanion stabilization is thought to be due to a combination of the inductive and polarizability effects of the group, and d–$\pi\pi$ resonance and negative hyperconjugation play a minor role, if any.[135] An α silicon atom also stabilizes carbanions.[136]
4. *Field effects*. Most of the groups that stabilize carbanions by resonance effects (either the kind discussed in paragraph 1 above or the kind discussed in paragraph 3) have electron-withdrawing field effects and thereby stabilize the carbanion further by spreading the negative charge, although it is difficult to separate the field effect from the resonance effect. However, in a nitrogen ylid $R_3N^+{-}{}^-CR_2$ (Sec. 2.H), where a positive nitrogen is adjacent to the negatively charged carbon, only the field effect operates. Ylids are more stable than the corresponding simple carbanions. Carbanions are stabilized by a field effect if there is any heteroatom (O, N, or S) connected to the carbanionic carbon, provided that the heteroatom bears a positive charge in at least one important canonical form,[137] e.g.,



[131] Richey Jr., H.G. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 49–56.
[132] See Oae, S.; Uchida, Y. in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 583–664; Wolfe, S. in Bernardi, F.; Csizmadia, I.G.; Mangini. A. *Organic Sulfur Chemistry*, Elsevier, NY, ***1985***, pp. 133–190; Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 42–56. Also see Reich, H.J. in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 243–276.
[133] See Wolfe, S.; Stolow, A.; LaJohn, L.A. *Tetrahedron Lett.* ***1983***, *24*, 4071.
[134] See Borden, W.T.; Davidson, E.R.; Andersen, N.H.; Denniston, A.D.; Epiotis, N.D. *J. Am. Chem. Soc.* ***1978***, *100*, 1604; Bernardi, F.; Bottoni, A.; Venturini, A.; Mangini, A. *J. Am. Chem. Soc.* ***1986***, *108*, 8171.
[135] Bernasconi, C.F.; Kittredge, K.W. *J. Org. Chem.* ***1998***, *63*, 1944.
[136] Wetzel, D.M.; Brauman, J.I. *J. Am. Chem. Soc.* ***1988***, *110*, 8333.
[137] See Beak, P.; Reitz, D.B. *Chem. Rev.* ***1978***, *78*, 275. See also Rondan, N.G.; Houk, K.N.; Beak, P.; Zajdel, W.J.; Chandrasekhar, J.; Schleyer, P.v.R. *J. Org. Chem.* ***1981***, *46*, 4108.

5. *Certain carbanions are stable because they are aromatic*. See the cyclopentadienyl anion in Sec. 2.I.ii, and other aromatic anions in Chapter 2.
6. *Stabilization by a nonadjacent π bond*.[138] In contrast to the situation with carbocations (Sec. 2.C.i), there have been fewer reports of carbanions stabilized by interaction with a nonadjacent π bond. One that may be mentioned is **30**, formed when optically active camphenilone (**28**) was treated with a strong base (potassium *tert*-butoxide).[139] That **30** was truly formed was shown by the following facts: (1) a proton was abstracted: ordinary CH_2 groups are not acidic enough for this base; (2) recovered **28** was racemized: **30** is symmetrical and can be attacked equally well from either side; (3) when the experiment was performed in deuterated solvent, the rate of deuterium uptake was equal to the rate of racemization; and (4) recovered **28** contained up to three atoms of deuterium per molecule, although if **29** were the only ion, no more than two could be taken up. Ions of this type, in which a negatively charged carbon is stabilized by a carbonyl group two carbons away, are called *homoenolate ions*.



28 **29** **30**

Based on the above categories, functional groups in the α position stabilize carbanions in the following order: $NO_2 > RCO > COOR > SO_2 > CN \approx CONH_2 >$ halogen $> H > R$.

It is unlikely that free carbanions exist in solution, although some of the stabilized carbanions noted above have reasonable lifetimes in solution. Like carbocations, they usually exist as either ion pairs or they are solvated.[140] Among experiments that demonstrate ion pairing or solvation was the treatment of $PhCOCHMe^- M^+$ with ethyl iodide, where M^+ was Li^+, Na^+, or K^+. The half-lives of the reaction were[141] for Li, 31×10^{-6}; Na, 0.39×10^{-6}; and K, 0.0045×10^{-6}, demonstrating that the species involved were not identical. Similar results[142] were obtained with Li, Na, and Cs triphenylmethides $Ph_3C^- M^+$.[143] Where ion pairs are unimportant, carbanions are solvated. Cram[144] has demonstrated solvation of carbanions in many solvents. There may be a difference in the structure of a carbanion depending on whether it is free (e.g., in the gas phase) or in solution. The negative charge may be more localized in solution in order to maximize the electrostatic attraction to the counterion.[145]

The structure of simple unsubstituted carbanions is not known with certainty since they have not been isolated, but it is likely that the central carbon is sp^3 hybridized, with the

[138] See Werstiuk, N.H. *Tetrahedron* ***1983***, *39*, 205; Hunter, D.H.; Stothers, J.B.; Warnhoff, E.W. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 410–437.

[139] See Peiris, S.; Ragauskas, A.J.; Stothers, J.B. *Can. J. Chem.* ***1987***, *65*, 789; Shiner, C.S.; Berks, A.H.; Fisher, A.M. *J. Am. Chem. Soc.* ***1988***, *110*, 957.

[140] For reviews of carbanion pairs, see Hogen-Esch, T.E. *Adv. Phys. Org. Chem.* ***1977***, *15*, 153; Jackman, L.M.; Lange, B.C. *Tetrahedron* ***1977***, *33*, 2737. See also Laube, T. *Acc. Chem. Res.* ***1995***, *28*, 399.

[141] Zook, H.D.; Gumby, W.L. *J. Am. Chem. Soc.* ***1960***, *82*, 1386.

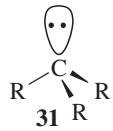
[142] Solov'yanov, A.A.; Karpyuk, A.D.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1981***, *17*, 381. See also Solov'yanov, A.A.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1983***, *19*, 1964.

[143] See Streitwieser Jr., A. *Acc. Chem. Res.* ***1984***, *17*, 353.

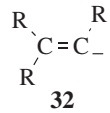
[144] Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***.

[145] See Schade, C.; Schleyer, P.v.R.; Geissler, M.; Weiss, E. *Angew. Chem. Int. Ed.* ***1986***, *21*, 902.

unshared pair occupying one apex of the tetrahedron. Carbanions are expected to have pyramidal structures such as **31**, similar to those of amines.



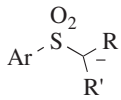
31

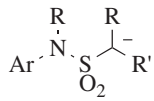


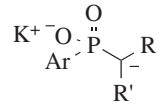
32

The methyl anion CH_3^- has been observed in the gas phase and reported to have a pyramidal structure.[146] If this is taken as a general structure for carbanions, then any carbanion in which the three R groups are different should be chiral and reactions in which it is an intermediate should give retention of configuration. Attempts have been made to demonstrate this principle, but without success.[147] A possible explanation is that pyramidal inversion takes place here, as in amines, so that the unshared pair and the central carbon rapidly oscillate from one side of the plane to the other. There is, however, other evidence for the sp^3 nature of the central carbon and for its tetrahedral structure. Carbons at bridgeheads, although extremely reluctant to undergo reactions in which they must be converted to carbocations, easily undergo reactions in which they must be carbanions and stable bridgehead carbanions are known.[148] Also, reactions at vinylic carbons proceed with retention,[149] indicating that the intermediate **32** has sp^2 hybridization and not the *sp* hybridization that would be expected in the analogous carbocation. A cyclopropyl anion can also hold its configuration.[150]

Carbanions in which the negative charge is stabilized by resonance involving overlap of the unshared-pair orbital with the π electrons of a multiple bond are essentially planar, as would be expected by the necessity for planarity in resonance, although unsymmetrical solvation or ion-pairing effects may cause the structure to deviate somewhat from true planarity.[151] Cram[151] showed that where chiral carbanions possessing this type of resonance are generated, retention, inversion, or racemization can result, depending on the solvent (Sec. 12.A.ii). This result is explained by unsymmetrical solvation of planar or near-planar carbanions. However, some carbanions that are stabilized by adjacent sulfur or phosphorus, such as those shown,







[146] Ellison, G.B.; Engelking, P.C.; Lineberger, W.C. *J. Am. Chem. Soc. 1978*, *100*, 2556.

[147] Retention of configuration has never been observed with simple carbanions. Cram has obtained retention with carbanions stabilized by resonance. However, these carbanions are known to be planar or nearly planar, and retention was caused by asymmetric solvation of the planar carbanions (Sec. 12.A.ii).

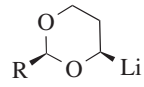
[148] See Peoples, P.R.; Grutzner, J.B. *J. Am. Chem. Soc.* ***1980***, *102*, 4709.

[149] See Feit, B.; Melamed, U.; Speer, H.; Schmidt, R.R. *J. Chem. Soc., Perkin Trans. 1* ***1984***, 775; Chou, P.K.; Kass, S.R. *J. Am. Chem. Soc.* ***1991***, *113*, 4357.

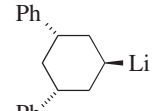
[150] Boche, G.; Harms, K.; Marsch, M. *J. Am. Chem. Soc.* ***1988***, *110*, 6925; Boche, G.; Walborsky, H.M. *Cyclopropane Derived Reactive Intermediates*, Wiley, NY, ***1990***. For a review, see Boche, G.; Walborsky, H.M. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, ***1987***, pp. 701–808.

[151] See Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 85–105.

are inherently chiral, since retention of configuration is observed where they are generated, even in solvents that cause racemization or inversion with other carbanions.[152] It is known that in THF, PhCH(Li)Me behaves as a prochiral entity,[153] and **33** has been prepared as an optically pure α-alkoxylithium reagent.[154] Cyclohexyllithium **34** shows some configurational stability, and it is known that isomerization is slowed by an increase in the strength of lithium coordination and by an increase in solvent polarity.[155] It is known that a vinyl anion is configurationally stable whereas a vinyl radical is not. This is due to the instability of the radical anion that must be an intermediate for conversion of one isomer of vinyllithium to the other.[156] The configuration about the carbanionic carbon, at least for some of the α-sulfonyl carbanions, seems to be planar,[157] and the inherent chirality is caused by lack of rotation about the C—S bond.[158]



33



34

5.B.ii. The Structure Of Organometallic Compounds[159]

Whether a carbon–metal bond is ionic or polar-covalent is determined chiefly by the electronegativity of the metal and the structure of the organic part of the molecule. Ionic bonds become more likely as the negative charge on the metal-bearing carbon is decreased by resonance or field effects. Thus the sodium salt of acetoacetic ester has a more ionic C—Na bond than methylsodium.

Most organometallic bonds are polar-covalent. Only the alkali metals have electronegativities low enough to form ionic bonds with carbon, and even here the behavior of lithium alkyls shows considerable covalent character. The simple alkyls and aryls of Na, K, Rb, and Cs[160] are nonvolatile solids[161] insoluble in benzene or other organic solvents, while alkyllithium reagents are soluble, although they too are generally nonvolatile solids. Organolithium reagents with alkyl units (alkyllithium reagents) do not exist as monomeric species

[152] Bordwell, F.G.; Phillips, D.D.; Williams Jr., J.M. *J. Am. Chem. Soc.* ***1968***, *90*, 426; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 105–113; Hirsch, R.; Hoffmann, R.W. *Chem. Ber.* ***1992***, *125*, 975.

[153] Hoffmann, R.W.; Rühl, T.; Chemla, F.; Zahneisen, T. *Liebigs Ann. Chem.* ***1992***, 719.

[154] Rychnovsky, S.D.; Plzak, K.; Pickering, D. *Tetrahedron Lett.* ***1994***, *35*, 6799.

[155] Reich, H.J.; Medina, M.A.; Bowe, M.D. *J. Am. Chem. Soc.* ***1992***, *114*, 11003.

[156] Jenkins, P.R.; Symons, M.C.R.; Booth, S.E.; Swain, C.J. *Tetrahedron Lett.* ***1992***, *33*, 3543.

[157] Gais, H.; Müller, J.; Vollhardt, J.; Lindner, H.J. *J. Am. Chem. Soc.* ***1991***, *113*, 4002. For a contrary view, see Trost, B.M.; Schmuff, N.R. *J. Am. Chem. Soc.* ***1985***, *107*, 396.

[158] Grossert, J.S.; Hoyle, J.; Cameron, T.S.; Roe, S.P.; Vincent, B.R. *Can. J. Chem.* ***1987***, *65*, 1407.

[159] See Elschenbroich, C.; Salzer, A. *Organometallics*, VCH, NY, ***1989***; Oliver, J.P. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 789–826; Coates, G.E.; Green, M.L.H.; Wade, K. *Organometallic Compounds*, 3rd ed., Vol. 1, Methuen, London, ***1967***; Grovenstein Jr., E. in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. C, Elsevier, NY, ***1987***, pp. 175–221.

[160] See Schade, C.; Schleyer, P.v.R. *Adv. Organomet. Chem.* ***1987***, *27*, 169.

[161] For X-ray crystallography studies, see Weiss, E.; Sauermann, G. *Chem. Ber.* ***1970***, *103*, 265; Weiss, E.; Köster, H. *Chem. Ber.* ***1977***, *110*, 717.

in hydrocarbon solvents or ether.[162] In benzene and cyclohexane, freezing point depression studies have shown that alkyllithium reagents are normally hexameric unless steric interactions favor tetrameric aggregates.[163] NMR studies, especially measurements of ^{13}C–^{6}Li coupling, have also shown aggregation in hydrocarbon solvents.[164] Boiling point elevation studies have been performed in ether solutions, where alkyllithium reagents exist in two- to five-fold aggregates.[165] Even in the gas phase[166] and in the solid state,[167] alkyllithium reagents exist as aggregates. X-ray crystallography has shown that methyllithium has the same tetrahedral structure in the solid state as in ether solution.[167] However, *tert*-butyllithium is monomeric in THF, although dimeric in ether and tetrameric in hydrocarbon solvents.[168] Neopentyllithium exists as a mixture of monomers and dimers in THF.[169]

The C—Mg bond in *Grignard reagents* is covalent and not ionic. The actual structure of Grignard reagents in solution has been a matter of much controversy over the years.[170] The 1929 discovery[171] that the addition of dioxane to an ethereal Grignard solution precipitates all the magnesium halide and leaves a solution of R_2Mg in ether was important to understanding the mechanism of this reaction. This discovery indicated that there can be no RMgX in the solution since there is no halide. The following equilibrium, now called the *Schlenk equilibrium*, was proposed as the composition of the Grignard solution:

$$2\,RMgX \rightleftharpoons R_2Mg + MgX_2 \rightleftharpoons \underset{\textbf{35}}{R_2Mg \bullet MgX_2}$$

in which **35** is a complex. Much work has demonstrated that the Schlenk equilibrium actually exists and that the position of the equilibrium depends on the identity of R, X, the solvent, the concentration, and the temperature.[172] It has been known for many years that the magnesium in a solution of a Grignard reagent, no matter whether it is RMgX, R_2Mg, or MgX_2, can coordinate with two molecules of ether in addition to the two covalent bonds to generate the solvent-coordinated species shown.

Rundle and co-workers performed X-ray diffraction studies on solid phenylmagnesium bromide dietherate and on ethylmagnesium bromide dietherate, which they obtained

[162] See Setzer, W.N.; Schleyer, P.v.R. *Adv. Organomet. Chem.* ***1985***, *24*, 353; Schleyer, P.v.R. *Pure Appl. Chem.* ***1984***, *56*, 151; Brown, T.L. *Pure Appl. Chem.* ***1970***, *23*, 447. For reviews of the structures of lithium enolate anions and related compounds, see Boche, G. *Angew. Chem. Int. Ed.* ***1989***, *28*, 277; Seebach, D. *Angew. Chem. Int. Ed.* ***1988***, *27*, 1624. Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, *The Chemistry of Organolithium Compounds*, Pergamon, Elmsford, NY, ***1974***.

[163] Lewis, H.L.; Brown, T.L. *J. Am. Chem. Soc.* ***1970***, *92*, 4664.

[164] Thomas, R.D.; Jensen, R.M.; Young, T.C. *Organometallics* ***1987***, *6*, 565. See also Kaufman, M.J.; Gronert, S.; Streitwieser Jr., A. *J. Am. Chem. Soc.* ***1988***, *110*, 2829.

[165] Wittig, G.; Meyer, F.J.; Lange, G. *Liebigs Ann. Chem.* ***1951***, *571*, 167. See also Bates, T.F.; Clarke, M.T.; Thomas, R.D. *J. Am. Chem. Soc.* ***1988***, *110*, 5109.

[166] Plavšić, D.; Srzić, D.; Klasinc, L. *J. Phys. Chem.* ***1986***, *90*, 2075.

[167] Weiss, E.; Sauermann, G.; Thirase, G. *Chem. Ber.* ***1983***, *116*, 74.

[168] Bauer, W.; Winchester, W.R.; Schleyer, P.v.R. *Organometallics* ***1987***, *6*, 2371.

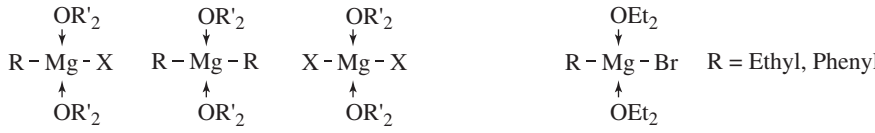
[169] Fraenkel, G.; Chow, A.; Winchester, W.R. *J. Am. Chem. Soc.* ***1990***, *112*, 6190.

[170] For reviews, see Ashby, E.C. *Bull. Soc. Chim. Fr.* ***1972***, 2133; Wakefield, B.J. *Organomet. Chem. Rev.* ***1966***, *1*, 131; Bell, N.A. *Educ. Chem.* ***1973***, 143.

[171] Schlenk, W.; Schlenk Jr., W. *Ber.* ***1929***, *62B*, 920.

[172] See Parris, G.; Ashby, E.C. *J. Am. Chem. Soc.* ***1971***, *93*, 1206; Salinger, R.M.; Mosher, H.S. *J. Am. Chem. Soc.* ***1964***, *86*, 1782.

by cooling ordinary ethereal Grignard solutions until the solids crystallized.[173] They found that the structures were magnesium bromides such as **36**. These solids still contained ether. When ordinary ethereal Grignard solutions[174] prepared from bromomethane, chloromethane, bromoethane, and chloroethane were evaporated at about 100 °C under vacuum so that the solid remaining contained no ether, X-ray diffraction showed *no* RMgX but a mixture of R_2Mg and MgX_2.[175]



36

These results indicate that in the presence of ether $RMgX \bullet 2Et_2O$ is the preferred structure, while the loss of ether drives the Schlenk equilibrium to $R_2Mg + MgX_2$. However, conclusions drawn from a study of the solid materials do not necessarily apply to the structures in solution.

$$2\,RMgX \rightleftharpoons R_2Mg + MgX_2$$

Boiling point elevation and freezing point depression measurements have demonstrated that in tetrahydrofuran at all concentrations and in ether at low concentrations (up to about 0.1 *M*) Grignard reagents prepared from alkyl bromides and iodides are monomeric, i.e., there are few or no molecules with two Mg atoms.[176] Thus, part of the Schlenk equilibrium is operating but not the other part; i.e., **35** is not present in measurable amounts. This was substantiated by ^{25}Mg NMR spectra of the ethyl Grignard reagent in THF, which showed the presence of three peaks, corresponding to EtMgBr, Et_2Mg, and $MgBr_2$.[177] That the equilibrium between RMgX and R_2Mg lies far to the left for "ethylmagnesium bromide" in ether was shown by Smith and Becker, who mixed 0.1 M ethereal solutions of Et_2Mg and $MgBr_2$ and found that a reaction occurred with a heat evolution of 3.6 kcal mol^{-1} (15 kJ mol^{-1}) of Et_2Mg, and that the product was *monomeric* (by boiling point elevation measurements).[178] When either solution was added little by little to the other, there was a linear output of heat until almost a 1:1 molar ratio was reached. Addition of an excess of either reagent gave no further heat output. These results show that at least under some conditions the Grignard reagent is largely RMgX (coordinated with solvent) but that the equilibrium can be driven to R_2Mg by evaporation of all the ether or by addition of dioxane.

For some aryl Grignard reagents it is possible to distinguish separate NMR chemical shifts for ArMgX and Ar_2Mg.[179] From the area under the peaks it is possible to calculate the concentrations of the two species, and from them, equilibrium constants for the

[173] Guggenberger, L.J.; Rundle, R.E. *J. Am. Chem. Soc.* ***1968***, *90*, 5375.
[174] See Sakamoto, S.; Imamoto, T.; Yamaguchi, K. *Org. Lett.* ***2001***, *3*, 1793.
[175] Weiss, E. *Chem. Ber.* ***1965***, *98*, 2805.
[176] Ashby, E.C.; Smith, M.B. *J. Am. Chem. Soc.* ***1964***, *86*, 4363; Vreugdenhil, A.D.; Blomberg, C. *Recl. Trav. Chim. Pays-Bas* ***1963***, *82*, 453, 461.
[177] Benn, R.; Lehmkuhl, H.; Mehler, K.; Rufińska, A. *Angew. Chem. Int. Ed.* ***1984***, *23*, 534.
[178] Smith, M.B.; Becker, W.E. *Tetrahedron* ***1966***, *22*, 3027.
[179] Evans, D.F.; Fazakerley, V. *Chem. Commun.* ***1968***, 974.

Schlenk equilibrium. These data show[179] that the position of the equilibrium depends very markedly on the aryl group and the solvent, but that conventional aryl Grignard reagents in ether are largely ArMgX. In THF the predominance of ArMgX is less, and with some aryl groups there is actually more Ar_2Mg present. Separate NMR chemical shifts have also been found for alkyl RMgBr and R_2Mg in HMPA[180] and in ether at low temperatures.[181] When Grignard reagents from alkyl bromides or chlorides are prepared in triethylamine the predominant species is RMgX.[182] Thus the most important factor determining the position of the Schlenk equilibrium is the solvent. For primary alkyl groups the equilibrium constant for the reaction as written above is lowest in Et_3N, higher in ether, and still higher in THF.[183]

However, Grignard reagents prepared from alkyl bromides or iodides in ether at higher concentrations (0.5 to 1 M) contain dimers, trimers, and higher polymers, and those prepared from alkyl chlorides in ether at all concentrations are dimeric,[184] so that **35** is in solution, probably in equilibrium with RMgX and R_2Mg; i.e., the complete Schlenk equilibrium seems to be present.

The Grignard reagent prepared from 1-chloro-3,3-dimethylpentane in ether undergoes rapid inversion of configuration at the Mg-containing carbon (demonstrated by NMR; this compound is not chiral).[185] The mechanism of this inversion is not completely known. Despite the mechanistic ambiguity, in almost all cases, it is not possible to retain the configuration of a stereogenic carbon while forming a Grignard reagent.

Organolithium reagents (RLi) are very important reagents in organic chemistry. In recent years a great deal has been learned about their structure[186] in both the solid state and in solution. X-ray analysis of complexes of *n*-butyllithium with TMEDA, THF, and DME shows them to be dimers and tetramers [e.g., $(BuLi{\bullet}DME)_4$];[187] they are aggregates.[188] X-ray analysis of isopropyllithium shows it to be a hexamer, $(iPrLi)_6$],[189] and unsolvated lithium aryls are tetramers.[190] α-Ethoxyvinyllithium [$CH_2{=}C(OEt)Li$] shows a polymeric structure with tetrameric subunits.[191] Aminomethyl aryllithium reagents have been shown to be chelated and dimeric in solvents such as THF.[192] There are several functionalized organolithium reagents.[193]

The dimeric, tetrameric, and hexameric structures of organolithium reagents[194] in the solid state is often retained in solution, but this is dependent upon the solvent and

[180] Ducom, J. *Bull. Chem. Soc. Fr.* ***1971***, 3518, 3523, 3529.
[181] See Parris, G.; Ashby, E.C. *J. Am. Chem. Soc.* ***1971***, *93*, 1206.
[182] Ashby, E.C.; Walker, F. *J. Org. Chem.* ***1968***, *33*, 3821.
[183] Parris, G.; Ashby, E.C. *J. Am. Chem. Soc.* ***1971***, *93*, 1206.
[184] Ashby, E.C.; Smith, M.B. *J. Am. Chem. Soc.* ***1964***, *86*, 4363.
[185] Fraenkel, G.; Cottrell, C.E.; Dix, D.T. *J. Am. Chem. Soc.* ***1971***, *93*, 1704; Pechhold, E.; Adams, D.G.; Fraenkel, G. *J. Org. Chem.* ***1971***, *36*, 1368; Maercker, A.; Geuss, R. *Angew. Chem. Int. Ed.* ***1971***, *10*, 270.
[186] See Pratt, L.M.; Kass, S.R. *J. Org. Chem.* ***2004***, *69*, 2123.
[187] Nichols, M.A.; Williard, P.G. *J. Am. Chem. Soc.* ***1993***, *115*, 1568.
[188] See Jones, A.C.; Sanders, A.W.; Bevan, M.J.; Reich, H.J. *J. Am. Chem. Soc.* ***2007***, *129*, 3492.
[189] Siemeling, U.; Redecker, T.; Neumann, B.; Stammler, H.-G. *J. Am. Chem. Soc.* ***1994***, *116*, 5507.
[190] Ruhlandt-Senge, K.; Ellison, J.J.; Wehmschulte, R.J.; Pauer, F.; Power, P.P. *J. Am. Chem. Soc.* ***1993***, *115*, 11353. Also see Betz, J.; Hampel, F.; Bauer, W. *Org. Lett.* ***2000***, *2*, 3805.
[191] Sorger, K.; Bauer, W.; Schleyer, P.v.R.; Stalke, D. *Angew. Chem. Int. Ed.* ***1995***, *34*, 1594.
[192] Reich, H.J.; Gudmundsson, B.O.; Goldenberg, W.S.; Sanders, A.W.; Kulicke, K.J.; Simon, K.; Guzei, I.A. *J. Am. Chem. Soc.* ***2001***, *123*, 8067.
[193] Nájera, C.; Yus, M. *Tetrahedron* ***2005***, *61*, 3137.
[194] See Parisel, O.; Fressigne, C.; Maddaluno, J.; Giessner-Prettre, C. *J. Org. Chem.* ***2003***, *68*, 1290.

complexing additives, if any. A tetrahedral organolithium compound is known,[195] and the X-ray of an α,α-dilithio hydrocarbon has been reported.[196] Phenyllithium is a mixture of tetramers and dimers in diethyl ether, but stoichiometric addition of THF, dimethoxyethane, or TMEDA leads to the dimer.[197] The solution structures of mixed aggregates of butyllithium and amino-alkaloids has been determined,[198] and also the solution structure of sulfur-stabilized allyllithium compounds.[199] Vinyllithium is an 8:1 mixture of tetramer:dimer in THF at −90 °C, but addition of TMEDA changes the ratio of tetramer:dimer to 1:13 at −80 °C.[200] Internally solvated allylic lithium compounds have been studied, showing the coordinated lithium to be closer to one of the terminal allyl carbons.[201] A relative scale of organolithium stability has been established,[202] and the issue of configurational stability of enantioenriched organolithium reagents has been examined.[203]

Enolate anions are an important class of carbanions that appear in a variety of important reactions, including alkylation α to a carbonyl group and the aldol (**16-34**) and *Claisen condensation* (**16-85**) reactions. Metal enolate anions of aldehydes, ketones, esters, and other acid derivatives exist as aggregates in ether solvents,[204] and there is evidence that the lithium enolate of isobutyrophenone is a tetramer in THF[205] but a dimer in dimethoxyethane (DME).[206] X-ray crystallography of ketone enolate anions have shown that they can exist as tetramers and hexamers.[207] There is also evidence that the aggregate structure is preserved in solution and is probably the actual reactive species. Lithium enolate anions derived from esters are dimers in the solid state[208] that contain four tetrahydrofuran molecules. It has also been established that the reactivity of enolate anions in alkylation and condensation reactions is influenced by the aggregate state of the enolate. It is also true that the relative proportions of *E* and *Z* enolate anions are influenced by the extent of solvation and the aggregation state. Addition of LiBr to a lithium enolate anion in THF suppresses the concentration of monomeric enolate.[209] *Ab initio* studies confirm the aggregate state of acetaldehyde.[210] It is also known that α-Li benzonitrile [PhCH(Li)CN] exists as a dimer in ether and with TMEDA.[211] Mixed aggregates of *tert*-butyllithium and lithium *tert*-butoxide are known to be hexameric.[212]

[195] Sekiguchi, A.; Tanaka, M. *J. Am. Chem. Soc.* ***2003***, *125*, 12684.
[196] Linti, G.; Rodig, A.; Pritzkow, H. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4503.
[197] Reich, H.J.; Green, D.P.; Medina, M.A.; Goldenberg, W.S.; Gudmundsson, B.Ö.; Dykstra, R.R.; Phillips. N.H. *J. Am. Chem. Soc.* ***1998***, *120*, 7201.
[198] Sun, X.; Winemiller, M.D.; Xiang, B.; Collum, D.B. *J. Am. Chem. Soc.* ***2001***, *123*, 8039. See also Rutherford, J.L.; Hoffmann, D.; Collum, D.B. *J. Am. Chem. Soc.* ***2002***, *124*, 264.
[199] Piffl, M.; Weston, J.; Günther, W.; Anders, E. *J. Org. Chem.* ***2000***, *65*, 5942.
[200] Bauer, W.; Griesinger, C. *J. Am. Chem. Soc.* ***1993***, *115*, 10871.
[201] Fraenkel, G.; Chow, A.; Fleischer, R.; Liu, H. *J. Am. Chem. Soc.* ***2004***, *126*, 3983.
[202] Graña, P.; Paleo, M.R.; Sardina, F.J. *J. Am. Chem. Soc.* ***2002***, *124*, 12511.
[203] Basu, A.; Thayumanavan, S. *Angew. Chem. Int. Ed.* ***2002***, *41*, 717. See also Fraenkel, G.; Duncan, J.H.; Martin, K.; Wang, J. *J. Am. Chem. Soc.* ***1999***, *121*, 10538.
[204] Bernstein, M.P.; Collum, D.B. *J. Am. Chem. Soc.* ***1993***, *115*, 789; Collum, D.B. *Acc. Chem. Res.* ***1992***, *25*, 448.
[205] Jackman, L.M.; Lange, B.C. *J. Am. Chem. Soc.* ***1981***, *103*, 4494.
[206] Jackman, L.M.; Lange, B.C. *Tetrahedron* ***1977***, *33*, 2737.
[207] Williard, P.G.; Carpenter, G.B. *J. Am. Chem. Soc.* ***1986***, *108*, 462; Williard, P.G.; Carpenter, G.B. *J. Am. Chem. Soc.* ***1985***, *107*, 3345 and references cited therein.
[208] Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W.B.; Dunitz, J.D. *J. Am. Chem. Soc.* ***1985***, *107*, 5403.
[209] Abu-Hasanayn, F.; Streitwieser, A. *J. Am. Chem. Soc.* ***1996***, *118*, 8136.
[210] Abbotto, A.; Streitwieser, A.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1997***, *119*, 11255.
[211] Carlier, P.R.; Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1994***, *116*, 11602.
[212] DeLong, G.T.; Pannell, D.K.; Clarke, M.T.; Thomas, R.D. *J. Am. Chem. Soc.* ***1993***, *115*, 7013.

It might be mentioned that matters are much simpler for organometallic compounds with less polar bonds. Thus Et_2Hg and EtHgCl are both definite compounds, the former a liquid and the latter a solid. Organocalcium reagents are also known, and they are formed from alkyl halides via a single electron transfer (SET) mechanism with free-radical intermediates.[213]

5.B.iii. The Generation And Fate Of Carbanions

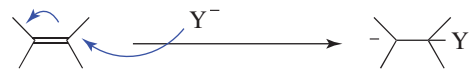
There are two principal ways in which most carbanions are generated.

1. *A group attached to a carbon leaves without its electron pair:*

$$R{-}H \longrightarrow R^- + H^+$$

The "leaving group" is most often a proton. In fact, the proton is removed by a suitable base, and this is a simple acid–base reaction.[214] However, other leaving groups are known (see Chapter 12), such as carboxyl:

2. *A negative ion adds to a carbon–carbon double or triple bond* (see Chapter 15):



The addition of a negative ion to a carbon–oxygen double bond (C═O) does not give a carbanion but an alkoxide ($R{-}O^-$), since the negative charge resides on the oxygen.

The most common reaction of carbanions is to donate electrons to a positive species, often a proton, or to another species that has an empty orbital in its outer shell (a Lewis acid–base reaction):

This means that carbanions react with electrophilic atoms (those functionalized so there is a δ + carbon atom). See Chapter 16.

Carbanions may also form a bond with a carbon that already has four bonds, by displacing one of the four groups (S_N2 reaction, see Chapter 10):

[213] Walborsky, H.M.; Hamdouchi, C. *J. Org. Chem.* ***1993***, *58*, 1187.

[214] For a review of such reactions, see Durst, T. in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry,* pt. B, Elsevier, NY, ***1984***, pp. 239–291.

Like carbocations, carbanions can also react in ways in which they are converted to species that are still charged. They can add to double bonds (usually C=O double bonds; see Chapters 10 and 16):

or rearrange, although this is rare (see Chapter 18):

$$Ph_3C\bar{C}H_2 \longrightarrow Ph_2\bar{C}CH_2Ph$$

or they are oxidized to free radicals.[215]

A system in which a carbocation [$Ph(p\text{-}Me_2NC_6H_4)_2C^+$] oxidizes a carbanion [$(p\text{-}NO_2C_6H_4)_3C^-$] to give two free radicals, reversibly, so that all four species are present in equilibrium, has been demonstrated.[216,217]

Organometallic compounds that are not ionic but polar-covalent behave very much as if they were ionic and give similar reactions.

5.C. FREE RADICALS

5.C.i. Stability and Structure[218]

A *free radical* (usually just called a *radical*) may be defined as a species that contains one or more unpaired electrons.[219] Note that this definition includes certain stable inorganic molecules such as NO and NO_2, as well as many individual atoms, such as Na and Cl. As with carbocations and carbanions, simple alkyl radicals are very reactive and are usually transient species.[220] For the most part, their lifetimes are extremely short in solution, but they can be kept for relatively long periods frozen within the crystal lattices of other molecules.[221] There are, however, many stable radicals,[222] some of which will be noted

[215] For a review, see Guthrie, R.D. in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. A, Elsevier, NY, 1980, pp. 197–269.

[216] Arnett, E.M.; Molter, K.E.; Marchot, E.C.; Donovan, W.H.; Smith, P. *J. Am. Chem. Soc.* ***1987***, *109*, 3788.

[217] Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Kinoshita, T.; Aonuma, S.; Nagai, M.; Miyabo, A. *J. Org. Chem.* ***1990***, *55*, 996. See also Okamoto, K.; Kitagawa, T.; Takeuchi, K.; Komatsu, K.; Miyabo, A. *J. Chem. Soc., Chem. Commun.* ***1988***, 923.

[218] See Alfassi, Z.B. *N-Centered Radicals*, Wiley, Chichester, ***1998***; Alfassi, Z.B. *Peroxyl Radicals*, Wiley, Chichester, ***1997***; Alfassi, Z.B. *Chemical Kinetics of Small Organic Radicals*, 4 Vols, CRC Press, Boca Raton, FL, ***1988***; Nonhebel, D.C.; Tedder, J.M.; Walton, J.C. *Radicals*, Cambridge University Press, Cambridge, ***1979***; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, Cambridge, ***1974***; Kochi, J.K. *Free Radicals*, 2 Vols, Wiley, NY, ***1973***; Hay, J.M. *Reactive Free Radicals*, Academic Press, NY, ***1974***;. For reviews, see Kaplan, L. *React. Intermed. (Wiley)* ***1985***, *3*, 227; Griller, D.; Ingold, K.U. *Acc. Chem. Res.* ***1976***, *9*, 13.

[219] See Beckwith, A.L.J. Schiesser, C.H. *Org. Biomol. Chem.* ***2011***, *9*, 1736.

[220] See Kubo, T.; Katada, Y.; Shimizu, A.; Hirao, Y.; Sato, K.; Takui, T.; Uruichi, M.; Yakushi, K.; Haddon, R.C. *J. Am. Chem. Soc.* ***2011***, *133*, 14240. See Hicks, R.G. (ed.) *Stable Radicals. Fundamentals and Applied Aspects of Odd-Electron Compounds*, Wiley, NJ, ***2010***.

[221] See Dunkin, I.R. *Chem. Soc. Rev.* ***1980***, *9*, 1; Jacox, M.E. *Rev. Chem. Intermed.* ***1978***, *2*, 1. For a review of the study of radicals at low temperatures, see Mile, B. *Angew. Chem. Int. Ed.* ***1968***, *7*, 507.

[222] See. Hicks, R.G. *Org. Biomol. Chem.* ***2007***, *5*, 1321. See also Hioe, J.; Zipse, H. *Org. Biomol. Chem.* ***2010***, *8*, 3609; Poutsma, M.L. *J. Org. Chem.* ***2011***, *76*, 270.

below. Many spectral[223] measurements have been made on radicals trapped in this manner. Even under these conditions the methyl radical decomposes with a half-life of 10 to 15 min in a methanol lattice at 77 K.[224] Since the lifetime of a radical depends not only on its inherent stability, but also on the conditions under which it is generated, the terms *persistent* and *stable* are usually used for the different senses. A stable radical is inherently stable; a persistent radical has a relatively long lifetime under the conditions in which it is generated, although it may not be very stable.

Radicals can be characterized by several techniques, such as mass spectrometry[225] or the characterization of alkoxycarbonyl radicals by Step-Scan Time-Resolved Infrared Spectroscopy.[226] Another technique makes use of the magnetic moment that is associated with the spin of an electron, which can be expressed by a quantum number of $+\frac{1}{2}$ or $-\frac{1}{2}$. According to the *Pauli principle*, any two electrons occupying the same orbital must have opposite spins, so the total magnetic moment is zero for any species in which all the electrons are paired. In radicals, however, one or more electrons are unpaired, so there is a net magnetic moment and the species is paramagnetic. Radicals can therefore be detected by magnetic-susceptibility measurements, but for this technique a relatively high concentration of radicals is required.

Propargyl/allenyl radicals, depending on the nature of the substituents, can irreversibly dimerize, exist as monomers in solution but dimerize in the solid state, or can even remain monomeric as solids and were characterized by an allenyl radical by single crystal X-ray crystallography.[227] The twisted diarylnitroxide structure helps stabilize radicals.[228]

A much more important technique is *electron spin resonance* (ESR), also called *electron paramagnetic resonance* (EPR).[229] The principle of ESR is similar to that of NMR, except that electron spin is involved rather than nuclear spin.[230] The two electron spin states ($m_s = \frac{1}{2}$ and $m_s = -\frac{1}{2}$) are ordinarily of equal energy, but in a magnetic field the energies are different. As in NMR, a strong external field is applied and electrons are caused to flip from the lower state to the higher by the application of an appropriate radio-frequency signal. Since two electrons paired in one orbital must have opposite spins that cancel, an ESR spectrum arises only from species that have one or more unpaired electrons, i.e., free radicals.

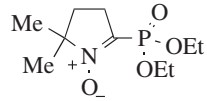
Since only free radicals give an ESR spectrum, the method can be used to detect the presence of radicals and to determine their concentration.[231] Furthermore, information concerning the electron distribution (and hence the structure) of free radicals can be obtained from

[223] See Andrews, L. *Annu. Rev. Phys. Chem.* ***1971***, *22*, 109.
[224] Sullivan, P.J.; Koski, W.S. *J. Am. Chem. Soc.* ***1963***, *85*, 384.
[225] Sablier, M.; Fujii, T. *Chem. Rev.* ***2002***, *102*, 2855.
[226] Bucher, G.; Halupka, M.; Kolano, C.; Schade, O.; Sander, W. *Eur. J. Org. Chem.* ***2001***, 545.
[227] Hansmann, M.M.; Melaimi, M.; Bertrand, G. *J. Am. Chem. Soc.* ***2017***, *139*, 15620.
[228] Levitskiy, O.A.; Eremin, D.B.; Bogdanov, A.V.; Magdesieva, T.V. *Eur. J. Org. Chem.* ***2017***, 4726.
[229] For reviews, see Bunce, N.J. *J. Chem. Educ.* ***1987***, *64*, 907; Hirota, N.; Ohya-Nishiguchi, H. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed., pt. 2, Wiley, NY, ***1986***, pp. 605–655; Fischer, H. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 435–491; Turro, N.J.; Kleinman, M.H.; Karatekin, E. *Angew. Chem. Int. Ed.* ***2000***, *39*, 4437; Kurreck, H.; Kirste, B.; Lubitz, W. *Angew. Chem. Int. Ed.* ***1984***, *23*, 173. Bersohn, R.; Baird, J.C. *An Introduction to Electron Paramagnetic Resonance*, W.A. Benjamin, NY, ***1966***. See also Poole Jr., C.P. *Electron Spin Resonance. A Comprehensive Treatise on Experimental Techniques*, 2nd ed., Wiley, NY, ***1983***.
[230] For a discussion of high-spin organic molecules, see Gallagher, N.M.; Olankitwanit, A.; Rajca, A. *J. Org. Chem.* ***2015***, *80*, 1291.
[231] Davies, A.G. *Chem. Soc. Rev.* ***1993***, *22*, 299.

the splitting pattern of the ESR spectrum (ESR peaks are split by nearby protons).[232] Fortunately (for the existence of most free radicals is very short), it is not necessary for a radical to be persistent for an ESR spectrum to be obtained. ESR spectra have been observed for radicals with lifetimes considerably less than 1 s. Failure to observe an ESR spectrum does not prove that radicals are not involved, since the concentration may be too low for direct observation. In such cases the *spin trapping* technique can be used.[233] In this technique a compound is added that is able to combine with very reactive radicals to produce more persistent radicals; the new radicals can be observed by ESR. Azulenyl nitrones have been developed as chromotropic spin-trapping agents.[234] An important class of spin-trapping compounds are nitroso compounds, which react with radicals to give stable nitroxide radicals:[235]

$$RN{=}O + R'\bullet \rightarrow RR'N{-}O\bullet$$

An *N*-oxide spin trap has been developed [**37**; 2(diethylphosphino)-5,5-dimethyl-1-pyrroline-*N*-oxide], and upon trapping a reactive free radical, ^{31}P NMR can be used to identify it.[236] This is an effective technique, and short-lived species such as the oxiranylmethyl radical has been detected by spin trapping.[237] Other molecules have been used to probe the intermediacy of radicals via single electron transfer (SET) processes. They are called SET probes.[238]



37

Because there is an equal probability that a given unpaired electron will have a quantum number of $+\frac{1}{2}$ or $-\frac{1}{2}$, radicals are observed as a single line in an ESR spectrum unless they interact with other electronic or nuclear spins or possess magnetic anisotropy, in which case two or more lines may appear in the spectrum.[239]

Another magnetic technique for the detection of free radicals uses an ordinary NMR instrument. It was discovered[240] that if an NMR spectrum is taken during the course of a reaction, certain signals might be enhanced, either in a positive or negative direction; others

[232] See Walton, J.C. *Rev. Chem. Intermed.* ***1984***, *5*, 249; Kochi, J.K. *Adv. Free-Radical Chem.* ***1975***, *5*, 189; Bielski, B.H.J.; Gebicki, J.M. *Atlas of Electron Spin Resonance Spectra*, Academic Press, NY, ***1967***.

[233] See Janzen, E.G.; Haire, D.L. *Adv. Free Radical Chem. (Greenwich, Conn.)* ***1990***, *1*, 253; Perkins, M.J. *Adv. Phys. Org. Chem.* ***1980***, *17*, 1; Zubarev, V.E.; Belevskii, V.N.; Bugaenko, L.T. *Russ. Chem. Rev.* ***1979***, *48*, 729; Evans, C.A. *Aldrichimica Acta* ***1979***, *12*, 23; Janzen, E.G. *Acc. Chem. Res.* ***1971***, *4*, 31. See also the collection of papers on this subject in *Can. J. Chem.* ***1982***, *60*, 1379.

[234] Becker, D.A.; Natero, R.; Echegoyen, L.; Lawson, R.C. *J. Chem. Soc., Perkin Trans. 2* ***1998***, 1289. Also see Klivenyi, P.; Matthews, R.T.; Wermer, M.; Yang, L.; MacGarvey, U.; Becker, D.A.; Natero, R.; Beal, M.F. *Experimental Neurobiology* ***1998***, *152*, 163.

[235] For a series of papers on nitroxide radicals, see *Pure Appl. Chem.* ***1990***, *62*, 177. Audran, G.; Brémond, P.; Marque, S.R.A.; Yamasaki, T. *J. Org. Chem.* ***2016***, *81*, 1981.

[236] Janzen, E.G.; Zhang, Y.-K. *J. Org. Chem.* ***1995***, *60*, 5441. For the preparation of a new but structurally related spin trap see Karoui, H.; Nsanzumuhire, C.; Le Moigne, F.; Tordo, P. *J. Org. Chem.* ***1999***, *64*, 1471.

[237] Grossi, L.; Strazzari, S. *Chem. Commun.* ***1997***, 917.

[238] Timberlake, J.W.; Chen, T. *Tetrahedron Lett.* ***1994***, *35*, 6043; Tanko, J.M.; Brammer Jr., L.E.; Hervas, M.; Campos, K. *J. Chem. Soc., Perkin Trans. 2* ***1994***, 1407.

[239] Harry Frank, University of Connecticut, Storrs, CT, Personal Communication.

[240] Ward, H.R.; Lawler, R.G.; Cooper, R.A. *J. Am. Chem. Soc.* ***1969***, *91*, 746; Lepley, A.R. *J. Am. Chem. Soc.* ***1969***, *91*, 749; Lepley, A.R.; Landau, R.L. *J. Am. Chem. Soc.* ***1969***, *91*, 748.

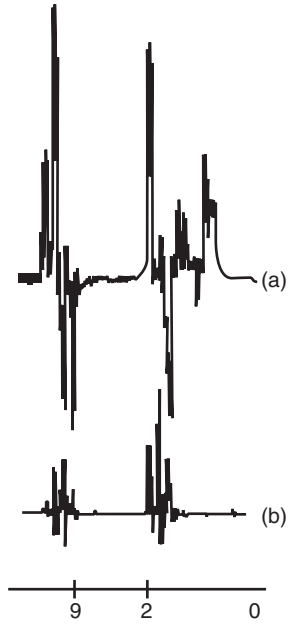


FIGURE 5.1.[241] (a) NMR spectrum taken during reaction between EtI and EtLi in benzene (the region between 0.5 and 3.5 δ was scanned with an amplitude twice that of the remainder of the spectrum). The signals at 1.0 to 1.6 δ are due to butane, some of which is also formed in the reaction. (b) Reference spectrum of EtI. Reprinted with permission from Ward, H.R.; Lawler, R.G.; Cooper, R.A. *J. Am. Chem. Soc.* ***1969****, 91*, 746. Copyright 1969 American Chemical Society.

may be reduced. When this type of behavior, called *chemically induced dynamic nuclear polarization*[242] (CIDNP), is found in the NMR spectrum of the product of a reaction, it means that *at least a portion of that product was formed via the intermediacy of a free radical*.[243] For example, the question was raised whether radicals were intermediates in the exchange reaction between ethyl iodide and ethyllithium (**12-38**):

$$\mathrm{EtI} + \mathrm{EtLi} \rightleftharpoons \mathrm{EtLi} + \mathrm{EtI}$$

Curve *a* in Figure 5.1[241] shows an NMR spectrum taken during the course of the reaction. Curve *b* is a reference spectrum of ethyl iodide (CH_3 protons at $\delta = 1.85$; CH_2 protons at $\delta = 3.2$). Note that in curve *a* some of the ethyl iodide signals are enhanced; others go below the base line (*negative enhancement*; also called *emission*).

The iodoethane formed in the exchange shows CIDNP and so was formed via a free-radical intermediate. CIDNP results when protons in a reacting molecule become dynamically coupled to an unpaired electron while traversing the path from reactants to products.

[241] Ward, H.R.; Lawler, R.G.; Cooper, R.A. *J. Am. Chem. Soc.* ***1969***, *91*, 746.

[242] For reviews, see Adrian, F.J. *Rev. Chem. Intermed.* ***1986***, *7*, 173; Closs, G.L.; Miller, R.J.; Redwine, O.D. *Acc. Chem. Res.* ***1985***, *18*, 196; Closs, G.L. *Adv. Magn. Reson.* ***1974***, *7*, 157; Lawler, R.G. *Acc. Chem. Res.* ***1972***, *5*, 25; Kaptein, R. *Adv. Free-Radical Chem.* ***1975***, *5*, 319. See Lepley, R.L.; Closs, G.L. *Chemically Induced Magnetic Polarization*, Wiley, NY, ***1973***. Bargon, J. *Helv. Chim. Acta 2006*, ***89***, 2082.

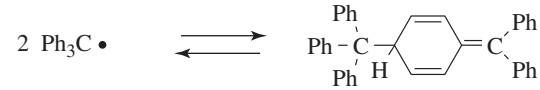
[243] A related technique is called chemically induced dynamic electron polarization (CIDEP). For a review, see Hore, P.J.; Joslin, C.G.; McLauchlan, K.A. *Chem. Soc. Rev.* ***1979***, *8*, 29.

Although the presence of CIDNP almost always means that a free radical is involved,[244] its absence does not prove that a free-radical intermediate is necessarily absent, since reactions involving free-radical intermediates can also take place without observable CIDNP. Also, the presence of CIDNP does not prove that *all* of a product was formed via a free-radical intermediate, only that some of it was. It is noted that dynamic nuclear polarization (DNP) enhances signal intensities in the NMR spectra of solids and liquids. In a contemporary DNP experiment, a diamagnetic sample is doped with a paramagnet and the large polarization of the electron spins is transferred to the nuclei via microwave irradiation of the EPR spectrum.[245] Dynamic nuclear polarization has been used to examine biradicals.[246]

As with carbocations, the stability order of free radicals is tertiary >secondary >primary, explainable by field effects and hyperconjugation, analogous to that in carbocations (Sec. 5.A.ii).[247]

With resonance possibilities, the stability of free radicals increases;[248] some can be kept indefinitely.[249] Benzylic and allylic[250] radicals for which canonical forms can be drawn similar to those shown for the corresponding cations (Sec. 5.A.ii) and anions (Sec. 5.B.i, category 1) are more stable than simple alkyl radicals but still have only a transient existence under ordinary conditions. Note that 2-phenylethyl radicals have been shown to exhibit bridging of the phenyl group.[251]

The triphenylmethyl and similar radicals[252] are stable enough to exist in solution at room temperature, although they are in equilibrium with a dimeric form. The concentration of triphenylmethyl radical in benzene solution is about 2% at room temperature. For many years it was assumed that $Ph_3C\bullet$, the first stable free radical known,[253] dimerized to hexaphenylethane ($Ph_3C{-}CPh_3$),[254] but UV and NMR investigations have shown that the true structure is **38**.[255]



38

[244] It has been shown that CIDNP can also arise in cases where para hydrogen (H2 in which the nuclear spins are opposite) is present: Eisenschmid, T.C.; Kirss, R.U.; Deutsch, P.P.; Hommeltoft, S.I.; Eisenberg, R.; Bargon, J.; Lawler, R.G.; Balch, A.L. *J. Am. Chem. Soc.* ***1987***, *109*, 8089.

[245] Wind, R.A.; Duijvestijn, M.J.; van der Lugt, C.; Manenschijn, A.; Vriend, J. *Prog. Nucl. Magn. Reson. Spectrosc.* ***1985***, *17*, 33.

[246] Hu, K.-N.; Yu, H.-h.; Swager, T.M.; Griffin, R.G. *J. Am. Chem. Soc.* ***2004***, *126*, 10844. A discussion of electronic effects is found in Wagner, P.J.; Wang, L. *Org. Lett.* ***2006***, *8*, 645.

[247] For a discussion of the role of alkyl substitution with respect to radical stabilization, see Gronert, S. *J. Org. Chem.* ***2006***, *71*, 7045. For a discussion concerning data that hyperconguation stabilizes alkyl radicals, see Gronert, S. *Org. Lett.* ***2007***, *9*, 2211.

[248] For a discussion, see Robaugh, D.A.; Stein, S.E. *J. Am. Chem. Soc.* ***1986***, *108*, 3224.

[249] See Forrester, A.R.; Hay, J.M.; Thomson, R.H. *Organic Chemistry of Stable Free Radicals*, Academic Press, NY, ***1968***.

[250] For an electron diffraction study of the allyl radical, see Vajda, E.; Tremmel, J.; Rozsondai, B.; Hargittai, I.; Maltsev, A.K.; Kagramanov, N.D.; Nefedov, O.M. *J. Am. Chem. Soc.* ***1986***, *108*, 4352.

[251] Asensio, A.; Dannenberg, J.J. *J. Org. Chem.* ***2001***, *66*, 5996.

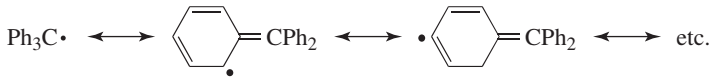
[252] For a review, see Sholle, V.D.; Rozantsev, E.G. *Russ. Chem. Rev.* ***1973***, *42*, 1011.

[253] Gomberg, M. *J. Am. Chem. Soc.* ***1900***, *22*, 757, *Ber.* ***1900***, *33*, 3150.

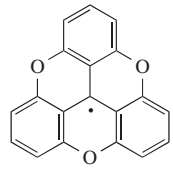
[254] For hexaphenylethane derivatives, see Stein, M.; Winter, W.; Rieker, A. *Angew. Chem. Int. Ed.* ***1978***, *17*, 692; Yannoni, N.; Kahr, B.; Mislow, K. *J. Am. Chem. Soc.* ***1988***, *110*, 6670.

[255] Volz, H.; Lotsch, W.; Schnell, H. *Tetrahedron* ***1970***, *26*, 5343; McBride, J. *Tetrahedron* ***1974***, *30*, 2009. See Peyman, A.; Peters, K.; von Schnering, H.G.; Rüchardt, C. *Chem. Ber.* ***1990***, *123*, 1899.

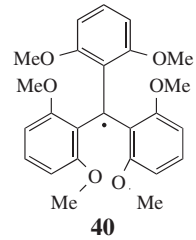
Although triphenylmethyl-type radicals are stabilized by resonance:



steric hindrance to dimerization and not resonance is the major cause of their stability.[256] This was demonstrated by the preparation of the radicals **39** and **40**.[257]



39



40

These radicals are electronically very similar, but **39**, being planar, has much less steric hindrance to dimerization than $Ph_3C•$, while **40**, with six groups in ortho positions, has much more. On the other hand, the planarity of **39** means that it has a maximum amount of resonance stabilization, while **40** must have much less, since its degree of planarity should be even less than $Ph_3C•$, which itself is propeller shaped and not planar. Thus if resonance is the chief cause of the stability of $Ph_3C•$, **40** should dimerize and **39** should not, but if steric hindrance is the major cause, the reverse should happen. It was found[245] that **40** gave no evidence of dimerization, even in the solid state, while **39** existed primarily in the dimeric form, which is dissociated to only a small extent in solution,[258] indicating that steric hindrance to dimerization is the major cause for the stability of triarylmethyl radicals.

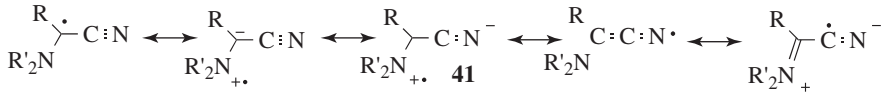
A similar conclusion was reached in the case of $(NC)_3C•$, which dimerizes readily although considerably stabilized by resonance.[259] Nevertheless, that resonance is still an important contributing factor to the stability of radicals is shown by the following facts. (i) the radical *t*-$Bu(Ph)_2C•$ dimerizes more than $Ph_3C•$, while *p*-$PhCOC_6H_4(Ph_2)C•$ dimerizes less.[260] The latter has more canonical forms than $Ph_3C•$, but steric hindrance should be about the same (for attack at one of the two rings). (ii) A number of radicals $(p\text{-}XC_6H_4)_3C•$, with X=F, Cl, O_2N, CN, etc. do not dimerize, but are kinetically stable.[261] Completely chlorinated triarylmethyl radicals are more stable than the unsubstituted kind, probably for steric reasons, and many are quite inert in solution and in the solid state.[262]

Allylic radical are relatively stable, and the pentadienyl radical is particularly stable, but (*E*,*E*)-, (*E*,*Z*)-, and (*Z*,*Z*)-stereoisomers can form. It has been calculated that (*Z*,*Z*)-pentadienyl radical is 5.6 kcal mol^{-1} less stable than (*E*,*E*)-pentadienyl radical.[263] It is noted that vinyl radicals have (*E*)- and (*Z*)-forms and the inversion barrier from one to the other

[256] For steric effects in free radical chemistry, see Rüchardt, C. *Top. Curr. Chem.* ***1980***, *88*, 1.
[257] Sabacky, M.J.; Johnson Jr., C.S.; Smith, R.G.; Gutowsky, H.S.; Martin, J.C. *J. Am. Chem. Soc.* ***1967***, *89*, 2054.
[258] Müller, E.; Moosmayer, A.; Rieker, A.; Scheffler, K. *Tetrahedron Lett.* ***1967***, 3877. See also Neugebauer, F.A.; Hellwinkel, D.; Aulmich, G. *Tetrahedron Lett.* ***1978***, 4871.
[259] Kaba, R.A.; Ingold, K.U. *J. Am. Chem. Soc.* ***1976***, *98*, 523.
[260] Zarkadis, A.K.; Neumann, W.P.; Marx, R.; Uzick, W. *Chem. Ber.* ***1985***, *118*, 450; Zarkadis, A.K.; Neumann, W.P.; Uzick, W. *Chem. Ber.* ***1985***, *118*, 1183.
[261] Dünnebacke, D.; Neumann, W.P.; Penenory, A.; Stewen, U. *Chem. Ber.* ***1989***, *122*, 533.
[262] For reviews, see Ballester, M. *Adv. Phys. Org. Chem.* ***1989***, *25*, 267 (pp. 354–405); *Acc. Chem. Res.* ***1985***, *18*, 380. See also Hegarty, A.F.; O'Neill, P. *Tetrahedron Lett.* ***1987***, *28*, 901.
[263] Fort Jr., R.C.; Hrovat, D.A.; Borden, W.T. *J. Org. Chem.* ***1993***, *58*, 211.

increases as the electronegativity of substituents increase.[264] Conjugated propargylic radicals are calculated to have diminished stability as the conjugation increases, in contrast to the behavior of alkenes.[265] Cyclopropyl alkynes have been used as mechanistic probes to distinguish between vinyl radicals and ionic intermediates.[266] Enolate radicals are also known.[267]

It has been postulated that the stability of free radicals is enhanced by the presence at the radical center of *both* an electron-donating and an electron-withdrawing group.[268] This is called the *push-pull* or *captodative effect* (see also Sec. 4.K.i). The effect arises from increased resonance, as in **41**.



41

There is some evidence in favor[269] of the captodative effect, some of it from ESR studies.[270] However, there is also experimental[271] and theoretical[272] evidence against it. There is evidence that while FCH_2• and F_2CH• are more stable than CH_3•, the radical CF_3• is less stable; that is, the presence of the third F destabilizes the radical.[273]

Certain radicals with the unpaired electron not on a carbon are also very stable.[274] Radicals can be stabilized by intramolecular hydrogen bonding.[275] Diphenylpicrylhydrazyl (**42**) is a solid that can be kept for years, and stable neutral azine radicals have been prepared.[276] Nitroxide radicals were mentioned previously,[277] and the commercially available TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl free radical, **43**) is a stable nitroxyl radical used in chemical reactions such as oxidations.[278] or as a spin trap.[279] Nitroxyl radical **44** is a

[264] Galli, C.; Guarnieri, A.; Koch, H.; Mencarelli, P.; Rappoport, Z. *J. Org. Chem.* ***1997***, *62*, 4072.

[265] Rogers, D.W.; Matsunaga, N.; Zavitsas, A.A. *J. Org. Chem.* ***2006***, *71*, 2214.

[266] Gottschling, S.E.; Grant, T.N.; Milnes, K.K.; Jennings, M.C.; Baines, K.M. *J. Org. Chem.* ***2005***, *70*, 2686.

[267] Giese, B.; Damm, W.; Wetterich, F.; Zeltz, H.-G.; Rancourt, J.; Guindon, Y. *Tetrahedron Lett.* ***1993***, *34*, 5885.

[268] For reviews, see Sustmann, R.; Korth, H. *Adv. Phys. Org. Chem.* ***1990***, *26*, 131; Viehe, H.G.; Janousek, Z.; Merényi, R.; Stella, L. *Acc. Chem. Res.* ***1985***, *18*, 148.

[269] See Pasto, D.J. *J. Am. Chem. Soc.* ***1988***, *110*, 8164. See also Ashby, E.C. *Bull. Soc. Chim. Fr.* ***1972***, 2133; Bell, N.A. *Educ. Chem.* ***1973***, 143.

[270] See Sakurai, H.; Kyushin, S.; Nakadaira, Y.; Kira, M. *J. Phys. Org. Chem.* ***1988***, *1*, 197; Rhodes, C.J.; Roduner, E. *Tetrahedron Lett.* ***1988***, *29*, 1437; Viehe, H.G.; Merényi, R.; Janousek, Z. *Pure Appl. Chem.* ***1988***, *60*, 1635; Bordwell, F.G.; Lynch, T. *J. Am. Chem. Soc.* ***1989***, *111*, 7558.

[271] See Bordwell, F.G.; Bausch, M.J.; Cheng, J.P.; Cripe, T.H.; Lynch, T.-Y.; Mueller, M.E. *J. Org. Chem.* ***1990***, *55*, 58; Bordwell, F.G.; Harrelson Jr., J.A. *Can. J. Chem.* ***1990***, *68*, 1714.

[272] See Pasto, D.J. *J. Am. Chem. Soc.* ***1988***, *110*, 8164.

[273] Jiang, X.; Li, X.; Wang, K. *J. Org. Chem.* ***1989***, *54*, 5648.

[274] For reviews of radicals with the unpaired electron on atoms other than carbon, see in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, the reviews by Nelson, S.F. pp. 527–593 (*N*-centered); Bentrude, W.G. pp. 595–663 (*P*-centered); Kochi, J.K. pp. 665–710 (*O*-centered); Kice, J.L. pp. 711–740 (*S*-centered); Sakurai, H. pp. 741–807 (Si, Ge, Sn, and Pb-centered).

[275] Maki, T.; Araki, Y.; Ishida, Y.; Onomura, O.; Matsumura, Y. *J. Am. Chem. Soc.* ***2001***, *123*, 3371.

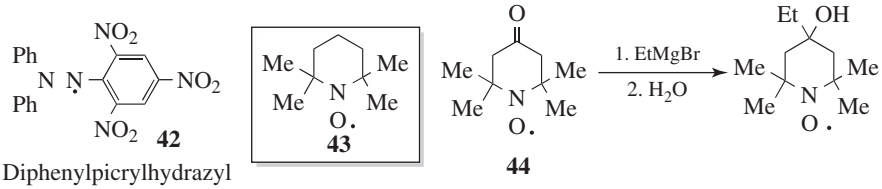
[276] Jeromin, G.E. *Tetrahedron Lett.* ***2001***, *42*, 1863.

[277] See Novak, I.; Harrison, L.J.; Kovač, B.; Pratt, L.M. *J. Org. Chem.* ***2004***, *69*, 7628.

[278] See Fritz-Langhals, E. *Org. Process Res. Dev.* ***2005***, *9*, 577. See also Rychnovsky, S.D.; Vaidyanathan, R.; Beauchamp, T.; Lin, R.; Farmer, P.J. *J. Org. Chem.* ***1999***, *64*, 6745.

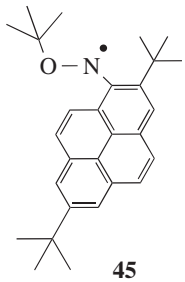
[279] Volodarsky, L.B.; Reznikov, V.A.; Ovcharenko, V.I. *Synthetic Chemistry of Stable Nitroxides*, CRC Press, Boca Raton, FL, ***1994***; Keana, J.F.W. *Chem. Rev.* ***1978***, *78*, 37; Aurich, H.G. *Nitroxides. In Nitrones, Nitronates, Nitroxides*, Patai, S.; Rappoport, Z. Eds, Wiley, NY, ***1989***; Chap. 4.

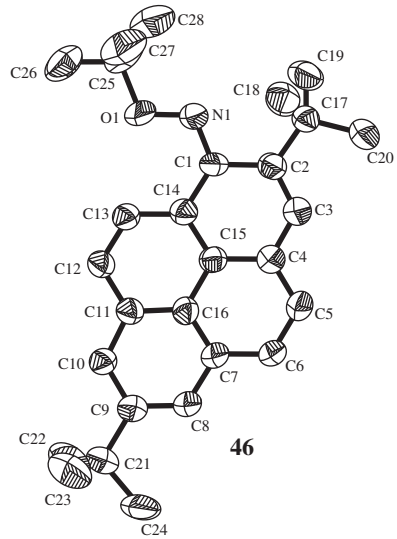
nitroxide radical so stable that reactions can be performed on it (such as the *Grignard reaction* shown with **44**; see **16-24**) without affecting the unpaired electron[280] (the same is true for some of the chlorinated triarylmethyl radicals mentioned above[281]).



Nitroxides have been used to scavenge organic C-centered radicals.[282]

Several nitrogen-containing groups are known to stabilize radicals, and the most effective radical stabilization is via spin delocalization.[283] A number of persistent *N-tert*-butoxy-1-aminopyrenyl radicals such as **45** have been isolated as monomeric radical crystals (see **46**, the X-ray crystal structure of **45**),[284] and monomeric *N*-alkoxyarylaminyls have been isolated.[285] The stability of nitrogen-centered radicals has been discussed.[286]





Reprinted with permission Miura, Y.; Matsuba, N.; Tanaka, R.; Teki, Y.; Takui, T. *J. Org. Chem.* ***2002****, 67*, 8764. Copyright 2002 American Chemical Society.

[280] Neiman, M.B.; Rozantsev, E.G.; Mamedova, Yu.G. *Nature* ***1963***, *200*, 256. See Breuer, E.; Aurich, H.G.; Nielsen, A. *Nitrones*, *Nitronates*, *and Nitroxides*, Wiley, NY, ***1989***, pp. 313–399; Rozantsev, E.G.; Sholle, V.D. *Synthesis* ***1971***, 190, 401.

[281] See Ballester, M.; Veciana, J.; Riera, J.; Castañer, J.; Armet, O.; Rovira, C. *J. Chem. Soc., Chem. Commun.* ***1983***, 982.

[282] Bagryanskaya, E.G.; Marque, S.R.A. *Chem. Rev.* ***2014***, *114*, 5011.

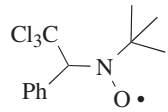
[283] Adam, W.; Ortega Schulte, C M. *J. Org. Chem.* ***2002***, *67*, 4569.

[284] Miura, Y.; Matsuba, N.; Tanaka, R.; Teki, Y.; Takui, T. *J. Org. Chem.* ***2002***, *67*, 8764. For another stable nitroxide radical, see Huang, W.-l.; Chiarelli, R.; Rassat, A. *Tetrahedron Lett.* ***2000***, *41*, 8787.

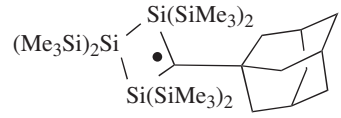
[285] Miura, Y.; Tomimura, T.; Matsuba, N.; Tanaka, R.; Nakatsuji, M.; Teki, Y. *J. Org. Chem.* ***2001***, *66*, 7456. See also Miura, Y.; Muranaka, Y.; Teki, Y. *J. Org. Chem.* ***2006***, *71*, 4786; Miura, Y.; Mu, Y. *Chem. Lett.* ***2005***, *34*, 48.

[286] Hioe, J.; Šakić, D.; Vrčiek, V.; Zipse, H. *Org. Biomol. Chem.* ***2015***, *13*, 157.

α-Trichloromethylbenzyl(*tert*-butyl)aminoxyl (**47**) is extremely stable.[287] In aqueous media it is stable for more than 30 days, and in solution in an aromatic hydrocarbon solvent it has survived for more than 90 days.[290] Although the stable nitroxide radicals have the α carbon blocked to prevent radical formation there, stable nitroxide radicals are also known with hydrogen at the α carbon,[288] and long-lived vinyl nitroxide radicals are known.[289] A stable organic radical lacking resonance stabilization has been prepared (**48**), and its X-ray crystal structure was obtained.[290]



47



48

Dissociation energies (*D* values) of R—H bonds provide a measure of the relative inherent stability of free radicals R.[291] Table 5.4 lists such values.[292] The higher the *D* value, the less stable the radical.

Bond dissociation energies have also been reported for the C—H bond of alkenes and dienes[293] and for the C—H bond in radical precursors XYC—H, where X,Y can be H, alkyl, COOR, COR, SR, CN, NO_2, etc.[294] Bond dissociation energies for the C—O bond in hydroperoxide radicals (ROO•) have also been reported.[295] However, it is noted that basing radical stabilization energy[296] on the difference between the bond dissociation energy (BDE) of CH_3—H, as a reference point, and of R—H has been observed to have shortcomings.[297] The problem is that these values are only applicable to carbon-centered radicals, and the stabilization energies are not transferable and cannot be used to estimate BDE of R—R′, R—R, or any R—X compounds.[300]

There are two possible structures for simple alkyl radicals.[298] They might have sp^2 bonding, in which case the structure would be planar, with the odd electron in a *p* orbital,[299] or the bonding might be sp^3, which would make the structure pyramidal and place the odd

[287] Janzen, E.G.; Chen, G.; Bray, T.M.; Reinke, L.A.; Poyer, J.L.; McCay, P.B. *J. Chem. Soc., Perkin Trans. 2.* ***1993***, 1983.

[288] Reznikov, V.A.; Volodarsky, L.B. *Tetrahedron Lett.* ***1994***, *35*, 2239.

[289] Reznikov, V.A.; Pervukhina, N.V.; Ikorskii, V.N.; Ovcharenko, V.I.; Grand, A. *Chem. Commun.* ***1999***, 539.

[290] Apeloig, Y.; Bravo-Zhivotovskii, D.; Bendikov, M.; Danovich, D.; Botoshansky, M.; Vakulrskaya, T.; Voronkov, M.; Samoilova, R.; Zdravkova, M.; Igonin, V.; Shklover, V.; Struchkov, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 8118.

[291] It has been claimed that relative *D* values do not provide such a measure: Nicholas, A.M. de P.; Arnold, D.R. *Can. J. Chem.* ***1984***, *62*, 1850, 1860.

[292] Except where noted, these values are from Lide, D.R. (ed.), *Handbook of Chemistry and Physics*, 87th ed., CRC Press, Boca Raton, FL, ***2007***, pp. 9-60–9-61. For another list of *D* values, see McMillen, D.F.; Golden, D.M. *Annu. Rev. Phys. Chem.* ***1982***, *33*, 493. See also Holmes, J.L.; Lossing, F.P.; Maccoll, A. *J. Am. Chem. Soc.* ***1988***, *110*, 7339; Holmes, J.L.; Lossing, F.P. *J. Am. Chem. Soc.* ***1988***, *110*, 7343; Roginskii, V.A. *J. Org. Chem. USSR* ***1989***, *25*, 403.

[293] Zhang, X.-M. *J. Org. Chem.* ***1998***, *63*, 1872.

[294] Brocks, J.J.; Beckhaus, H.-D.; Beckwith, A.L.J.; Rüchardt, C. *J. Org. Chem.* ***1998***, *63*, 1935.

[295] Pratt, D.A.; Porter, N.A. *Org. Lett.* ***2003***, *5*, 387.

[296] Wodrich, M.D.; McKee, W.C.; Schleyer, P.v.R. *J. Org. Chem.* ***2011***, *76*, 2439.

[297] Zavitsas, A.A.; Rogers, D.W.; Matsunaga, N. *J. Org. Chem.* ***2010***, *75*, 5697.

[298] See Kaplan, L. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 361–434.

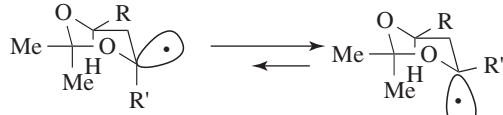
[299] See Mailman, A.; Winter, S.M.; Wong, J.W.L.; Robertson, C.M.; Assoud, A.; Dube, P.A.; Oakley, R.T. *J. Am. Chem. Soc.* ***2015***, *137*, 1044.

TABLE 5.4 D_{298} values for some R—H bonds.[292] Free-radical stability is in the reverse order

R	D_{298}, kcal mol^{-1}	D_{298}, kJ mol^{-1}
Ph•[300]	111	464
CF_3•	107	446
CH_2=CH•	106	444
Cyclopropyl[301]	106	444
Me•	105	438
Et•	100	419
Me_3CCH_2•	100	418
Pr•	100	417
Cl_3C•	96	401
Me_2CH•	96	401
Me_3C•[302]	95.8	401
Cyclohexyl	95.5	400
$PhCH_2$•	88	368
HCO•	87	364
CH_2=CH—CH_2•	86	361

Reprinted with permission from Lide, D.R. (Ed.), *Handbook of Chemistry and Physics*, 87th ed.; CRC Press: Boca Raton, FL, ***2007***, pp. 9-60–9-61. Copyright © 2007, with permission from Taylor & Francis Group LLC.

electron in an sp^3 orbital. ESR spectra of $\bullet CH_3$ and other simple alkyl radicals as well as other evidence indicate that these radicals have planar structures.[303] This is in accord with the known loss of optical activity when a free radical is generated at a stereogenic carbon.[304] In addition, electronic spectra of the $\bullet CH_3$ and $\bullet CD_3$ radicals (generated by flash photolysis) in the gas phase have definitely established that under these conditions the radicals are planar or near-planar.[305] The IR spectra of $\bullet CH_3$ trapped in solid argon led to a similar conclusion.[306] Despite the usual loss of optical activity noted above, asymmetric radicals can be prepared in some cases. For example, asymmetric nitroxide radicals are known.[307] An anomeric effect was observed in alkoxy radical **49**, where the ratio of **49a**:**49b** was 1:1.78.[308]



49a **49b**

[300] For the infrared of a matrix-isolated phenyl radical see Friderichsen, A.V.; Radziszewski, J.G.; Nimlos, M.R.; Winter, P.R.; Dayton, D.C.; David, D.E.; Ellison, G.B. *J. Am. Chem. Soc.* ***2001***, *123*, 1977.

[301] For a review of cyclopropyl radicals, see Walborsky, H.M. *Tetrahedron* ***1981***, *37*, 1625. See also Boche, G.; Walborsky, H.M. *Cyclopropane Derived Reactive Intermediates*, Wiley, NY, ***1990***.

[302] This value is from Gutman, D. *Acc. Chem. Res.* ***1990***, *23*, 375.

[303] See Giese, B.; Beckhaus, H. *Angew. Chem. Int. Ed.* ***1978***, *17*, 594; Ellison, G.B.; Engelking, P.C.; Lineberger, W.C. *J. Am. Chem. Soc.* ***1978***, *100*, 2556. See, however, Paddon-Row, M.N.; Houk, K.N. *J. Am. Chem. Soc.* ***1981***, *103*, 5047.

[304] There are a few exceptions. See Sec. 14.A.iv.

[305] Herzberg, G. *Proc. R. Soc. London*, *Ser. A* ***1961***, *262*, 291. See also Yamada, C.; Hirota, E.; Kawaguchi, K. *J. Chem. Phys.* ***1981***, *75*, 5256.

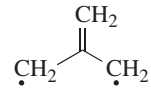
[306] Andrews, L.; Pimentel, G.C. *J. Chem. Phys.* ***1967***, *47*, 3637; Milligan, D.E.; Jacox, M.E. *J. Chem. Phys.* ***1967***, *47*, 5146.

[307] Tamura, R.; Susuki, S.; Azuma, N.; Matsumoto, A.; Todda, F.; Ishii, Y. *J. Org. Chem.* ***1995***, *60*, 6820.

[308] Rychnovsky, S.D.; Powers, J.P.; LePage, T.J. *J. Am. Chem. Soc.* ***1992***, *114*, 8375.

Evidence from studies on bridgehead compounds shows that although a planar configuration is more stable, pyramidal structures are not impossible. In contrast to the situation with carbocations, free radicals have often been generated at bridgeheads, although studies have shown that bridgehead free radicals are less rapidly formed than the corresponding open-chain radicals.[309] The available evidence indicates that *although simple alkyl free radicals prefer a planar, or near-planar shape, the energy difference between a planar and a pyramidal free radical is not great*. However, free radicals in which the carbon is connected to atoms of high electronegativity, e.g., $\bullet CF_3$, prefer a pyramidal shape;[310] increasing the electronegativity increases the deviation from planarity.[311] Cyclopropyl radicals are also pyramidal.[312] Free radicals with resonance are definitely planar, although triphenylmethyl-type radicals are propeller shaped,[313] like the analogous carbocations (Sec. 5.A.i). Radicals possessing simple alkyl substituents attached to the radical carbon (C•) have C(sp^3)–C(sp^3) bonds, and rotation about those bonds is possible. The internal rotation barrier for the *tert*-butyl radical ($Me_3C\bullet$), for example, was estimated to be about 1.4 kcal mol^{-1} (6 kJ mol^{-1}).[314]

A number of diradicals (also called biradicals) are known,[315] and the thermodynamic stability of diradicals has been examined.[316] Orbital phase theory has been applied to the development of a theoretical model of localized 1,3-diradicals, and used to predict the substitution effects on the spin preference and S-T gaps, and to design stable localized carbon-centered 1,3-diradicals.[317] When the unpaired electrons of a diradical are widely separated, for example, as in $\bullet CH_2CH_2CH_2CH_2\bullet$, the species behaves spectrally like two doublets. When they are close enough for interaction or can interact through an unsaturated system (as in trimethylenemethane),[318]



Trimethylenemethane

[309] Danen, W.C.; Tipton, T.J.; Saunders, D.G. *J. Am. Chem. Soc.* ***1971***, *93*, 5186; Fort Jr., R.C.; Hiti, J. *J. Org. Chem.* ***1977***, *42*, 3968; Lomas, J.S. *J. Org. Chem.* ***1987***, *52*, 2627.

[310] Pauling, L. *J. Chem. Phys.* ***1969***, *51*, 2767.

[311] See Chen, K.S.; Tang, D.Y.H.; Montgomery, L.K.; Kochi, J.K. *J. Am. Chem. Soc.* ***1974***, *96*, 2201. For a discussion, see Krusic, P.J.; Bingham, R.C. *J. Am. Chem. Soc.* ***1976***, *98*, 230.

[312] See Deycard, S.; Hughes, L.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1987***, *109*, 4954.

[313] Adrian, F.J. *J. Chem. Phys.* ***1958***, *28*, 608; Andersen, P. *Acta Chem. Scand.* ***1965***, *19*, 629.

[314] Kubota, S.; Matsushita, M.; Shida, T.; Abu-Raqabah, A.; Symons, M.C.R.; Wyatt, J.L. *Bull. Chem. Soc. Jpn.* ***1995***, *68*, 140. See also Cui, Z.-h.; Lischka, H.; Beneberu, H.Z.; Kertesz, M. *J. Am. Chem. Soc.* ***2014***, *136*, 5539.

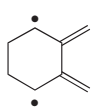
[315] Abe, M. *Chem. Rev.* ***2013***, *113*, 7011. See Borden, W.T. *Diradicals*, Wiley, NY, ***1982***; Johnston, L.J.; Scaiano, J.C. *Chem. Rev.* ***1989***, *89*, 521; Doubleday Jr., C.; Turro, N.J.; Wang, J. *Acc. Chem. Res.* ***1989***, *22*, 199; Borden, W.T.; Davidson, E.R. *Acc. Chem. Res.* ***1981***, *14*, 69. See also Döhnert, D.; Koutecky, J. *J. Am. Chem. Soc.* ***1980***, *102*, 1789. For a series of papers on diradicals, see *Tetrahedron* ***1982***, *38*, 735. For a stable hydrocarbon diradical, see Rajca, A.; Shiraishi, K.; Vale, M.; Han, H.; Rajca, S. *J. Am. Chem. Soc.* ***2005***, *127*, 9014. For a review of quinoidal biradicals, see Kubo, T. *Chem. Lett.* ***2015***, *44*, 111.

[316] Zhang, D. Y.; Borden, W. T. *J. Org. Chem.* ***2002***, *67*, 3989. Abe, M.; Furunaga, H.; Ma, D.; Gagliardi, L.; Bodwell, G.J. *J. Org. Chem.* ***2012***, *77*, 7612.

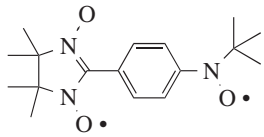
[317] Ma, J.; Ding, Y.; Hattori, K.; Inagaki, S. *J. Org. Chem.* ***2004***, *69*, 4245.

[318] For reviews of trimethylenemethane, see Borden, W.T.; Davidson, E.R. *Ann. Rev. Phys. Chem.* ***1979***, *30*, 125; Bergman, R.G. in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 141–149.

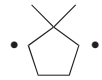
they can have total spin numbers of +1, 0, or −1, since each electron could be either $+\frac{1}{2}$ or $-\frac{1}{2}$. Spectroscopically they are called *triplets*,[319] since each of the three possibilities is represented among the molecules and gives rise to its own spectral peak. In triplet molecules the two unpaired electrons have the same spin. Not all diradicals have a triplet ground state. In 2,3-dimethylelecycohexane-1,4-diyl (**50**), the singlet and triplet states were found to be almost degenerate.[320] Diradicals such as **51** are very stable with a triplet ground state.[321] Diradicals are generally short-lived species. The lifetime of **52** was measured to be < 0.1 ns and other diradicals were found to have lifetimes in the 4–316 ns range.[322] Diradical **53** [3,5-di-*tert*-butyl-3'-(*N*-*tert*-butyl-*N*-aminoxy)-4-oxybiphenyl] was found to have a lifetime of weeks even in the presence of oxygen, and survived brief heating in toluene up to ∼60 °C.[323] Other very stable diradicals are known.[324]



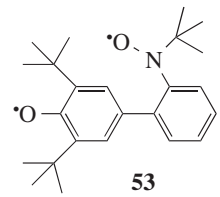
50



51



52



53

Radicals with both unpaired electrons on the same carbon are discussed under carbenes.

1,4-Biradicals are known, and α-carbonyl substituents increase the lifetime of the radical, and negative α-hyperconjugation (Sec. 2.M) has been suggested as the cause.[325]

Triradicals are known.[326]

5.C.ii. The Generation and Fate of Free Radicals[327]

Free radicals are formed from molecules by breaking a bond so that each fragment keeps one electron.[328,329] The energy necessary to break the bond is supplied in one of two ways.

1. *Thermal cleavage*. Subjection of any organic molecule to a high enough temperature in the gas phase results in the formation of free radicals. When the molecule contains

[319] See Turro, N.J. *J. Chem. Educ.* ***1969***, *46*, 2; Wasserman, E.; Hutton, R.S. *Acc. Chem. Res.* ***1977***, *10*, 27; Ichinose, N.; Mizuno, K.; Otsuji, Y.; Caldwell, R.A.; Helms, A.M. *J. Org. Chem.* ***1998***, *63*, 3176.

[320] Matsuda, K.; Iwamura, H. *J. Chem. Soc., Perkin Trans. 2* ***1998***, 1023. Also see Roth, W.R.; Wollweber, D.; Offerhaus, R.; Rekowski, V.; Lenmartz, H.-W.; Sustmann, R.; Müller, W. *Chem. Ber.* ***1993***, *126*, 2701.

[321] Inoue, K.; Iwamura, H. *Angew. Chem. Int. Ed.* ***1995***, *34*, 927. Also see Ulrich, G.; Ziessel, R.; Luneau, D.; Rey, P. *Tetrahedron Lett.* ***1994***, *35*, 1211.

[322] Engel, P.S.; Lowe, K.L. *Tetrahedron Lett.* ***1994***, *35*, 2267.

[323] Liao, Y.; Xie, C.; Lahti, P.M.; Weber, R.T.; Jiang, J.; Barr, D.P. *J. Org. Chem.* ***1999***, *64*, 5176.

[324] Gallagher, N.M.; Bauer, J.J.; Pink, M.; Rajca, S.; Rajca, A. *J. Am. Chem. Soc.* ***2016***, *138*, 9377.

[325] Cai, X.; Cygon, P.; Goldfuss, B.; Griesbeck, A.G.; Heckroth, H.; Fujitsuka, M.; Majima, T. *Chemistry: European J.* ***2006***, *12*, 4662.

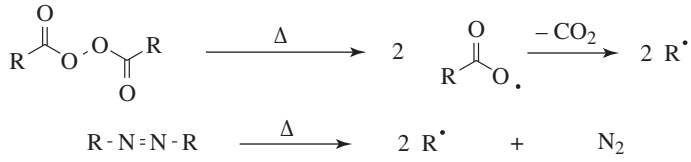
[326] Winkler, M.; Sander, W. *Acc. Chem. Res.* ***2014***, *47*, 31.

[327] See Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***, pp. 267–281; Brown, R.F.C. *Pyrolytic Methods in Organic Chemistry*, Academic Press, NY, ***1980***, pp. 44–61.

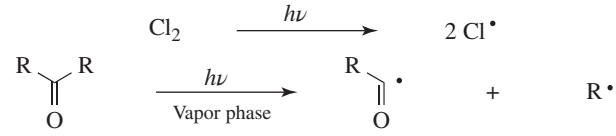
[328] See Harmony, J.A.K. *Methods Free-Radical Chem.* ***1974***, *5*, 101.

[329] See Barker, P.J.; Winter, J.N. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 151–218.

bonds with D values of 20–40 kcal mol^{-1} (80–170 kJ mol^{-1}), cleavage can occur in the liquid phase. Two common examples are cleavage of diacyl peroxides to acyl radicals that decompose to alkyl radicals[330] and cleavage of azo compounds to alkyl radicals.[331]



2. *Photochemical cleavage* (Sec. 7.A.v). The energy of light of 600–300 nm is 48–96 kcal mol^{-1} (200–400 kJ mol^{-1}), which is of the order of magnitude of covalent-bond energies. Typical examples are photochemical cleavage of alkyl halides in the presence of triethylamine,[332] of alcohols in the presence of mercuric oxide and iodine,[333] of alkyl 4-nitrobenzenesulfenates,[334] of chlorine and of ketones:



Photolytic decomposition of *N*-hydroxypyridin-2-thione is a method that generates hydroxyl radicals.[335] A stable dialkylphosphinyl radical has been reported[336] and other phosphinyl radicals are known.[337] Thiyl radicals are useful in organic synthesis.[338] A photoreductive method has been used to generate radicals from epoxides or aziridines.[339] The photochemistry of radicals and biradicals has been reviewed.[340]

Radicals are also formed from other radicals, either by the reaction between a radical and a molecule (which *must* give another radical, since the total number of electrons is

[330] Matsuyama, K.; Sugiura, T.; Minoshima, Y. *J. Org. Chem.* ***1995***, *60*, 5520; Ryzhkov, L.R. *J. Org. Chem.* ***1996***, *61*, 2801. See Howard, J.A. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 235–258; Batt, L.; Liu, M.T.H. in the same volume, pp. 685–710.

[331] See Engel, P.S. *Chem. Rev.* ***1980***, *80*, 99; Adams, J.S.; Burton, K.A.; Andrews, B.K.; Weisman, R.B.; Engel, P.S. *J. Am. Chem. Soc.* ***1986***, *108*, 7935; Schmittel, M.; Rüchardt, C. *J. Am. Chem. Soc.* ***1987***, *109*, 2750.

[332] Cossy, J.; Ranaivosata, J.-L.; Bellosta, V. *Tetrahedron Lett.* ***1994***, *35*, 8161.

[333] Courtneidge, J.L. *Tetrahedron Lett.* ***1992***, *33*, 3053.

[334] Pasto, D.J.; Cottard, F. *Tetrahedron Lett.* ***1994***, *35*, 4303.

[335] Halliwell, B.; Gutteridge, J.M.C. in *Free Radicals in Biology and Medicine*, Oxford University Press, Oxford, ***1999***, pp. 246–350; DeMatteo, M.P.; Poole, J.S.; Shi, X.; Sachdeva, R.; Hatcher, P.G.; Hadad, C.M.; Platz, M.S. *J. Am. Chem. Soc.* ***2005***, *127*, 7094.

[336] Ishida, S.; Hirakawa, F.; Iwamoto, T. *J. Am. Chem. Soc.* ***2011***, *133*, 12968.

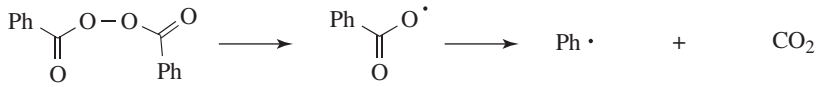
[337] Power, P.P. *Chem. Rev.* ***2003***, *103*, 789; Scheer, M.; Kuntz, C.; Stubenhofer, M.; Linseis, M.; Winter, R.F.; Sierka, M. *Angew. Chem. Int. Ed.* ***2009***, *48*, 2600; Back, O.; Donnadieu, B.; Parameswaran, P.; Frenking, G.; Bertrand, G. *Nat. Chem.* ***2010***, *2*, 369; Kinjo, R.; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed.* ***2010***, *49*, 5930. Also see Ishida, S.; Hirakawa, F.; Iwamoto, T. *Chem. Lett.* ***2015***, *44*, 94.

[338] Dénès, F.; Pichowicz, M.; Povie, G.; Renaud, P. *Chem. Rev.* ***2014***, *114*, 2587.

[339] Larraufie, M-H.; Pellet, R.; Fensterbank, L.; Goddard, J.-P.; Lacôte, E.; Malacria, M.; Ollivier, C. *Angew. Chem. Int. Ed.* ***2011***, *50*, 4463.

[340] Johnston, L.J. *Chem. Rev.* ***1993***, *93*, 251.

odd) or by cleavage of a radical[341] to give another radical, for example, the decomposition of benzoyl peroxide to give the benzoyl radical:



55

Radicals can also be formed by oxidation or reduction, including electrolytic methods. Photoredox catalysts for the generation of carbon-centered radicals has been reviewed.[342]

Reactions of free radicals either give nonradical products (termination reactions) or lead to other radicals, which must usually react further (propagation reactions).[343] The most common termination reactions are simple coupling of similar or different radicals:

$$R\bullet + R'\bullet \longrightarrow R{-}R'$$

Another termination process is disproportionation:[344]

$$2\ CH_3{-}CH_2\bullet \longrightarrow CH_3{-}CH_3 + CH_2{=}CH_2$$

A propagation reaction is one in which a radical reacts to give at least one radical product, which continues the radical reaction sequence.

There are four principal propagation reactions, of which the first two are most common:

1. *Abstraction of another atom or group, usually a hydrogen atom* (also see Chapter 14):

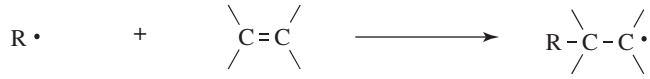
$$R\bullet + R'{-}H \longrightarrow R{-}H + R'\bullet$$

A radical may abstract hydrogen atoms from a second molecule, or by an intramolecular process.[345] A bromine radical (Br•) reacts with an alkane, for example, to give HBr and a carbon radical. This type of reaction is known as hydrogen atom transfer.[346] Water is an excellent hydrogen atom source for many reactions involving metals.[347] Hydrogen abstraction from amines is known.[348] The reduction of a carbon radical with Bu_3SnH is an example of a hydrogen transfer reaction (Sec. 14.A.i). Indeed, carbon radicals react as hydrogen bond acceptors.[349] Other atoms may be removed by a radical via atom transfer reactions. A halogen atom can be

[341] See Costentin, C.; Robert, M.; Saveant, J.-M. *J. Am. Chem. Soc.* ***2003***, *125*, 105.
[342] Goddard, J.P.; Ollivier, C.; Fensterbank, L. *Acc. Chem. Res.* ***2016***, *49*, 1924.
[343] Hancock, A.N.; Schiesser, C.H. *Chem. Commun.* ***2013***, *49*, 9892.
[344] See Pilling, M.J. *Int. J. Chem. Kinet.* ***1989***, *21*, 267; Khudyakov, I.V.; Levin, P.P.; Kuz'min, V.A. *Russ. Chem. Rev.* ***1980***, *49*, 982; Gibian, M.J.; Corley, R.C. *Chem. Rev.* ***1973***, *73*, 441.
[345] For a discussion of kinetic solvent effects, see Gallagher, N.M.; Olankitwanit, A.; Rajca, A. *J. Org. Chem.* ***2015***, *80*, 1291.
[346] Mayer, J.M. *Acc. Chem. Res.* ***2011***, *44*, 36.
[347] Cuerva, J.M.; Campaña, A.G.; Justicia, J.; Rosales, A.; Oller-López, J.L.; Robles, R.; Cárdenas, D.J.; Buñuel, E.; Oltra, J.E. *Angew. Chem. Int. Ed.* ***2006***, *45*, 5522.
[348] Salamone, M.; Martella, R.; Bietti, M. *J. Org. Chem.* ***2012***, *77*, 8556.
[349] Hammerum, S. *J. Am. Chem. Soc.* ***2009***, *131*, 8627.

transferred in some cases, including the transfer of an iodine atom from an aryl iodide to give an aryl radical.[350] Solvent effects play a role in hydrogen atom transfer (hydrogen abstraction), and hydrogen bonding plays a role.[351] Radical reactions have been reported in supercritical carbon dioxide.[352]

2. *Addition to a multiple bond* (see Chapter 15):



The radical formed from an alkene may add to the double bond of a second equivalent of alkene, and so on. This is one of the chief mechanisms for vinyl polymerization.

3. *Decomposition*. This process can be illustrated by the decomposition of the benzoxy radical (see **55**).
4. *Rearrangement*:

This rearrangement is less common than rearrangement of carbocations, but it does occur (although not when R = alkyl or hydrogen; see Chapter 18). Perhaps the best-known rearrangement is that of cyclopropylcarbinyl radicals to a butenyl radical.[353] The rate constant for this rapid ring opening has been measured in certain functionalized cyclopropylcarbinyl radicals by picosecond radical kinetics.[354] Substituent effects on the kinetics of ring opening in substituted cyclopropylcarbinyl radicals have been studied.[355]

"The cyclopropylcarbinyl radical (**56**) has found an important application as a radical clock.[356] Various radical processes can be clocked by the competition of direct reaction with the cyclopropylcarbinyl radical (k_t) and opening of that radical to the 1-buten-4-yl radical (k_r) followed by trapping. Relative rates (k_t/k_r) can be determined from yields of 4-X-but-1-ene and cyclopropylcarbinyl products as a function of the radical trap[357] (X—Y) concentration. Absolute rate constants have been determined for a number of radicals with various radical traps by laser flash photolysis methods.[358] From these absolute rate constants, reasonably accurate values of k_t can be estimated, and with the relative rate (k_t/k_r), a value for k_r can be

[350] Dolenc, D.; Plesniar, B. *J. Org. Chem.* ***2006***, *71*, 8028.
[351] Bietti, M.; Salamone, M. *Org. Lett.* ***2010***, *12*, 3654.
[352] Cormier, P.J.; Clarke, R.M.; McFadden, R.M.L.; Ghandi, K. *J. Am. Chem. Soc.* ***2014***, *136*, 2200.
[353] See Stevenson, J. P.; Jackson, W.F.; Tanko, J.M. *J. Am. Chem. Soc.* ***2002***, *124*, 4271.
[354] See Cooksy, A.L.; King, H.F.; Richardson, W.H. *J. Org. Chem.* ***2003***, *68*, 9441; Tian, F.; Dolbier Jr., W.R. *Org. Lett.* ***2000***, *2*, 835.
[355] Halgren, T.A.; Roberts, J.D.; Horner, J.H.; Martinez, F.N.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.* ***2000***, *122*, 2988.
[356] Newcomb, M.; Choi, S.-Y.; Toy, P.H. *Can. J. Chem.* ***1999***, *77*, 1123; Nevill, S.M.; Pincock, J.A. *Can. J. Chem.* ***1997***, *75*, 232.
[357] See Barton, D.H.R.; Jacob, M.; Peralez, E. *Tetrahedron Lett.* ***1999***, *40*, 9201.
[358] Choi, S.-Y.; Horner, J.H.; Newcomb, M. *J. Org. Chem.* ***2000***, *65*, 4447; Engel, P.S.; He, S.-L.; Banks, J.T.; Ingold, K.U.; Lusztyk, J. *J. Org. Chem.* ***1997***, *62*, 1210.

calculated. From the calibrated radical-clock reaction rate (k_r), rates (k_t) of other competing reactions can be determined from relative rate data (k_t/k_r)."[354]

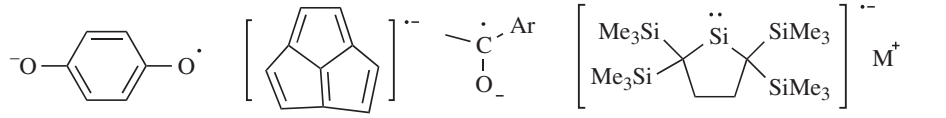
56

Other radical clocks are known.[359] The rearrangement of cubycarbinyl radicals is known.[360]

Free radicals can also be oxidized to carbocations or reduced to carbanions.[361]

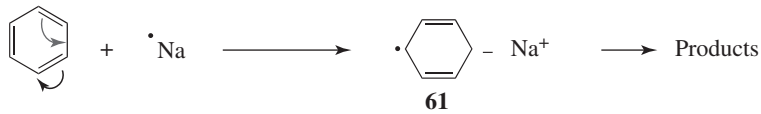
5.C.iii. Radical Ions[362]

Several types of radical anions are known with the unpaired electron, the charge, or both on atoms other than carbon. Examples include semiquinones (**57**),[363] acepentalenes (**58**),[364] ketyls (**59**),[365] and the radical anion of the isolable dialkylsilylene **60**.[366] Radical anions are formed by the reaction of carbene anions with chloromethanes.[367]



57 **58** **59** **60** M = Cs, Rb, Na, Li

A diphosphorus-centered radical anion and diradical dianion has been reported.[368] Reactions in which alkali metals are reducing agents often involve radical anion intermediates (*Birch reduction* for example, reaction **19-36**) that proceed via radical anion **61**.



61

[359] See Leardini, R.; Lucarini, M.; Pedulli, G.F.; Valgimigli, L. *J. Org. Chem.* ***1999***, *64*, 3726; Roschek, Jr., B.; Tallman, K.A.; Rector, C.L.; Gillmore, J.G.; Pratt, D.A.; Punta, C.; Porter, N.A. *J. Org. Chem.* ***2006***, *71*, 3527.

[360] Zhang, Q.-L.; Chen, B.-Z. *J. Phys. Org. Chem.* ***2011***, *24*, 147.

[361] See Khudyakov, I.V.; Kuz'min, V.A. *Russ. Chem. Rev.* ***1978***, *47*, 22.

[362] See Kaiser, E.T.; Kevan, L. *Radical Ions*, Wiley, NY, ***1968***; Gerson, F.; Huber, W. *Acc. Chem. Res.* ***1987***, *20*, 85; Todres, Z.V. *Tetrahedron* ***1985***, *41*, 2771; Holy, N.L.; Marcum, J.D. *Angew. Chem. Int. Ed.* ***1971***, *10*, 115. See Chanon, M.; Rajzmann, M.; Chanon, F. *Tetrahedron* ***1990***, *46*, 6193. For a series of papers on this subject, see *Tetrahedron* ***1986***, *42*, 6097.

[363] See Depew, M.C.; Wan, J.K.S. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 2, Wiley, NY, ***1988***, pp. 963–1018; Huh, C.; Kang, C.H.; Lee, H.W.; Nakamura, H.; Mishima, M.; Tsuno, Y.; Yamataka, H. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 1083.

[364] de Meijere, A.; Gerson, F.; Schreiner, P.R.; Merstetter, P.; Schüngel, F.-M. *Chem. Commun.* ***1999***, 2189.

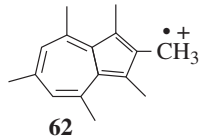
[365] See Russell, G.A. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, ***1989***, pp. 471–512. See Davies, A.G.; Neville, A.G. *J. Chem. Soc., Perkin Trans. 2* ***1992***, 163, 171.

[366] Inoue, S.; Ichinohe, M.; Sekiguchi, A. *J. Am. Chem. Soc.* ***2007***, *129*, 6096.

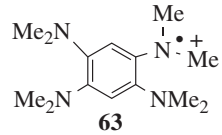
[367] Villano, S.M.; Eyet, N.; Lineberger, W.C.; Bierbaum, V.M. *J. Am. Chem. Soc.* ***2008***, *130*, 7214.

[368] Tan, G.; Li, S.; Chen, S.; Sui, Y.; Zhaom Y.; Wang, X. *J. Am. Chem. Soc.* ***2016***, *138*, 6735.

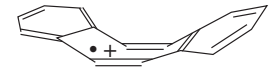
Several types of radical cation are also known.[369] Typical examples include alkyl azulene cation radicals (**62**),[370] trialkyl amine radical cations,[371] 1,2-*bis*-(dialkylamino)benzenes radical cations such as **63**,[372] dimethylsulfonium cation radicals ($Me_2S^{+\bullet}$),[373] *N*-alkyl substituted imine cation radicals ($Ph_2C{=}NEt^{\bullet+}$),[374] dibenzo[*a,e*]cyclooctene (**64**, a nonplanar cation radical),[375] and [*n.n*]paracyclophane cation radicals.[376] A twisted radical cation derived from bicyclo[2.2.2]oct-2-ene has been reported.[377] A stable tetraaryldiphosphine radical cation and dication has been reported.[378] An odd-electron-bonded sulfur radical cation is known.[379]



62



63



64

5.D. CARBENES

5.D.i. Stability and Structure[380]

Carbenes are highly reactive species, and practically all have lifetimes considerably under 1 s. With exceptions noted below (Sec. 5.D.ii), carbenes have been isolated only by entrapment in matrices at low temperatures (77 K or less).[381] The parent species CH_2 is usually called *methylene*, although derivatives are more often named by the carbene nomenclature. Thus CCl_2 is generally known as dichlorocarbene, although it can also be called dichloromethylene.

The two nonbonded electrons of a carbene can be either paired or unpaired. If they are paired, the species is spectrally a *singlet*, while, as seen above (Sec. 5.C.i), two unpaired electrons appear as a *triplet*.[382] An ingenious method of distinguishing between the two

[369] See Roth, H.D. *Acc. Chem. Res.* ***1987***, *20*, 343; Courtneidge, J.L.; Davies, A.G. *Acc. Chem. Res.* ***1987***, *20*, 90; Symons, M.C.R. *Chem. Soc. Rev.* ***1984***, *13*, 393; Marchetti, F.; Pinzino, C.; Zacchini. S.; Guido, G. *Angew. Chem. Int. Ed.* ***2010***, *49*, 5268.

[370] Gerson, F.; Scholz, M.; Hansen, H.-J.; Uebelhart, P. *J. Chem. Soc., Perkin Trans. 2* ***1995***, 215.

[371] de Meijere, A.; Chaplinski, V.; Gerson, F.; Merstetter, P.; Haselbach, E. *J. Org. Chem.* ***1999***, *64*, 6951.

[372] Neugebauer, F.A.; Funk, B.; Staab, H.A. *Tetrahedron Lett.* ***1994***, *35*, 4755. See Stickley, K.R.; Blackstock, S.C. *Tetrahedron Lett.* ***1995***, *36*, 1585.

[373] Dauben, W.G.; Cogen, J.M.; Behar, V.; Schultz, A.G.; Geiss, W.; Taveras, A.G. *Tetrahedron Lett.* ***1992***, *33*, 1713.

[374] Rhodes, C.J.; AgirBas H. *J. Chem. Soc., Perkin Trans. 2* ***1992***, 397.

[375] Gerson, F.; Felder, P.; Schmidlin, R.; Wong, H.N.C. *J. Chem. Soc., Chem. Commun.* ***1994***, 1659.

[376] Wartini, A.R.; Valenzuela, J.; Staab, H.A.; Neugebauer, F.A. *Eur. J. Org. Chem.* ***1998***, 139.

[377] Nelson, S.F.; Reinhardt, L.A.; Tran, H.Q.; Clark, T.; Chen, G.-F.; Pappas, R.S.; Williams, F. *Chem. Eur. J.* ***2002***, *8*, 1074.

[378] Pan, X.; Su, Y.; Chen, X.; Zhao, Y.; Zuo, Y.L.; Wang, X. *J. Am. Chem. Soc.* ***2013***, *135*, 5561.

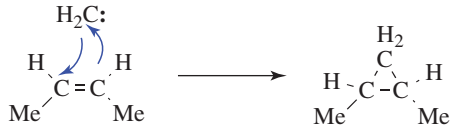
[379] Zhang, S.; Wang, X.; Sui, Y.; Wang, X. *J. Am. Chem. Soc.* ***2014***, *136*, 14666.

[380] See Jones Jr., M.; Moss, R.A. *Carbenes*, 2 Vols, Wiley, NY, ***1973–1975***; Rees, C.W.; Gilchrist, T.L. *Carbenes, Nitrenes, and Arynes*, Nelson, London, ***1969***; Minkin, V.I.; Simkin, B.Ya.; Glukhovtsev, M.N. *Russ. Chem. Rev.* ***1989***, *58*, 622; Moss, R.A.; Jones Jr., M. *React. Intermed. (Wiley)* ***1985***, *3*, 45; Liebman, J.F.; Simons, *J. Mol. Struct. Energ.* ***1986***, *1*, 51.

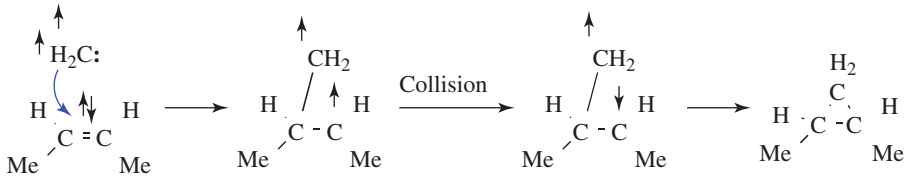
[381] For reviews, see Zuev, P.S.; Nefedov, O.M. *Russ. Chem. Rev.* ***1989***, *58*, 636; Sheridan, R.S. *Org. Photochem.* ***1987***, *8*, 159 (pp. 196–216); Trozzolo, A.M. *Acc. Chem. Res.* ***1968***, *1*, 329.

[382] For a discussion of carbene stability, see Gronert, S.; Keeffe, J.R.; More O'Ferrall, R.A. *J. Am. Chem. Soc.* ***2011***, *133*, 3381.

possibilities was developed by Skell,[383] based on the common reaction of addition of carbenes to double bonds to form cyclopropane derivatives (**15-47**).



If the singlet species adds to *cis*-but-2-ene, the resulting cyclopropane should be the *cis* isomer since the movements of the two pairs of electrons should occur either simultaneously or with one rapidly succeeding another. However, if the attack is by a triplet species, the two unpaired electrons cannot both go into a new covalent bond, since by *Hund's rule* they have parallel spins. So one of the unpaired electrons will form a bond with the electron from the double bond that has the opposite spin, leaving two unpaired electrons that have the same spin and therefore cannot form a bond at once but must wait until, by some collision process, one of the electrons can reverse its spin.[384] During this time, there is free rotation about the C—C bond and a mixture of *cis*- and *trans*-1,2-dimethylcyclopropanes should result.[385]



The results of this type of experiment show that CH_2 itself is usually formed as a singlet species, which can decay to the triplet state, which consequently has a lower energy (molecular-orbital calculations[386] and experimental determinations show that the difference in energy between singlet and triplet CH_2 is ~8–10 kcal mol^{-1} or 33–42 kJ mol^{-1}).[387] However, it is possible to prepare triplet CH_2 directly by a photosensitized decomposition of diazomethane.[388] The CH_2 group is so reactive[389] that it generally reacts as the singlet before it has a chance to decay to the triplet state.[390]

As to other carbenes, some react as triplets, some as singlets, and others as singlets or triplets, depending on how they are generated. There are, however, molecules that generate persistent triplet carbenes.[391] Indeed, remarkably stable diaryl triplet carbenes have been

[383] Skell, P.S. *Tetrahedron* ***1985***, *41*, 1427.

[384] For a discussion of switching the spin state of diphenylcarbene, see Henkel, S.; Costa, P.; Klute, L.; Sokkar, P.; Fernandez-Oliva, M.; Thiel, W.; Sanchez-Garcia, E.; Sander, W. *J. Am. Chem. Soc.* ***2016***, *138*, 1689.

[385] See Closs, G.L. *Top. Stereochem.* ***1968***, *3*, 193 (pp. 203–210); Bethell, D. *Adv. Phys. Org. Chem.* ***1969***, *7*, 153 (p. 194); Hoffmann, R. *J. Am. Chem. Soc.* ***1968***, *90*, 1475.

[386] Richards Jr., C.A.; Kim, S.-J.; Yamaguchi, Y.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1995***, *117*, 10104.

[387] See Lengel, R.K.; Zare, R.N. *J. Am. Chem. Soc.* ***1978***, *100*, 7495; Borden, W.T.; Davidson, E.R. *Ann. Rev. Phys. Chem.* ***1979***, *30*, 125 (pp. 128–134); Leopold, D.G.; Murray, K.K.; Lineberger, W.C. *J. Chem. Phys.* ***1984***, *81*, 1048.

[388] Kopecky, K.R.; Hammond, G.S.; Leermakers, P.A. *J. Am. Chem. Soc.* ***1961***, *83*, 2397; ***1962***, *84*, 1015; Duncan, F.J.; Cvetanović, R.J. *J. Am. Chem. Soc.* ***1962***, *84*, 3593.

[389] For the kinetics of CH_2 reactions, see Laufer, A.H. *Rev. Chem. Intermed.* ***1981***, *4*, 225.

[390] See Turro, N.J.; Cha, Y.; Gould, I.R. *J. Am. Chem. Soc.* ***1987***, *109*, 2101.

[391] Tomioka, H. *Acc. Chem. Res.* ***1997***, *30*, 315; Kirmse, W. *Angew. Chem. Int. Ed.* ***2003***, *42*, 2117; Hirai, K.; Itoh, T.; Tomioka, H. *Chem. Rev.* ***2009***, *109*, 3275.

prepared,[392] and protected diphenylcarbenes are particularly stable.[393] There are also persistent singlet carbenes, although radical fragmentation is a problem.[394]

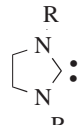
There is a limitation to the use of stereospecificity of addition as a diagnostic test for singlet or triplet carbenes.[395] When carbenes are generated by photolytic methods, they are often in a highly excited singlet state. When they add to the double bond, the addition is stereospecific, but the cyclopropane formed carries excess energy; that is, it is in an excited state. It has been shown that under certain conditions (low pressures in the gas phase) the excited cyclopropane may undergo *cis–trans* isomerization *after* it is formed, so that triplet carbene may seem to be involved although in reality the singlet was present.[396]

Studies of the IR spectrum of CCl_2 trapped at low temperatures in solid argon indicate that the ground state for this species is the singlet.[397] The geometrical structure of triplet methylene can be investigated by ESR measurements,[398] since triplet species are diradicals. Such measurements made on triplet CH_2 trapped in matrices at very low temperatures (4 K) show that triplet CH_2 is a bent molecule, with an angle of ~136°.[399] EPR measurements cannot be made on singlet species, but from electronic spectra of CH_2 formed in flash photolysis[400] of diazomethane it was concluded that singlet CH_2 is also bent, with an angle of about 103°.[401] Singlet CCl_2[316] and CBr_2[402] are also bent, with angles of 100° and 114°, respectively. It has long been known that triplet aryl carbenes are bent.[403]

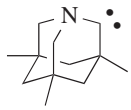
The most common carbenes are $:CH_2$ and $:CCl_2$,[404] but many others have been reported,[405] including heterocyclic carbenes,[406] diboron carbenes,[407] **65** (stabilized by

[392] Woodcock, H.L.; Moran, D.; Schleyer, P.v.R.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***2001***, *123*, 4331.
[393] Itoh, T.; Nakata, Y.; Hirai, K.; Tomioka, H. *J. Am. Chem. Soc.* ***2006***, *128*, 957.
[394] Cattoën, X.; Miqueu, K.; Gornitzka, H.; Bourissou, D.; Bertrand, G. *J. Am. Chem. Soc.* ***2005***, *127*, 3292.
[395] For other methods of distinguishing singlet from triplet carbenes, see Hendrick, M.E.; Jones Jr., M. *Tetrahedron Lett.* ***1978***, 4249; Creary, X. *J. Am. Chem. Soc.* ***1980***, *102*, 1611.
[396] Rabinovitch, B.S.; Tschuikow-Roux, E.; Schlag, E.W. *J. Am. Chem. Soc.* ***1959***, *81*, 1081; Lambert, J.B.; Larson, E.G.; Bosch, R.J. *Tetrahedron Lett.* ***1983***, *24*, 3799.
[397] Andrews, L. *J. Chem. Phys.* ***1968***, *48*, 979.
[398] The technique of spin trapping (Sec. 5.C.i) has been applied to the detection of transient triplet carbenes: Forrester, A.R.; Sadd, J.S. *J. Chem. Soc., Perkin Trans. 2* ***1982***, 1273.
[399] Wasserman, E.; Kuck, V.J.; Hutton, R.S.; Anderson, E.D.; Yager, W.A. *J. Chem. Phys.* ***1971***, *54*, 4120; Bernheim, R.A.; Bernard, H.W.; Wang, P.S.; Wood, L.S.; Skell, P.S. *J. Chem. Phys.* ***1971***, *54*, 3223.
[400] Hahn, F.E. *Angew. Chem. Int. Ed.* ***2006***, *45*, 1348. For imidazopyridine carbenes, see Moss, R.A.; Tian, J.; Sauers, R.R.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* ***2007***, *129*, 10019.
[401] Herzberg, G.; Johns, J.W.C. *J. Chem. Phys.* ***1971***, *54*, 2276 and cited references.
[402] Ivey, R.C.; Schulze, P.D.; Leggett, T.L.; Kohl, D.A. *J. Chem. Phys.* ***1974***, *60*, 3174.
[403] Gilbert, B.C.; Griller, D.; Nazran, A.S. *J. Org. Chem.* ***1985***, *50*, 4738.
[404] For reviews of halocarbenes, see Burton, D.J.; Hahnfeld, J.L. *Fluorine Chem. Rev.* ***1977***, *8*, 119; Margrave, J.L.; Sharp, K.G.; Wilson, P.W. *Fort. Chem. Forsch.* ***1972***, *26*, 1 (pp. 3–13).
[405] See Stang, P.J. *Acc. Chem. Res.* ***1982***, *15*, 348; *Chem. Rev.* ***1978***, *78*, 383; Marchand, A.P.; Brockway, N.M. *Chem. Rev.* ***1974***, *74*, 431; Schuster, G.B. *Adv. Phys. Org. Chem.* ***1986***, *22*, 311. For a review of carbenes with neighboring heteroatoms, see Taylor, K.G. *Tetrahedron* ***1982***, *38*, 2751.
[406] Alcarazo, M.; Roseblade, S.J.; Cowley, A.R.; Fernández, R.; Brown, J.M.; Lassaletta, J.M. *J. Am. Chem. Soc.* ***2005***, *127*, 3290. See also Kassaee, M.Z.; Shakib, F.A.; Momeni, M.R.; Ghambarian, M.; Musavi, S.M. *J. Org. Chem.* ***2010***, *75*, 2539.
[407] Krahulic, K.E.; Enright, G.D.; Parvez, M.; Roesler, R. *J. Am. Chem. Soc.* ***2005***, *127*, 4142.

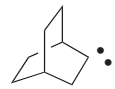
the steric constraints of the ring geometry),[408] **66** (an aminocarbene without π conjugation),[409] bicyclo[2.2.2]octylidene, **67**,[410] alkylidene carbenes, such as **68**,[411] conformationally restricted cyclopropylcarbenes, such as **69**,[412] β-silylcarbenes such as **70**,[413] α-keto carbenes,[414] vinyl carbenes,[415] and chiral carbenoids.[416] Fluoro(phenoxy)carbene is stable for several days if it is generated within the cavity of a hemicarcerand (Sec. 3.C.iii).[417] In the case of **65** (R=Ph),[418] the precursor is a tetraaminoethylene, and when potassium hydride is present to preclude electrophilic catalysis, starting tetraaminoethylenes are recovered unchanged.

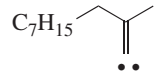


65



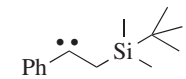
66


67



68


69



70

Flash photolysis of $CHBr_3$ produced the intermediate CBr,[419] which is a *carbyne*.[420]

$$CHBr_3 \xrightarrow[\text{photolysis}]{\text{Flash}} \bullet\bar{C}{-}Br$$

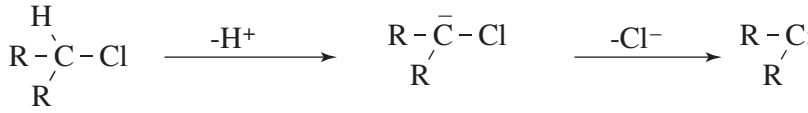
The intermediates CF and CCl were generated similarly from $CHFBr_2$ and $CHClBr_2$, respectively. Triplet acetylenes have been reported as equivalents for 1,2-bicarbenes.[421]

5.D.ii. The Generation and Fate of Carbenes[348,422]

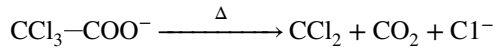
There are two primary methods to form carbenes, although other pathways are also known.[423]

[408] Herrmann, W.A. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1290.
[409] Ye, Q.; Komarov, I. V.; Kirby, A.J.; Jones Jr., M. *J. Org. Chem.* ***2002***, *67*, 9288.
[410] Ye, Q.; Jones Jr., M.; Chen, T.; Shevlin, P.B. *Tetrahedron Lett.* ***2001***, *42*, 6979.
[411] Ohira, S.; Yamasaki, K.; Nozaki, H.; Yamato, M.; Nakayama, M. *Tetrahedron Lett.* ***1995***, *36*, 8843. For dimethylvinylidene carbene see Reed, S.C.; Capitosti, G.J.; Zhu, Z.; Modarelli, D.A. *J. Org. Chem.* ***2001***, *66*, 287. For a review of akylidenecarbenes, see Knorr, R. *Chem. Rev.* ***2004***, *104*, 3795.
[412] Fernamberg, K.; Snoonian, J.R.; Platz, M.S. *Tetrahedron Lett.* ***2001***, *42*, 8761.
[413] Creary, X.; Butchko, M.A. *J. Org. Chem.* ***2002***, *67*, 112.
[414] Bonnichon, F.; Richard, C.; Grabner, G. *Chem. Commun.* ***2001***, 73.
[415] Zuev, P.S.; Sheridan, R.S. *J. Am. Chem. Soc.* ***2004***, *126*, 12220.
[416] Topolski, M.; Duraisamy, M.; Rachoń, J.; Gawronski, J.; Gawronska, K.; Goedken, V.; Walborsky, H.M. *J. Org. Chem.* ***1993***, *58*, 546.
[417] Kirmse, W. *Angew. Chem. Int. Ed.* ***2005***, *44*, 2476.
[418] See Wanzlick, H.-W.; Schikora, E. *Angew. Chem.* ***1960***, *72*, 494.
[419] Ruzsicska, B.P.; Jodhan, A.; Choi, H.K.J.; Strausz, O.P. *J. Am. Chem. Soc.* ***1983***, *105*, 2489.
[420] For a discussion as to whether carbyne radicals really exist in aqueous solution, see Bogoslavsky, B.; Levy, O.; Kotlyar, A.; Salem, M.; Gelman, F.; Bino, A. *Angew. Chem. Int. Ed.* ***2012***, *51*, 90.
[421] Zeidan, T.A.; Kovalenko, S.V.; Manoharan, M.; Clark, R.J.; Ghiviriga, I.; Alabugin, I.V. *J. Am. Chem. Soc.* ***2005***, *127*, 4270.
[422] See Jones Jr., M. *Acc. Chem. Res.* ***1974***, *7*, 415; Kirmse, W. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9; Elsevier, NY, ***1973***, pp. 373–415; Petrosyan, V.E.; Niyazymbetov, M.E. *Russ. Chem. Rev.* ***1989***, *58*, 644.
[423] See Zhang, M.; Moss, R.A.; Thompson, J.; Krogh-Jespersen, K. *J. Org. Chem.* ***2012***, *77*, 843.

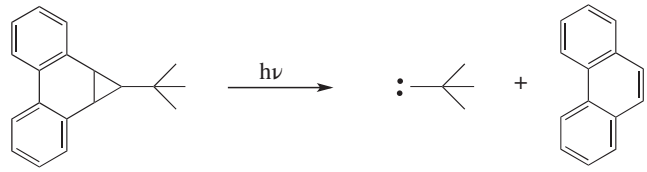
1. In α elimination, a carbon loses a group without its electron pair, usually a proton, and then a group with its electron pair, usually a halide ion:[424]



The most common example is formation of dichlorocarbene by treatment of chloroform with a base (see reaction **10-3**) and geminal alkyl dihalides with Me_3Sn^-,[425] but many other examples are known:

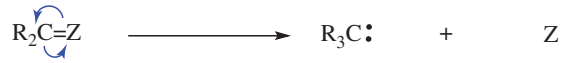


(Ref. 426)

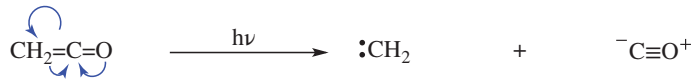


(Ref. 427)

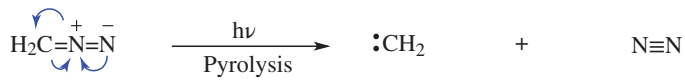
2. Disintegration of compounds containing certain types of double bonds:



The two most important ways of forming $:CH_2$ are the photolysis of ketene:



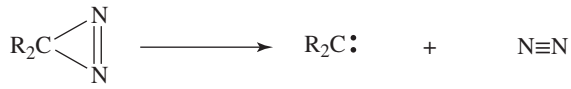
and the isoelectronic decomposition of diazomethane.[428]



Some diazoalkanes decompose to the corresponding carbene.[429] Diazo compounds reacted with CO at atmospheric pressure to give the corresponding ketene.[430] Diazirines[431]

[424] For a review of formation of carbenes in this manner, see Kirmse, W. *Angew. Chem. Int. Ed.* ***1965***, *4*, 1.
[425] Ashby, E.C.; Deshpande, A.K.; Doctorovich, F. *J. Org. Chem.* ***1993***, *58*, 4205. For a preparation from dichlorodiazirine, see Chu, G.; Moss, R.A.; Sauers, R.R. *J. Am. Chem. Soc.* ***2005***, *127*, 14206. Also see Moss, R.A.; Tian, J.; Sauers, R.R.; Ess, D.H.; Houk, K.N.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* ***2007***, *129*, 5167.
[426] Wagner, W.M. *Proc. Chem. Soc.* ***1959***, 229.
[427] Stang, P.J. *Acc. Chem. Res.* ***1982***, *15*, 348; *Chem. Rev.* ***1978***, *78*, 383.
[428] See Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 170–184.
[429] For example, see Mieusset, J.-L.; Brinker, U.H. *J. Org. Chem.* ***2006***, *71*, 6975.
[430] Zhang, Z.; Liu, Y.; Ling, L.; Li, Y.; Dong, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* ***2011***, *133*, 4330.
[431] See Martinu, T.; Dailey, W.P. *J. Org. Chem.* ***2004***, *69*, 7359. For reactions of diazines, see Erbland, G.; Ruch, J.; Goddard, J.-P. *Tetrahedron* ***2016***, *72*, 7826.

(isomeric with diazoalkanes) give carbenes,[432] but arylmethyl radicals have also been generated from diazirines.[433] In a different study, thermolysis of diaryloxydiazirines (**71**) gave the anticipated carbene products, but photolysis gave both carbenes and aryloxy radicals by α scission.[434]



71

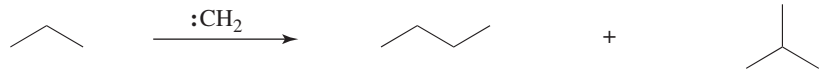
Because most carbenes are so reactive,[435] it is often difficult to prove that they are actually present in a given reaction.[436] The lifetime of formylcarbene was measured to be 0.15–0.73 ns by transient absorption and transient grating spectroscopy in dichloromethane.[437] In many instances where a carbene is *apparently* produced by an α elimination or by disintegration of a double-bond compound there is evidence that no free carbene is actually involved. The neutral term *carbenoid* is used where it is known that a free carbene is not present or in cases where there is doubt. α-Halo organometallic compounds, R_2CXM, are often called *carbenoids* because they readily give α-elimination reactions[438] (e.g., see **12-38**).

The reactions of carbenes are more varied than those of the species previously discussed in this chapter.[439] Solvent effects have been observed in carbene reactions.[440] The selectivity of certain carbenes is influenced by the nature of the solvent.[441] The distribution of rearrangement products (see below) from *tert*-butylcarbene[442] is influenced by changes in solvent.[443] It is known that singlet methylene forms a charge-transfer complex with benzene.[444] Solvent interactions for chlorophenylcarbene and fluorophenylcarbene, however, are weak.[445]

1. Additions to carbon–carbon double bonds have already been mentioned. Carbenes also add to aromatic systems, but the immediate products rearrange, usually with ring enlargement (see **15-61**). Additions of carbenes to other double bonds, such as C=N (**16-46** and **16-48**), and to triple bonds have also been reported.

[432] Liu, M.T.H. *Chemistry of Diazirines*, 2 Vols, CRC Press, Boca Raton, FL, ***1987***. For reviews, see Moss, R.A. *Acc. Chem. Res.* ***2006***, *39*, 267; Liu, M.T.H. *Chem. Soc. Rev.* ***1982***, *11*, 127.
[433] Moss, R.A.; Fu, X. *Org. Lett.* ***2004***, *6*, 3353.
[434] Fede, J.-M.; Jockusch, S.; Lin, N.; Moss, R.A.; Turro, N.J. *Org. Lett.* ***2003***, *5*, 5027.
[435] Moss, R.A.; Krogh-Jespersen, K. *Tetrahedron Lett.* ***2013***, *54*, 4303. Moss, R.A.; Wang, L.; Cang, H.; Krogh-Jespersen, K. *J. Phys. Org. Chem.* ***2017***, *30*, e3555.
[436] Wentrup, C. *Acc. Chem. Res.* ***2011***, *44*, 393.
[437] Toscano, J.P.; Platz, M.S.; Nikolaev, V.; Cao, Y.; Zimmt, M.B. *J. Am. Chem. Soc.* ***1996***, *118*, 3527. See Hanzlová, E.; Navrátil, R.; Čejka, J.; Böhm, S.; Martinů, T. *Org. Lett.* ***2014***, *16*, 852.
[438] For a review, see Nefedov, O.M.; D'yachenko, A.I.; Prokof'ev, A.K. *Russ. Chem. Rev.* ***1977***, *46*, 941.
[439] For a discussion of the nucleophilcity of dichlorocarbene, see Moss, R.A.; Zhang, M.; Krogh-Jespersen, K. *Org. Lett.* ***2009***, *11*, 1947.
[440] Moss, R.A. *J. Phys. Org. Chem.* ***2011***, *24*, 866.
[441] Tomioka, H.; Ozaki, Y.; Izawa, Y. *Tetrahedron* ***1985***, *41*, 4987.
[442] Krogh-Jespersen, K.; Yan, S.; Moss, R.A. *J. Am. Chem. Soc.* ***1999***, *121*, 6269.
[443] Ruck, R.T.; Jones Jr., M. *Tetrahedron Lett.* ***1998***, *39*, 2277.
[444] Khan, M.I.; Goodman, J.L. *J. Am. Chem. Soc.* ***1995***, *117*, 6635.
[445] Sun, Y.; Tippmann, E.M.; Platz, M.S. *Org. Lett.* ***2003***, *5*, 1305.

2. An unusual reaction of carbenes is that of insertion into C—H bonds (**12-21**). Thus $:CH_2$ reacts with methane to give ethane and with propane to give *n*-butane and 2-methylpropane, as shown.

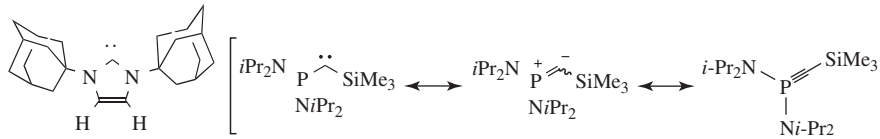


Elimination to give an alkene is a competing side reaction in polar solvents, but this is suppressed in nonpolar solvents.[446] Simple alkyl carbenes, such as this, are not very useful for synthetic purposes, but do illustrate the extreme reactivity of carbene. However, carbenoids generated by rhodium-catalyzed decomposition of diazoalkanes are very useful (see **12-23**) and have been used in a variety of syntheses. Treatment in the liquid phase of an alkane, such as pentane, with carbene formed from the photolysis of diazomethane gives the three possible products in statistical ratios[447] demonstrating that carbene is displaying no selectivity. For many years, it was a generally accepted principle that the lower the selectivity the greater the reactivity; however, this principle is no longer regarded as general because many exceptions have been found.[448] Singlet CH_2 generated by photolysis of diazomethane is probably the most reactive organic species known, but triplet CH_2 is somewhat less reactive, and other carbenes are still less reactive.

The following series of carbenes of decreasing reactivity has been proposed on the basis of discrimination between insertion and addition reactions: CH_2 > HCCOOR > PhCH > BrCH ~ClCH.[449]

Dihalocarbenes generally do not give insertion reactions at all. Insertion of carbenes into other bonds has also been demonstrated, although not insertion into C—C bonds.[450]

Two carbenes that are stable at room temperature have been reported:[451] **72** and **73**. In the absence of oxygen and moisture, **72** exists as stable crystals with a melting point of 240–241 °C.[452] This structure was proved by X-ray crystallography.



72 **73**

3. It would seem that dimerization to form an alkene should be an important reaction of carbenes, but it is not. Generally, the reactivity is so great that the carbene species

[446] Ruck, R.T.; Jones Jr., M. *Tetrahedron Lett.* ***1998***, *39*, 2277.

[447] See Halberstadt, M.L.; McNesby, J.R. *J. Am. Chem. Soc.* ***1967***, *89*, 3417.

[448] See Buncel, E.; Wilson, H. *J. Chem. Educ.* ***1987***, *64*, 475; Johnson, C.D. *Tetrahedron* ***1980***, *36*, 3461; Giese, B. *Angew. Chem. Int. Ed.* ***1977***, *16*, 125; Pross, A. *Adv. Phys. Org. Chem.* ***1977***, *14*, 69. See also Srinivasan, C.; Formosinho, S.J. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 839; Johnson, C.D.; Stratton, B. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 1903. For a group of papers on this subject, see *Isr. J. Chem.* ***1985***, *26*, 303.

[449] Closs, G.L.; Coyle, J.J. *J. Am. Chem. Soc.* ***1965***, *87*, 4270.

[450] See Tomioka, H.; Ozaki, Y.; Izawa, Y. *Tetrahedron* ***1985***, *41*, 4987; Frey, H.M.; Walsh, R.; Watts, I.M. *J. Chem. Soc., Chem. Commun.* ***1989***, 284.

[451] For a discussion, see Regitz, M. *Angew. Chem. Int. Ed.* ***1991***, *30*, 674.

[452] Arduengo III, A.J.; Harlow, R.L.; Kline, M. *J. Am. Chem. Soc.* ***1991***, *113*, 361.

do not have time to find each other and because the dimer generally has so much energy that it dissociates again. Apparent dimerization:

$$R_2C: + R_2C: \longrightarrow R_2C = CR_2$$

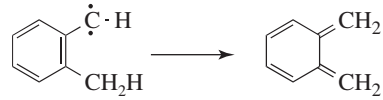
has been observed, but it is likely that the products in many reported instances of "dimerization" do not arise from an actual dimerization of two carbenes but from attack by a carbene on a molecule of a carbene precursor, for example:

$$R_2C: + R_2CN_2 \longrightarrow R_2C = CR_2 + N_2$$

4. Alkylcarbenes can undergo rearrangement, with migration of alkyl or hydrogen.[453] Indeed, these rearrangements are generally so rapid[454] that additions to multiple bonds and insertion reactions, which are so common for CH_2, are seldom encountered with alkyl or dialkyl carbenes. Unlike rearrangement of the species previously encountered in this chapter, most rearrangements of carbenes directly give stable molecules. A carbene intermediate has been suggested for the isomerization of cyclopropane.[455] Some examples of carbene rearrangement are:


(Ref. 456)


(Ref. 457)


(Ref. 458)


(Ref. 459)

[453] See Locatelli, F.; Candy, J.-P.; Didillon, B.; Niccolai, G.P.; Uzio, D.; Basset, J.-M. *J. Am. Chem. Soc.* ***2001***, *123*, 1658; Brown, R.F.C. *Pyrolytic Methods in Organic Chemistry,* Academic Press, NY, ***1980***, pp. 115–163; Wentrup, C. *Adv. Heterocycl. Chem.* ***1981***, *28*, 231; Jones, W.M. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 95–160; Schaefer III, H.F. *Acc. Chem. Res.* ***1979***, *12*, 288; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 457–496.

[454] The activation energy for the 1,2-hydrogen shift has been estimated at 1.1 kcal mol^{-1} (4.5 kJ mol^{-1}), an exceedingly low value: Stevens, I.D.R.; Liu, M.T.H.; Soundararajan, N.; Paike, N. *Tetrahedron Lett.* ***1989***, *30*, 481. Also see Pezacki, J.P.; Couture, P.; Dunn, J.A.; Warkentin, J.; Wood, P.D.; Lusztyk, J.; Ford, F.; Platz, M.S. *J. Org. Chem.* ***1999***, *64*, 4456.

[455] Bettinger, H.F.; Rienstra-Kiracofe, J.C.; Hoffman, B.C.; Schaefer III, H.F.; Baldwin, J.E.; Schleyer, P.v.R. *Chem. Commun.* ***1999***, 1515.

[456] Liu, M.T.H.; Bonneau, R. *J. Am. Chem. Soc.* ***1989***, *111*, 6873; Jackson, J.E.; Soundararajan, N.; White, W.; Liu, M.T.H.; Bonneau, R.; Platz, M.S. *J. Am. Chem. Soc.* ***1989***, *111*, 6874; Ho, G.; Krogh-Jespersen, K.; Moss, R.A.; Shen, S.; Sheridan, R.S.; Subramanian, R. *J. Am. Chem. Soc.* ***1989***, *111*, 6875; LaVilla, J.A.; Goodman, J.L. *J. Am. Chem. Soc.* ***1989***, *111*, 6877; Graves, K.S.; Thamattoor, D.M.; Rablen, P.R. *J. Org. Chem.* ***2011***, *76*, 1584.

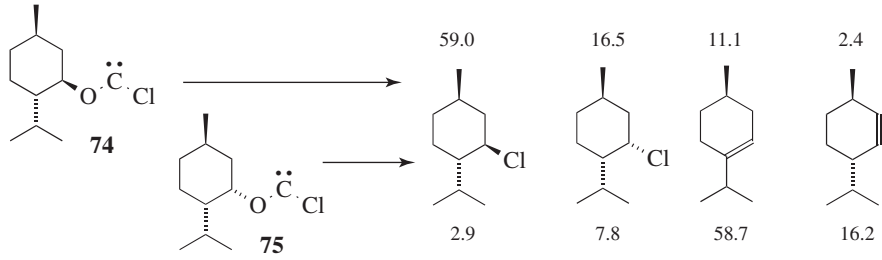
[457] Friedman, L.; Shechter, H. *J. Am. Chem. Soc.* ***1960***, *82*, 1002.

[458] McMahon, R.J.; Chapman, O.L. *J. Am. Chem. Soc.* ***1987***, *109*, 683.

[459] Friedman, L.; Berger, J.G. *J. Am. Chem. Soc.* ***1961***, *83*, 492, 500.

The rearrangement of acylcarbenes to ketenes is called the *Wolff rearrangement* (reaction **18-8**). A few rearrangements in which carbenes rearrange to other carbenes are also known.[460] Of course, the new carbene must stabilize itself in one of the ways that have been mentioned.

5. The fragmentation reactions of alicyclic oxychlorocarbenes such as **74** and **75**[461] give substitution and elimination products. Menthyloxychlorocarbene, **74**, gave primarily the substitution product, whereas neomenthyloxychlorocarbene, **75**, gave primarily the elimination product, as shown. In this case, the substitution product is likely due to rearrangement of the chlorocarbene.[462]



It is known that fragmentation of nortricyclyloxychlorocarbene in pentane occurs by an S_Ni-like process to give nortricyclyl chloride.[463] In more polar solvents, fragmentation leads to nortricyclyl cation–chloride anion pair that gives nortricyclyl chloride and a small amount of *exo*-2-norbornenyl chloride. Fragmentation can also lead to radicals.[464]

6. Triplet carbenes can abstract hydrogen or other atoms to give free radicals, for example:

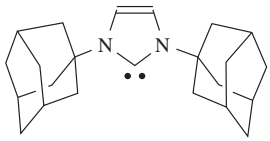
This is not surprising, since triplet carbenes are free radicals. But singlet carbenes[465] can also give this reaction, although in this case only halogen atoms are abstracted, not hydrogen.[466]

5.D.iii. *N*-Heterocyclic Carbenes (NHCs)[467]

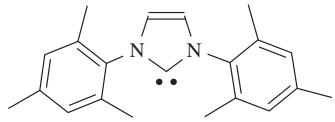
N-Heterocyclic carbenes (NHCs) were first reported by Arduengo and co-workers[468] for the synthesis of NHC **76**. NHCs are electron-rich, and are neutral, donor ligands[469] for transition metals since they form very strong bonds to most, and are considered to be

[460] For a review, see Jones, W.M. *Acc. Chem. Res.* ***1977***, *10*, 353.
[461] Moss, R.A.; Johnson, L.A.; Kacprzynski, M.; Sauers, R.R. *J. Org. Chem.* ***2003***, *68*, 5114.
[462] See Yao, G.; Rempala, P.; Bashore, C.; Sheridan, R.S. *Tetrahedron Lett.* ***1999***, *40*, 17.
[463] Moss, R.A.; Ma, Y.; Sauers, R.R.; Madni, M. *J. Org. Chem.* ***2004***, *69*, 3628.
[464] Mekley, N.; El-Saidi, M.; Warkentin, J. *Can. J. Chem.* ***2000***, *78*, 356.
[465] Vignolle, J.; Catton, X.; Bourissou, D. *Chem. Rev.* ***2009***, *109*, 3333.
[466] Roth, H.D. *J. Am. Chem. Soc.* ***1971***, *93*, 1527, 4935, *Acc. Chem. Res.* ***1977***, *10*, 85.
[467] *N-Heterocyclic Carbenes. Effective Tools for Organometallic Synthesis* Nolan, S.P. (ed.) Wiley-VCH, Weinheim, ***2014***.
[468] Arduengo III, A.J.; Harlow, R.L.; Kline, M. *J. Am. Chem. Soc.* ***1991***, *113*, 361.
[469] Ramsden, C.A.; Oziminski, W.P. *J. Org. Chem.* ***2016***, *81*, 10295.

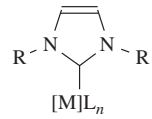
stronger ligands than phosphines. There are applications in important organic transformations, including their use as ligands for transition metals (see **77**) and as organocatalysts (see **78**).[470] Water plays an important role.[471] A typical example is the dimsyl MHC, **79**.[472]



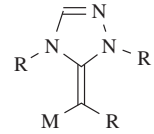
76



77



78



79

There is a discussion on the immobilization of NHC compounds.[473] The influence of *N*-substituents on the nucleophilicity and Lewis basicity has been discussed.[474] The stability, nucleophilicity, and basicity of NHCs has been discussed.[475] There is a computational study for saturated five-membered ring HNCs.[476] Continuous flow techniques (Sec. 7.D) have been applied to the generation and organocatalysts activity of *N*-heterocyclic carbenes.[477]

N-Heterocyclic carbenes play a role as stabilizing ligands for palladium oxidation reactions.[478] They have been used for allylic alkylation (**10-58**),[479] in the Heck reaction (**13-13**),[480] the arylation of carbonyl compounds,[481] reactions of homoenolates (Sec. 5.B-1; **10-68**),[482] for transesterification reactions (**16-63**),[483] and Ru complexes are important catalysts in alkene metathesis (**18-37**).[484] Enantioselective organic transformations are being examined.[485]

[470] Hopkinson, M.N.; Richter, C.; Schedler, M.; Glorius, F. *Nature, Nature Res.* ***2014***, *510*, 485; Nolan, S.P. *N-Heterocyclic Carbenes in Synthesis*, Wiley-VCH, Weinheim, ***2006***, pp. 1–304; Glorius, F. *N-Heterocyclic Carbenes in Transition Metal Catalysis; Topics in Organometallic Chemistry*, Springer-Verlag, Berlin/Heidelberg, ***2006***, Vol. 21, pp. 1–218.

[471] Levin, E.; Ivry, E.; Diesendruck, C.E.; Lemcoff, N.G. *Chem. Rev.* ***2015***, *115*, 4607.

[472] Arduengo, III, A.J.; Dias, H.V.R.; Harlow, R.L.; Kline, M. *J. Am. Chem. Soc.* ***1992***, *114*, 5530.

[473] Zhong, R.; Lindhorst, A.C.; Groche, F.J.; Kühn, F.E. *Chem. Rev.* ***2017***, *117*, 1970.

[474] Levens, A.; An, F.; Breugst, M.; Mayr, H.; Lupton, D.W. *Org. Lett.* ***2016***, *18*, 3566; Also see Maji, B.; Breugst, M.; Mayr, H. *Angew. Chem. Int. Ed.* ***2011***, *50*, 6915.

[475] Azizi, Z.; Ghambarian, M.; Rezaei, M.A.; Ghashghaee, M. *Aust. J. Chem.* ***2015***, *68*, 1438.

[476] Ghambarian, M.; Azizi, Z.; Ghashghaee, M. *Chem. Lett.* ***2015***, *44*, 1586.

[477] Di Marco, L.; Hans, M.; Delaude, L.; Monbaliu, J.-C.M. *Chem. Eur. J.* ***2016***, *22*, 4508.

[478] Stahl, S.S; Thorman, J.L.; Nelson, R.C.; Kozee, M.A. *J. Am. Chem. Soc.* ***2001***, *123*, 7188; Konnick M.M.; Guzei, I.A.; Stahl, S.S. *J. Am. Chem. Soc.* ***2004***, *126*, 10212; Yamasita, M.; Goto, K.; Kawashima, T. *J. Am. Chem. Soc.* ***2005***, *127*, 7294. For a discussion of synthetic routes, see Benhamou, L.; Chardon, E.; Lavigne, G.; Bellemin-Laponnaz, S.; César, V. *Chem. Rev.* ***2011***, *111*, 2705.

[479] Sato, Y.; Yoshiro, T.; Mori, M. *Org. Lett.* ***2003***, *5*, 31; Bonnet, L.G.; Douthwaite, R.E.; Kariuki, B.M. *Organometallics* ***2003***, *22*, 4187.

[480] Herrmann, W.A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G.R. *Angew. Chem. Int. Ed.* ***1995***, *34*, 2371.

[481] Navarro, O.; Marion, N.; Scott, N.M.; Gonzalez, J.; Amoroso, D.; Bell, A.; Nolan, S.P. *Tetrahedron* ***2005***, *61*, 9716.

[482] Sohn, S.S.; Bode, J.W. *Org. Lett.* ***2005***, *7*, 3873; Chan, A.; Scheidt, K.A. *Org. Lett.* ***2005***, *7*, 905.

[483] Grasa, G.A.; Kissling, R.M.; Nolan, S.P. *Org. Lett.* ***2002***, *4*, 3583; Nyce, G.W.; Lamboy, J.A.; Connor, E.F.; Waymouth, R.M.; Heddrick, J.L. *Org. Lett.* ***2002***, *4*, 3587.

[484] Nguyen, S.T.; Johnson, L.K.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* ***1992***, *114*, 3974; Nguyen, S.T.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* ***1993***, *115*, 9858; Schwab, P.; France, M.B.; Grubbs, R.H.; Ziller, J.W. *Angew. Chem. Int. Ed. Engl.* ***1995***, *34*, 2039; Belderrain, T.R.; Grubbs, R.H. *Organometallics* ***1997***, *16*, 4001; Wilhelm, T.E.; Belderrain, T.R.; Brown, S.N.; Grubbs, R.H. *Organometallics* ***1997***, *16*, 3867; Huang, J.; Stevens, E.D.; Nolan, S.P.; Petersen, L. *J. Am. Chem. Soc.* ***1999***, *121*, 2674; Scholl, M.; Ding, S.; Lee, C.W.; Grubbs, R.H. *Org. Lett.* ***1999***, *1*, 953.

[485] Patil, N.T. *Angew. Chem. Int. Ed.* ***2011***, *50*, 1759. See Strand, R.B.; Helgerud, T.; Solvang, T.; Dolva, A.; Sperger, C.A.; Fiksdahl, A. *Tetrahedron: Asymmetry* ***2012***, *23*, 1350; Zhang, J.-L.; Chen, L.-A.; Xu, R.-B.; Wang, C.-F.; Ruan, Y.-P.; Wang, A.-E.; Huang, P.-Q. *Tetrahedron: Asymmetry* ***2013***, *24*, 492.

5.E. NITRENES

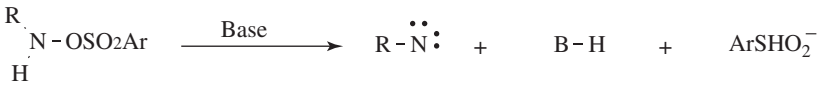
Nitrenes,[486] R—N, are the nitrogen analogs of carbenes, and most of the comments about carbenes also apply to them. Nitrenes are too reactive for isolation under ordinary conditions,[487] although *ab initio* calculations show that nitrenes are more stable than carbenes with an enthalpy difference of 25–26 kcal mol^{-1} (104.7–108.8 kJ mol^{-1}).[488] Alkyl nitrenes have been isolated by trapping in matrices at 4 K,[489] while aryl nitrenes, which are less reactive, can be trapped at 77 K.[490] The ground state of NH, and probably of most nitrenes,[491] is a triplet, although nitrenes can be generated in both triplet[492] and singlet states.

Singlet Triplet

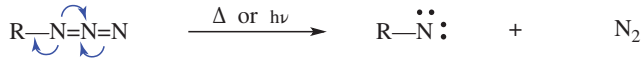
A quartet ground state nitreno radical has been reported.[493] In additions of EtOOC—N to C=C double bonds two species are involved, one of which adds in a stereospecific manner and the other not. By analogy with Skell's proposal involving carbenes (Sec. 5.D.i) these are taken to be the singlet and triplet species, respectively.[494]

The two principal means of generating nitrenes are analogous to those used to form carbenes.

1. *Elimination*. An example is



2. *Breakdown of certain double-bond compounds*. The most common method of forming nitrenes is photolytic or thermal decomposition of azides,[495]



[486] See Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, ***1984***; Lwowski, W. *React. Intermed. (Wiley)* ***1985***, *3*, 305; ***1981***, *2*, 315; ***1978***, *1*, 197; Abramovitch, R.A. in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 127–192; Kuznetsov, M.A.; Ioffe, B.V. *Russ. Chem. Rev.* ***1989***, *58*, 732 (*N*- and *O*-nitrenes); Meth-Cohn, O. *Acc. Chem. Res.* ***1987***, *20*, 18 (oxycarbonylnitrenes); Abramovitch, R.A.; Sutherland, R.G. *Fortsch. Chem. Forsch.* ***1970***, *16*, 1 (sulfonyl nitrenes); Ioffe, B.V.; Kuznetsov, M.A. *Russ. Chem. Rev.* ***1972***, *41*, 131 (*N*-nitrenes).

[487] McClelland, R.A. *Tetrahedron* ***1996***, *52*, 6823.

[488] Kemnitz, C.R.; Karney, W.L.; Borden, W.T. *J. Am. Chem. Soc.* ***1998***, *120*, 3499.

[489] Wasserman, E.; Smolinsky, G.; Yager, W.A. *J. Am. Chem. Soc.* ***1964***, *86*, 3166. See Carrick, P.G.; Brazier, C.R.; Bernath, P.F.; Engelking, P.C. *J. Am. Chem. Soc.* ***1987***, *109*, 5100.

[490] For a review, see Sheridan, R.S. *Org. Photochem.* ***1987***, *8*, 159 (pp. 159–248).

[491] See Sigman, M.E.; Autrey, T.; Schuster, G.B. *J. Am. Chem. Soc.* ***1988***, *110*, 4297.

[492] See Singh, P.N.D.; Mandel, S.M.; Robinson, R.M.; Zhu, Z.; Franz, R.; Ault, B.S.; Gudmundsdottir, A.D. *J. Org. Chem.* ***2003***, *68*, 7951.

[493] Sander, W.; Grote, D.; Kossmann, S.; Neese, F. *J. Am. Chem. Soc.* ***2008***, *130*, 4396.

[494] Mishra, A.; Rice, S.N.; Lwowski, W. *J. Org. Chem.* ***1968***, *33*, 481.

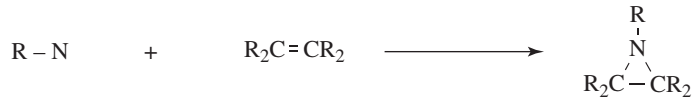
[495] See Dyall, L.K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement D*, pt. 1, Wiley, NY, ***1983***, pp. 287–320; Dürr, H.; Kober, H. *Top. Curr. Chem.* ***1976***, *66*, 89; L'Abbé, G. *Chem. Rev.* ***1969***, *69*, 345.

The unsubstituted nitrene NH was generated by photolysis of or by electric discharge through NH_3, N_2H_4, or HN_3.

The reactions of nitrenes are also similar to those of carbenes.[496] As in that case, many reactions in which nitrene intermediates are suspected probably do not involve free nitrenes. It is often very difficult to obtain proof in any given case that a free nitrene is or is not an intermediate.

1. *Insertion* (see reaction **12-13**). Nitrenes, especially acyl nitrenes and sulfonyl nitrenes, can insert into C—H and certain other bonds, for example,

2. *Addition to C=C bonds* (see reaction **15-50**):

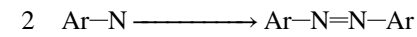


3. *Rearrangements*.[453] Alkyl nitrenes do not generally give either of the two preceding reactions because rearrangement is more rapid, for example,

Such rearrangements are so rapid that it is usually difficult to exclude the possibility that a free nitrene was never present at all, i.e., that migration takes place at the same time that the nitrene is formed[497] (see **18-12**). However, the rearrangement of naphthylnitrenes to novel bond-shift isomers has been reported.[498]

4. *Abstraction*, for example,

5. *Dimerization*. One of the principal reactions of NH is dimerization to diimide N_2H_2. Azobenzenes are often obtained in reactions where aryl nitrenes are implicated:[499]

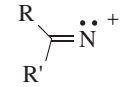


It would thus seem that dimerization is more important for nitrenes than it is for carbenes, but again it has not been proven that free nitrenes are actually involved.

[496] See Subbaraj, A.; Subba Rao, O.; Lwowski, W. *J. Org. Chem.* ***1989***, *54*, 3945.
[497] See Abramovitch, R.A.; Kyba, E.P. *J. Am. Chem. Soc.* ***1971***, *93*, 1537.
[498] Maltsev, A.; Bally, T.; Tsao, M.-L.; Platz, M.S.; Kuhn, A.; Vosswinkel, M.; Wentrup, C. *J. Am. Chem. Soc.* ***2004***, *126*, 237.
[499] See, for example, Leyva, E.; Platz, M.S.; Persy, G.; Wirz, J. *J. Am. Chem. Soc.* ***1986***, *108*, 3783.

At least two types of *nitrenium ions*,[500] the nitrogen analogs of carbocations, can exist as intermediates, although much less work has been done in this area than on carbocations. In one type (**80**) the nitrogen is bonded to two atoms (R or R' can be H)[501] and in the other (**81**) to only one atom.[502]

80



81

When R=H in **80** the species is a protonated nitrene. Like carbenes and nitrenes, nitrenium ions can exist in singlet or triplet states.[503]

[500] Novak, M.; Rajagopal, S. *Adv. Phys. Org. Chem.* ***2001***, *36*, 167; Falvey, D.E. in Moss, R.A.; Platz, M.S.; Jones, Jr., M. *Reactive Intermediate Chemistry*, Wiley-Interscience, Hoboken, NJ, ***2004***, Vol. 1, pp. 593–650.

[501] Winter, A.H.; Falvey, D.E.; Cramer, C.J. *J. Am. Chem. Soc.* ***2004***, *126*, 9661.

[502] See Abramovitch, R.A.; Jeyaraman, R. in Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, ***1984***, pp. 297–357; Gassman, P.G. *Acc. Chem. Res.* ***1970***, *3*, 26; Lansbury, P.T. in Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***, pp. 405–419.

[503] Gassman, P.G.; Cryberg, R.L. *J. Am. Chem. Soc.* ***1969***, *91*, 5176.

CHAPTER 6

Mechanisms and Methods of Determining Them

A mechanism is the actual process by which a reaction takes place: which bonds are broken, in what order, how many steps are involved, the relative rate of each step, and so on. In order to state a mechanism completely, the positions of all atoms should be specified, including those in solvent molecules, and the energy of the system at every point in the process. A proposed mechanism must fit all the facts available. It is always subject to change as new facts are discovered. The usual course is that the gross features of a mechanism are the first to be known and then increasing attention is paid to finer details. The tendency is always to probe more deeply, to get more detailed descriptions.

Although for most reactions gross mechanisms can be written today with a good degree of assurance, no mechanism is known completely.[1] There is much about the fine details that is still puzzling, and for some reactions even the gross mechanism is not yet clear. The problems involved are difficult because there are so many variables. Many examples are known where reactions proceed by different mechanisms under different conditions. In some cases there are several proposed mechanisms, each of which completely explains all the data.

6.A. TYPES OF MECHANISM

In most reactions of organic compounds one or more covalent bonds are broken. Organic mechanisms may be divided into three basic types, depending on how the bonds break.

1. If a bond breaks in such a way that both electrons remain with one fragment, the mechanism is called *heterolytic*. Such reactions do not necessarily involve ionic intermediates, although they often do. The important thing is that the electrons are never unpaired. It is convenient to call one reactant the *attacking reagent* and the other the *substrate*. In other words, such a process usually involves one fragment attacking (donating electrons) to another fragment, the substrate. In this book, the substrate is always designated as that molecule that supplies carbon to the new bond. When C—C bonds are formed via heterolytic reactions, the reagent generally brings

[1] *Perspectives on Structure and Mechanism in Organic Chemistry*, Carroll, F.A., Wiley, ***2010***; *Arrow-Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms*, Levy, D.E., Wiley-Interscience, ***2008***; *Guidebook to Mechanism in Organic Chemistry*, 6th ed., Sykes, P., Prentice Hall, ***1996***.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

a pair of electrons to the substrate or takes a pair of electrons from it.[2] A reagent that brings an electron pair is called a *nucleophile* and the reaction is *nucleophilic*. A reagent that takes an electron pair is called an *electrophile* and the reaction is *electrophilic*. For a reaction in which the substrate molecule becomes cleaved, part of it (the part not containing the carbon) is usually called the *leaving group*. A leaving group that carries away an electron pair is called a *nucleofuge*. If it comes away without the electron pair, it is called an *electrofuge* (Sec. 5.A.2).

2. If a bond breaks in such a way that each fragment gets one electron, free radicals are formed and such reactions are said to take place by *homolytic* or *free-radical mechanisms*.
3. It would seem that all bonds must break in one of the two ways previously noted. But there is a third type of mechanism in which electrons (usually six, but sometimes some other number) move in a closed ring. There are no intermediates, ions, or free radicals, and it is impossible to say whether the electrons are paired or unpaired. Reactions with this type of mechanism are called *pericyclic*[3] (**15-54** to **15-57** and **18-29** to **18-33**).

Examples of all three types of mechanism are given in the next section.

6.B. TYPES OF REACTION

The number and range of organic reactions is so great as to seem bewildering, but actually almost all of them can be fitted into just six categories. In the description of the six types that follows, the immediate products are shown, although in many cases they then react with something else. All the species are shown without charges, since differently charged reactants can undergo analogous changes.[4] The descriptions given here are purely for the purpose of classification and comparison. All are discussed in detail in Part 2 of this book.

1. *Substitutions*. If heterolytic, these reactions can be classified as nucleophilic or electrophilic, depending on which reactant is designated as the substrate and which as the attacking reagent. Very often Y must first be formed by a previous bond cleavage.
   a. Nucleophilic substitution (Chapters 10 and 13).

   b. Electrophilic substitution (Chapters 11 and 12).

[2] For a discussion of electron flow in reaction mechanism, see Knizia, G.; Klein, J.E.M.N. *Angew. Chem. Int. Ed.* ***2015***, *54*, 5518.

[3] For a classification of pericyclic reactions, see Hendrickson, J.B. *Angew. Chem. Int. Ed.* ***1974***, *13*, 47. Also see Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, ***1999***.

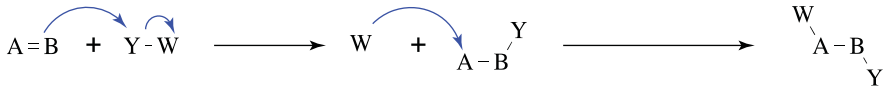
[4] A switch of reaction pathway can be induced by solid support and ultrasound: see Doan, T.L.H.; Le, T.N. *Synth. Commun.* ***2012***, *42*, 337. Steric factors play a role in the direction of reactions: see Shklyaev, Yu.V.; Stryapunina, O.G.; Maiorova, O.A. *Russ. J. Org. Chem.* ***2011***, *47*, 1236.

c. Free-radical substitution (Chapter 14).

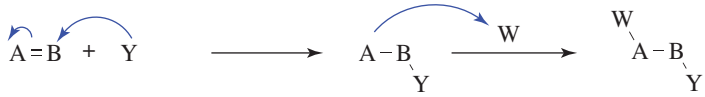
In free-radical substitution, Y• is usually produced by a previous free-radical cleavage, and X• goes on to react further.

2. *Additions to double or triple bonds* (Chapters 15 and 16). These reactions can take place by all three of the mechanistic possibilities.

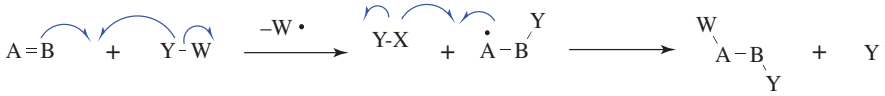
a. Electrophilic addition (heterolytic).



b. Nucleophilic addition (heterolytic).



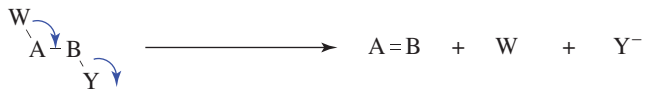
c. Free-radical addition (homolytic).



d. Simultaneous addition (pericyclic).

The examples show Y and W coming from the same molecule, but very often (except in simultaneous addition) they come from different molecules, as illustrated in part b. Cleavage of the Y—W bond may occur at the same time that Y is bonding to B, but the cleavage may also occur earlier.

3. β *elimination* (Chapter 17).



These reactions can take place by either heterolytic or pericyclic mechanisms. Examples of the latter are shown in Sec. 17.C.i. Free-radical β eliminations are extremely rare. In heterolytic eliminations, W and X may or may not leave simultaneously and may or may not combine afterwards.

4. *Rearrangement* (Chapter 18). Many rearrangements involve migration of an atom or group from one atom to another. There are three types, depending on how many electrons the migrating atom or group carries with it.
   a. Migration with electron pair (nucleophilic; common).

   b. Migration with one electron (free-radical; rare).

   c. Migration without electrons (electrophilic; rare).

   The generic examples show 1,2 rearrangements, in which the migrating group moves to the adjacent atom. These are the most common, although longer rearrangements are also possible. There are also some rearrangements that do not involve simple migration at all, but rather migration across a π framework (see Chapter 18). Some of the latter involve pericyclic mechanisms.
5. *Oxidation and reduction* (Chapter 19). Many oxidation and reduction reactions fall naturally into one of the four types mentioned above, but many others do not. For a description of oxidation–reduction mechanistic types, see Sec. 19.A.
6. *Combinations of the above*. Note that arrows[5] are used to show movement of *electrons*. An arrow always follows the motion of electrons and never of a nucleus or anything else (it is understood that the rest of the molecule follows the electrons). Ordinary arrows (double-headed) follow electron pairs, while single-headed arrows follow unpaired electrons. Double-headed arrows are also used in pericyclic reactions for convenience, but in these reactions how or in which direction the electrons are moving is usually unknown.

While not mentioned here as a distinct category, it must be said that many reactions, including some examples of types 1–6 are actually acid–base reactions. In other cases, an acid–base reaction initiates the process or sometimes ends the process. In type 2a, for example, if Y = H and this is an acid–base reaction in which the π bond is the base and the proton is the acid. If W = H in type 3a, then the elimination process begins with an acid–base reaction in which a base donates two electrons to H (= W). In type 2b, if A donates electrons to W and W = H, this is another example of an acid–base reaction. Always be mindful of the acid–base properties of reactions.

Many, if not most, of the reactions noted above are subject to modification of the reactivity by the introduction of π bonds. Most reactions involve the transfer of two electrons to

[5] See Williams, R.V.; Shaffer, A.A. *Can. J. Chem.* ***2017***, *95*, 334.

make or break a bond. The presence of two electrons in a π bond allows this two-electron transfer process to proceed through the intervening atoms. In effect, the reactivity of a given center is extended by the presence of π bonds. This is the concept of *vinylogy*: *the extension of points of reactivity by intervening π bonds*. In other words, if a system X—C1—C2 undergoes a reaction at C2 with loss of X from C1, X—C1—C2 = C3—C4 may undergo reaction at C4. Reaction at C4 initiates electron transfer via the π bond that is extended to C1 for loss of X. Several examples of this type of reaction will be presented in later chapters.

6.C. THERMODYNAMIC REQUIREMENTS FOR REACTION

In order for a reaction to take place spontaneously, the free energy of the products must be lower than the free energy of the reactants; that is, ΔG must be negative. Reactions can go the other way, of course, but only if free energy is added. Like water on the surface of the earth, which naturally flows only downhill and never uphill, molecules seek the lowest possible potential energy. Free energy is made up of two components, enthalpy H and entropy S. These quantities are related by the equation:

$$\Delta G = \Delta H - T\Delta S$$

The enthalpy change in a reaction is essentially the difference in bond energies (including resonance, strain,[6] and solvation energies) between the reactants and the products. The enthalpy change can be calculated by totaling the bond energies of all the bonds broken, subtracting from this the total of the bond energies of all the bonds formed, and adding any changes in resonance, strain, or solvation energies. Entropy changes are quite different, and refer to the disorder or randomness of the system. The lower the order in a system, the greater the entropy. The preferred conditions in nature are *low* enthalpy and *high* entropy, and in reacting systems, enthalpy spontaneously decreases while entropy spontaneously increases.

For many reactions entropy effects are small and it is the enthalpy that mainly determines whether the reaction can take place spontaneously. However, entropy is important in certain processes and can sometimes dominate enthalpy. Several examples will be discussed.

1. In general, liquids have lower entropies than gases, since the molecules of gas have much more freedom and randomness. Solids, of course, have still lower entropies. Any reaction in which the reactants are all liquids and one or more of the products is a gas is therefore thermodynamically favored by the increased entropy; the equilibrium constant for that reaction will be higher than it would otherwise be.[7] Similarly, the entropy of a gaseous substance is higher than that of the same substance dissolved in a solvent.
2. In a reaction in which the number of product molecules is equal to the number of reactant molecules, for example A + B → C + D, entropy effects are usually small, but if the number of molecules is increased, for example, A → B + C, there is a gain in

[6] For a discussion of the activation strain model of chemical reactivity, see van Zeist, W.-J.; Bickelhaupt, F.M. *Org. Biomol. Chem.* ***2010***, *8*, 3118. For the use of cyclobutanes as a contributor to strain in organic reactions, see Seiser,T.; Saget, T.; Tran, D.N.; Cramer, N. *Angew. Chem. Int. Ed.* ***2011***, *50*, 7740.

[7] See Douglass Jr., E.F.; Miller, C.J.; Sparer, G.; Shapiro, H.; Spiegel, D.A. *J. Am. Chem. Soc.* ***2013***, *135*, 6092.

entropy because more arrangements in space are possible when more molecules are present. Reactions in which a molecule is cleaved into two or more parts are likely to be thermodynamically favored by the entropy factor. Conversely, reactions in which the number of product molecules is less than the number of reactant molecules show entropy decreases, and in such cases there must be a sizable decrease in enthalpy to overcome the unfavorable entropy change.

3. Although reactions in which molecules are cleaved into two or more pieces have favorable entropy effects, many potential cleavages do not take place because of large increases in enthalpy.[8] An example is cleavage of ethane into two methyl radicals. In this case, a bond of ~79 kcal mol^{-1} (330 kJ mol^{-1}) is broken, and no new bond is formed to compensate for this enthalpy increase. However, ethane can be cleaved at very high temperatures, which illustrates the principle that *entropy becomes more important as the temperature increases*, as is obvious from the equation $\Delta G = \Delta H - T\Delta S$. The enthalpy term is independent of temperature, while the entropy term is directly proportional to the absolute temperature.
4. An acyclic molecule has more entropy than a similar cyclic molecule because there are more conformations (cf. hexane and cyclohexane). Ring opening therefore correlates with a gain in entropy and ring closing a loss.

6.D. KINETIC REQUIREMENTS FOR REACTION

Just because a reaction has a negative ΔG does not necessarily mean that it will take place in a reasonable period of time.[9] A negative ΔG is a *necessary*, but not a *sufficient*, condition for a reaction to occur spontaneously. For example, the reaction between H_2 and O_2 to give H_2O has a large negative ΔG, but mixtures of H_2 and O_2 can be kept at room temperature for many centuries without reacting to any significant extent. In order for a reaction to take place, *free energy of activation* $\Delta G^{\ddagger}$ must be added.[10] This situation is illustrated in Figure 6.1,[11] which is an energy profile for a one-step reaction without an intermediate. In this type of diagram, the horizontal axis (called the *reaction coordinate*)[12] signifies the progression of the reaction. The parameter $\Delta G_f^{\ddagger}$ is the free energy of activation for the forward reaction. If the reaction shown in Figure 6.1 is reversible, $\Delta G_f^{r\ddagger}$ must be $> \Delta G_f^{\ddagger}$, since $\Delta G_f^{r\ddagger}$ is the sum of ΔG and $\Delta G_f^{\ddagger}$.

When a reaction between two or more molecules has progressed to the point corresponding to the top of the curve, the term *transition state* is applied to the positions of the nuclei and electrons. The transition state possesses a definite geometry and charge distribution but has no finite existence; the system passes through it. The system at this point is called an *activated complex*.[13]

[8] For calculations of long-chain alkane energies see Song, J.-W.; Tsuneda, T.; Sato, T.; Hirao, K. *Org. Lett.* ***2010***, *12*, 1440.

[9] See Yang, L.; Liu, C.-W.; Shao, Q.; Zhang, J.; Gao, Y.-Q. *Acc. Chem. Res.* ***2015***, *48*, 947.

[10] To initiate a reaction of a mixture of H_2 and O_2, energy must be added, such as by striking a match.

[11] Strictly speaking, this is an energy profile for a reaction of the type XY + Z → X + YZ. However, it may be applied, in an approximate way, to other reactions.

[12] For a review of reaction coordinates and structure–energy relationships, see Grunwald, E. *Prog. Phys. Org. Chem.* ***1990***, *17*, 55.

[13] For a discussion of transition states, see Laidler, K.J. *J. Chem. Educ.* ***1988***, *65*, 540.

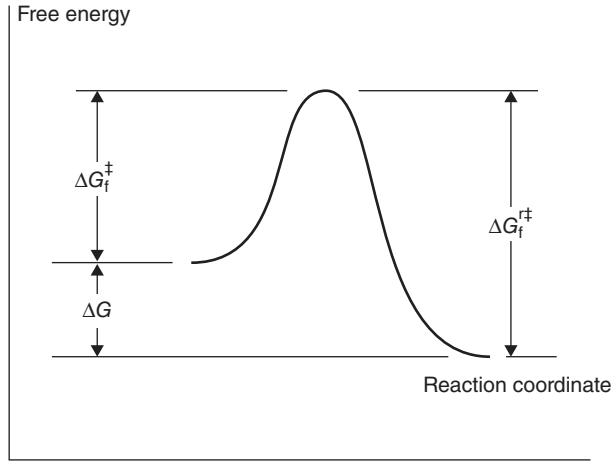


FIGURE 6.1. Free-energy profile of a reaction without an intermediate where the products have a lower free energy than the reactants.

In the *transition-state theory*[14] the starting materials and the activated complex are taken to be in equilibrium, the equilibrium constant being designated $K^{\ddagger}$. According to the theory, all activated complexes go on to product at the same rate (which, although at first sight surprising, is not unreasonable since they are all "falling downhill") so that the rate constant (Sec. 6.J.vi) of the reaction depends only on the position of the equilibrium between the starting materials and the activated complex, that is, on the value of $K^{\ddagger}$. The parameter $\Delta G^{\ddagger}$ is related to $K^{\ddagger}$ by

$$\Delta G^{\ddagger} = -2.3\ RT\ \log\ \ K^{\ddagger}$$

so that a higher value of $\Delta G^{\ddagger}$ is associated with a smaller rate constant. The rates of nearly all reactions increase with increasing temperature because the additional energy thus supplied helps the molecules to overcome the activation energy barrier.[15] Some reactions have no free energy of activation at all, meaning that $K^{\ddagger}$ is essentially infinite and that virtually all collisions lead to reaction. Such processes are said to be *diffusion controlled*.[16]

Like ΔG, $\Delta G^{\ddagger}$ is made up of enthalpy and entropy components:

$$\Delta G^{\ddagger} = \ \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$

$\Delta H^{\ddagger}$, the *enthalpy of activation*, is the difference in bond energies, including strain, resonance, and solvation energies, between the starting compounds and the *transition state*. In many reactions bonds have been broken or partially broken by the time the transition state is reached; the energy necessary for this is $\Delta H^{\ddagger}$. It is true that additional energy will

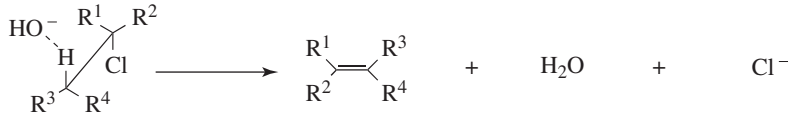
[14] See Kreevoy, M.M.; Truhlar, D.G. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 13–95; Moore, J.W.; Pearson, R.G. *Kinetics and Mechanism*, 3rd ed., Wiley, NY, ***1981***, pp. 137–181; Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 227–378. See Zevaskii, Y.E.; Samoilov, D.V. *Russ. J. Org. Chem.* ***2007***, *43*, 483.

[15] See Donahue, N.M. *Chem. Rev.* ***2003***, *103*, 4593.

[16] For a monograph on diffusion-controlled reactions, see Rice, S.A. *Comprehensive Chemical Kinetics*, Vol. 25, edited by Bamford, C.H.; Tipper, C.F.H.; Compton, R.G., Elsevier, NY, ***1985***.

be supplied by the formation of new bonds, but if this occurs after the transition state, it can affect only ΔH and not $\Delta H^{\ddagger}$.

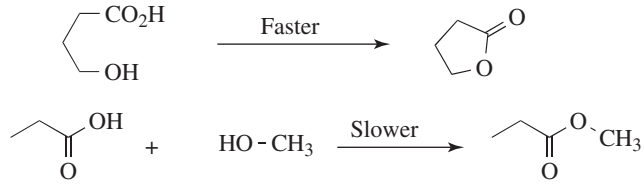
Entropy of activation, $\Delta S^{\ddagger}$, which is the difference in entropy between the starting compounds and the transition state, becomes important when two reacting molecules must approach each other in a specific orientation in order for the reaction to take place. For example, the reaction between a simple noncyclic alkyl chloride and hydroxide ion to give an alkene (reaction **17-11**) takes place only if, in the transition state, the reactants are oriented as shown.



This is an acid–base reaction because the proton on the carbon β to the chlorine is polarized δ+, and is a weak acid. Removal of that proton initiates loss of the chlorine atom and formation of the alkene. The electrons in the C—H bond (the acidic proton) must align *anti* to the leaving groups (Cl) for the reaction to proceed.[17]

When the two reacting molecules collide, if the $^{-}$OH should approach the molecule near the chlorine atom or near R^1 or R^2, no reaction can take place. In order for a reaction to occur, the molecules must surrender the freedom they normally have to assume many possible arrangements in space because only one leads to reaction. Thus, a considerable loss in entropy is involved, that is, $\Delta S^{\ddagger}$, is negative.

Entropy of activation is also responsible for the difficulty in closing rings[18] larger then six membered. Consider a ring-closing reaction in which the two groups that must interact are situated on the ends of a 10-carbon chain. In order for reaction to take place, the groups must encounter each other. But a 10-carbon chain has many conformations, and in only a few of these are the ends of the chain near each other. Thus, forming the transition state requires a great loss of entropy.[19] This factor is also present, although less so, in closing rings of six members or less (except three-membered rings), but with rings of this size the entropy loss is less than that of bringing two individual molecules together. For example, a reaction between an OH group and a COOH group in the same molecule to form a lactone with a five- or six-membered ring takes place much faster than the same reaction between a molecule containing an OH group and another containing a COOH group.

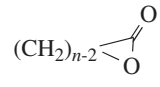


[17] As will be seen in Chapter 17, elimination is also possible with some molecules if the hydrogen is oriented *syn*, instead of *anti*, to the chlorine atom. Of course, this orientation also requires a considerable loss of entropy.

[18] See De Tar, D.F.; Luthra, N.P. *J. Am. Chem. Soc.* ***1980***, *102*, 4505; Mandolini, L. *Bull. Soc. Chim. Fr.* ***1988***, 173. For a related discussion, see Menger, F.M. *Acc. Chem. Res.* ***1985***, *18*, 128.

[19] See Nakagaki. R.; Sakuragi, H.; Mutai, K. *J. Phys. Org. Chem.* ***1989***, *2*, 187; Mandolini, L. *Adv. Phys. Org. Chem.* ***1986***, *22*, 1; Winnik, M.A. *Chem. Rev.* ***1981***, *81*, 491; Valters, R. *Russ. Chem. Rev.* ***1982***, *51*, 788.

TABLE 6.1 Relative rate constants at 50 °C[a]

$Br(CH_2)_{n\text{-}2}CO_2^-$ ⟶ $(CH_2)_{n\text{-}2}$  , where n = the ring size.

Ring size	Relative rate
3	21.7
4	5.4×10^3
5	1.5×10^6
6	1.7×10^4
7	97.3
8	1.00
9	1.12
10	3.35
11	8.51
12	10.6
13	32.2
14	41.9
15	45.1
16	52.0
18	51.2
23	60.4

[a]The rate for an eight-membered ring = 1 for the reaction.
Reprinted with permission from Mandolini, L. *J. Am. Chem. Soc.* ***1978***, *100*, 550. Copyright 1978 American Chemical Society. Reprinted with permission from Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* ***1977***, *99*, 2591. Copyright 1977 American Chemical Society.

Although $\Delta H^{\ddagger}$ is about the same, $\Delta S^{\ddagger}$ is much less for the cyclic case. However, if the ring to be closed has three or four members, small-angle strain is introduced and the favorable $\Delta S^{\ddagger}$ may not be sufficient to overcome the unfavorable $\Delta H^{\ddagger}$ change. Table 6.1[20] shows the relative rate constants for the closing of rings of 3–23 members all by the same reaction. Reactions in which the transition state has more disorder than the starting compounds, for example, the pyrolytic conversion of cyclopropane to propene, have positive $\Delta S^{\ddagger}$ values and are thus favored by the entropy effect.

Reactions with intermediates are two-step (or more) processes. In these reactions there is an energy "well." There are two transition states, each with an energy higher than the intermediate (Figure 6.2). The deeper the well, the more stable the intermediate. In Figure 6.2a, the second peak is higher than the first. The opposite situation is shown in Figure 6.2b. Note that in reactions in which the second peak is higher than the first, the overall $\Delta G^{\ddagger}$ is less than the sum of the $\Delta G^{\ddagger}$ values for the two steps. Minima in free-energy profile diagrams (*intermediates*) correspond to real species that have a finite although usually short existence.[21]

[20] The values for ring sizes 4, 5, and 6 are from Mandolini, L. *J. Am. Chem. Soc.* ***1978***, *100*, 550; the others are from Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* ***1977***, *99*, 2591. See also, Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* ***1981***, *14*, 95. See, however, Benedetti, F.; Stirling, C.J.M. *J. Chem. Soc., Perkin Trans. 2* ***1986***, 605.

[21] For development of ultrafast spectroscopy and the application to reaction mechanisms, see Kobayashi, T. *Bull. Chem. Soc. Jpn.* ***2013***, *86*, 167.

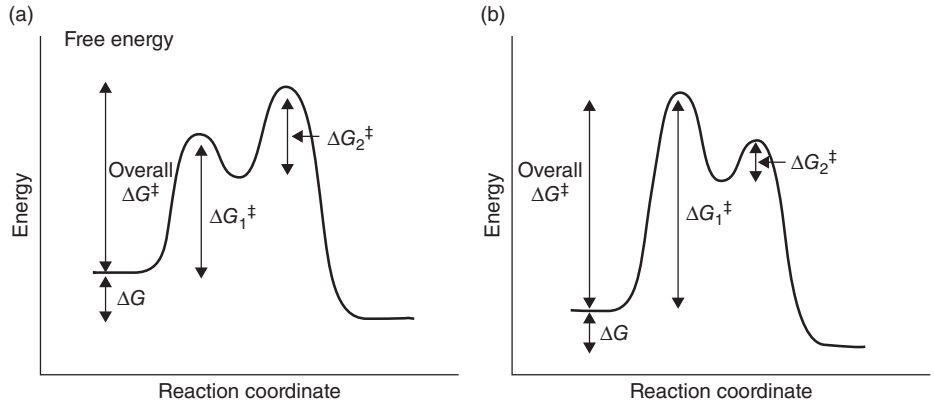
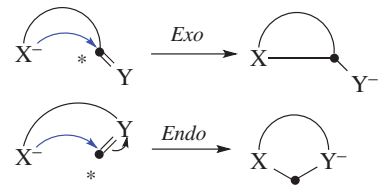


FIGURE 6.2. (a) Free-energy profile for a reaction with an intermediate $\Delta G_1^{\ddagger}$ and $\Delta G_2^{\ddagger}$, the free energy of activation for the first and second stages, respectively. (b) Free-energy profile for a reaction with an intermediate in which the first peak is higher than the second.

These may be the carbocations, carbanions, free radicals, etc., discussed in Chapter 5 or molecules in which all the atoms have their normal valences. In either case, under the reaction conditions they do not live long (because $\Delta G_2^{\ddagger}$ is small) but rapidly go on to products. Maxima in these curves, however, do not correspond to actual species but only to transition states in which bond breaking and/or bond making have partially taken place. Transition states have only a transient existence with an essentially zero lifetime.[22]

6.E. THE BALDWIN RULES FOR RING CLOSURE[23]

In previous sections, the kinetic and thermodynamic aspects of ring-closure reactions were discussed in a general way. J.E. Baldwin has supplied a more specific set of rules for certain closings of three- to seven-membered rings.[24] These rules distinguish two types of ring closure, called *exo* and *endo*, and three kinds of atoms at the starred positions: *Tet* for sp^3, *trig* for sp^2, and *dig* for *sp*. The following are Baldwin's rules for closing rings of three to seven members.



[22] See laser femtochemistry: Zewail, A.H.; Bernstein, R.B. *Chem. Eng. News* ***1988***, *66*, No. 45 (Nov. 7), 24–43. For another method, see Collings, B.A.; Polanyi, J.C.; Smith, M.A.; Stolow, A.; Tarr, A.W. *Phys. Rev. Lett.* ***1987***, *59*, 2551.

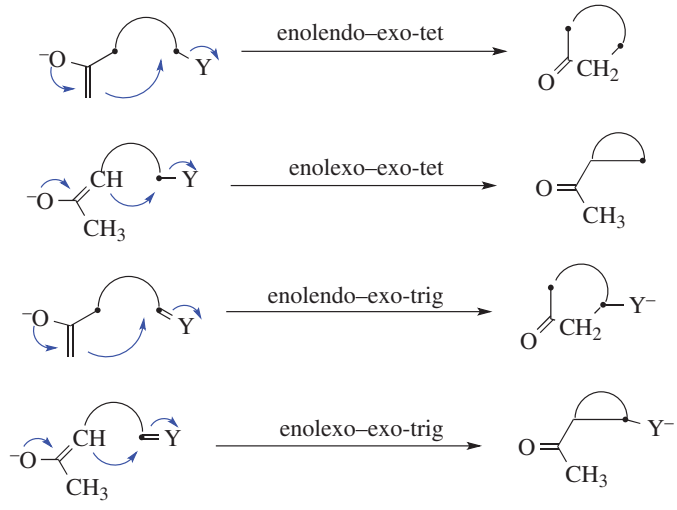
[23] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 538–544.

[24] Baldwin, J.E. *J. Chem. Soc., Chem. Commun.* ***1976***, 734; Baldwin, J.E. in *Further Perspectives in Organic Chemistry (Ciba Foundation Symposium 53)*, Elsevier, Amsterdam, ***1979***, pp. 85–99. See also, Baldwin, J.E.; Thomas, R.C.; Kruse, L.I.; Silberman, L. *J. Org. Chem.* ***1977***, *42*, 3846; Baldwin, J.E.; Lusch, M.J. *Tetrahedron* ***1982***, *38*, 2939; Fountain, K.R.; Gerhardt, G. *Tetrahedron Lett.* ***1978***, 3985.

1. Rule 1. Tetrahedral systems
   (a) 3–7 *exo-tet* are all favored processes
   (b) 5–6 *endo-tet* are disfavored
   (c) 6–7 *endo-trig* are favored
2. Rule 2. Trigonal systems
   (a) 3–7 *exo-trig* are favored
   (b) 3–5 *endo-trig* are disfavored[25]
3. Rule 3. Digonal systems
   (a) 3–4 *exo-dig* are disfavored
   (b) 5–7 *exo-dig* are favored
   (c) 3–7 *endo-dig* are favored

"Disfavored" does not mean it cannot be done, only that it is more difficult than the favored cases. These rules are empirical and have a stereochemical basis. The favored pathways are those in which the length and nature of the linking chain will enable the terminal atoms to achieve the proper geometries for reaction. The disfavored cases require severe distortion of bond angles and distances. Many cases in the literature are in substantial accord with these rules, and they are important in the formation of five- and six-membered rings.[26]

Although Baldwin's rules can be applied to ketone enolates,[27] additional rules were added to make the terminology more specific.[28] The orientation of the orbital as it approaches the reactive center must be considered for determining the correct angle of approach. Diagrams that illustrate the enolate rules are shown.



[25] For some exceptions to the rule in this case, see Trost, B.M.; Bonk, P.J. *J. Am. Chem. Soc.* ***1985***, *107*, 1778; Torres, L.E.; Larson, G.L. *Tetrahedron Lett.* ***1986***, *27*, 2223.
[26] Johnson, C.D. *Acc. Chem. Res.* ***1997***, *26*, 476.
[27] Baldwin, J.E.; Kruse, L.I. *J. Chem. Soc., Chem. Commun.* ***1977***, 233.
[28] Baldwin, J.E.; Lusch, M.J. *Tetrahedron* ***1982***, *38*, 2939.

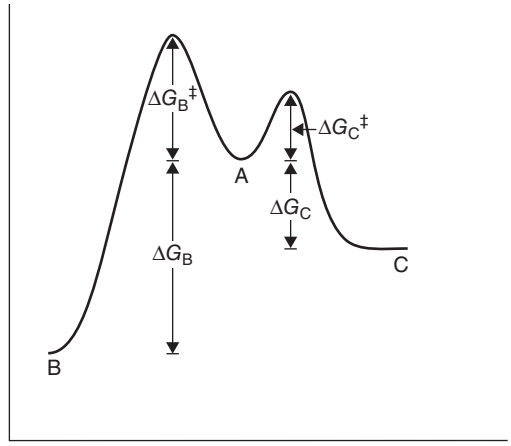


FIGURE 6.3. Free-energy profile illustrating kinetic versus thermodynamic control of products. The starting compounds (**A**) can react to give either **B** or **C**.

The rules are:

(a) 6–7 *enolendo–exo-tet* reactions are favored
(b) 3–5 *enolendo–exo-tet* reactions are disfavored
(c) 3–7 *enolexo–exo-tet* reactions are favored
(d) 3–7 *enolexo–exo-trig* reactions are favored
(e) 6–7 *enolendo–exo-trig* reactions are favored
(f) 3–5 *enolendo–exo-trig* reactions are disfavored

6.F. KINETIC AND THERMODYNAMIC CONTROL

$$\mathrm{C} \longleftarrow \mathrm{A} \longrightarrow \mathrm{B}$$

There are many cases in which a compound under a given set of reaction conditions can undergo competing reactions to give different products. Starting material **A** may give either **B** or **C**, for example. Figure 6.3 shows a free-energy profile for a reaction in which **B** is thermodynamically more stable than **C** (ΔG**B** is > than ΔG**C**), but **C** is formed faster (lower $\Delta G^{\ddagger}$). If neither reaction is reversible, **C** will be formed in larger amounts because it is formed faster. The product is said to be *kinetically controlled*. However, if the reactions are reversible, this will not necessarily be the case. If such a process is stopped well before the equilibrium has been established, the reaction will be kinetically controlled since more of the faster-formed product will be present. However, if the reaction is permitted to approach equilibrium, the predominant or even exclusive product will be **B**. Under these conditions the **C** that is first formed reverts to **A**, while the more stable **B** does so much less. We say the product is *thermodynamically controlled*.[29] Of course, Figure 6.3 does not describe all reactions in which a compound **A** can give two different products. In many cases the more stable product is also the one that is formed faster. In such cases the product of kinetic control is also the product of thermodynamic control.

[29] See Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 36–89.

Tunneling control is a new reactivity paradigm that describes a tunneling reaction with a high but narrow potential energy barrier that leads to formation of a product that would be disfavored if the reaction proceeded by passage over kinetic barriers and should be considered along with thermodynamic and kinetic control.[30]

6.G. THE HAMMOND POSTULATE

Transition states *are not detectable and they have zero lifetimes*, so it is impossible to observe them directly. Information about their geometries must be obtained from inference and modeling. In some cases the inferences can be very strong. For example, in the S_N2 reaction (Sec. 10.A.i) between CH_3I and I^- (a reaction in which the product is identical to the starting compound), the transition state should be perfectly symmetrical. In most cases, however, it is not possible to reach such easy conclusions, and conclusions are greatly aided by the *Hammond postulate*,[31] which states that for any single reaction step, *the geometry of the transition state for that step resembles the side to which it is closer in free energy*. Thus, for an exothermic reaction, like that shown in Figure 6.1, the transition state resembles the reactants more than the products, although not much more because there is a substantial $\Delta G^{\ddagger}$ on both sides.

The postulate is most useful in dealing with reactions with intermediates. In the reaction illustrated in Figure 6.2a, the first transition state lies much closer in energy to the intermediate than to the reactants, and it is possible to predict that the geometry of the transition state resembles that of the intermediate more than it does that of the reactants. Likewise, the second transition state also has a free energy much closer to that of the intermediate than to the products, so that both transition states resemble the intermediate more than they do the products or reactants. This is generally the case in reactions that involve very reactive intermediates. More is usually known about the structure of intermediates than of transition states, so a knowledge of intermediates is used to draw conclusions about the transition states (e.g., Sec. 10.G.i and Sec. 15.B.i).

6.H. MICROSCOPIC REVERSIBILITY

In the course of a reaction, the nuclei and electrons assume positions that at each point correspond to the lowest free energies possible. If the reaction is reversible, these positions must be the same in the reverse process, too. This means that the forward and reverse reactions (run under the same conditions) must proceed by the same mechanism. This is called the *principle of microscopic reversibility*. For example, if in a reaction **A** → **B** there is an intermediate **C**, then **C** must also be an intermediate in the reaction **B** → **A**. This is a useful principle since it enables one to know the mechanism of reactions in which the equilibrium lies far over to one side. Reversible photochemical reactions are an exception, since a molecule that has been excited photochemically does not have to lose its energy in the same way (Chapter 7).

[30] Schreiner, P.R. *J. Am. Chem. Soc.* ***2017***, *139*, 15276.

[31] Hammond, G.S. *J. Am. Chem. Soc.* ***1955***, *77*, 334. For a discussion, see Farcasiu, D. *J. Chem. Educ.* ***1975***, *52*, 76.

6.I. MARCUS THEORY

It is often useful to compare the reactivity of one compound with that of similar compounds. The real goal is to find out how a reaction coordinate (and in particular the transition state) changes when one reactant molecule is replaced by a similar molecule. *Marcus theory* is a method for doing this.[32]

In this theory, the activation energy $\Delta G^{\ddagger}$ is thought of as consisting of two parts.

1. One is an *intrinsic* free energy of activation, which would exist if the reactants and products had the same ΔG°.[33] This is a kinetic part, called the *intrinsic barrier* $\Delta G^{\ddagger}_{\text{int}}$
2. The other is a thermodynamic part, which arises from the ΔG° for the reaction.

The Marcus equation says that the overall $\Delta G^{\ddagger}$ for a one-step reaction is[34]

$$\Delta G^{\ddagger} = \Delta G^{\ddagger}_{\text{int}} + \frac{1}{2}\Delta G^{\Delta} + \frac{(\Delta G^{\Delta})^2}{16(\Delta G^{\ddagger}_{\text{int}} - w^{\text{R}})}$$

where the term ΔG^{Δ} stands for

$$\Delta G^{\Delta} = \Delta G^{\circ} - w^{\text{R}} + w^{\text{P}}$$

w^{R}, a work term, is the free energy required to bring the reactants together, and w^{P} is the work required to form the successor configuration from the products.

For a reaction of the type $\text{AX} + \text{B} \rightarrow \text{BX}$, the intrinsic barrier[35] $\Delta G^{\ddagger}_{\text{int}}$ is taken to be the average $\Delta G^{\ddagger}$ for the two symmetrical reactions:

$$\begin{aligned} \text{AX} + \text{A} &\longrightarrow \text{AX} + \text{A} \quad \Delta G^{\ddagger}_{\text{A,A}} \\ \text{BX} + \text{B} &\longrightarrow \text{BX} + \text{B} \quad \Delta G^{\ddagger}_{\text{B,B}} \end{aligned}$$

so that

$$\Delta G^{\ddagger}_{\text{int}} + \frac{1}{2}\left(\Delta G^{\ddagger}_{\text{A,A}} + \Delta G^{\ddagger}_{\text{B,B}}\right)$$

One type of process that can successfully be treated by the Marcus equation is the S_N2 mechanism, which is shown (see also Sec. 10.A.i.).

$$\text{R—X} + \text{Y} \longrightarrow \text{R—Y} + \text{X}$$

[32] See Albery, W.J. *Annu. Rev. Phys. Chem.* ***1980***, *31*, 227; Kreevoy, M.M.; Truhlar, D.G. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 13–95.

[33] The parameter ΔG° is the standard free energy; that is, ΔG at atmospheric pressure.

[34] Albery, W.J.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* ***1978***, *16*, 87 (pp. 98–99).

[35] See Lee, I. *J. Chem. Soc., Perkin Trans. 2* ***1989***, 943, *Chem. Soc. Rev.* ***1990***, *19*, 133.

When R is CH_3 the process is called *methyl transfer*.[36] For such reactions the work terms w^R and w^P are assumed to be very small compared to $\Delta G°$, and can be neglected, so that the Marcus equation simplifies to

$$\Delta G^{\ddagger} = \Delta G^{\ddagger}_{int} + \frac{1}{2}\Delta G° + \frac{(\Delta G)^2}{16\Delta G^{\ddagger}_{int}}$$

The Marcus equation allows $\Delta G^{\ddagger}$ for $RX + Y \rightarrow RY + X$ to be calculated from the barriers of the two symmetrical reactions $RX + X \rightarrow RX + X$ and $RY + Y \rightarrow RY + Y$. The results of such calculations are generally in agreement with the *Hammond postulate*.

Marcus theory can be applied to any single-step process where something is transferred from one particle to another. It was originally derived for electron transfers,[37] and then extended to transfers of H^+ (see Sec. 8.D), H^-,[38] and H•[39] as well as methyl transfers.

6.J. METHODS OF DETERMINING MECHANISMS[40]

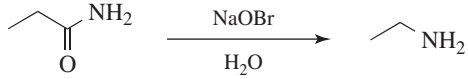
There are a number of commonly used methods for determining mechanisms.[41] In most cases, one method is not sufficient, and the problem is generally approached from several directions.

6.J.i. Identification of Products

Obviously any mechanism proposed for a reaction must account for all the products obtained and for their relative proportions, including products formed by side reactions. Incorrect mechanisms for the von Richter reaction (**13-31**) were accepted for many years because it was not realized that nitrogen was a major product. A proposed mechanism cannot be correct if it fails to predict the products in approximately the observed proportions. For example, any mechanism for the reaction:

$$CH_4 + C1_2 \xrightarrow{h\nu} CH_3C1$$

that fails to account for the formation of a small amount of ethane cannot be correct (see **14-1**), and any mechanism proposed for the *Hofmann rearrangement* (**18-13**):



must account for the fact that the carbonyl carbon is lost as CO_2.

[36] See Albery, W.J.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* ***1978***, *16*, 87. See also, Lee, I. *J. Chem. Soc., Perkin Trans. 2* ***1989***, 943; Lewis, E.S. *Bull. Soc. Chim. Fr.* ***1988***, 259.

[37] Marcus, R.A. *J. Phys. Chem.* ***1963***, *67*, 853, *Annu. Rev. Phys. Chem.* ***1964***, *15*, 155; Eberson, L. *Electron Transfer Reactions in Organic Chemistry*, Springer, NY, ***1987***.

[38] Kim, D.; Lee, I.H.; Kreevoy, M.M. *J. Am. Chem. Soc.* ***1990***, *112*, 1889 and references cited therein.

[39] See, for example, Dneprovskii, A.S.; Eliseenkov, E.V. *J. Org. Chem. USSR* ***1988***, *24*, 243.

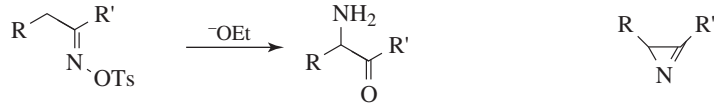
[40] *The Investigation of Organic Reactions and their Mechanisms*, Maskill, H. (ed.), Blackwell, Oxford, ***2006***.

[41] See Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), 2 pts, Wiley, NY, ***1986***; Carpenter, B.K. *Determination of Organic Reaction Mechanisms*, Wiley, NY, ***1984***.

6.J.ii. Determination of the Presence of an Intermediate

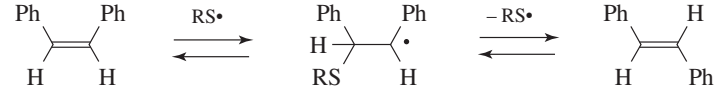
Intermediates are postulated in many mechanisms, and the presence or absence of an intermediate is essential information. There are several methods, none of them foolproof,[42] for attempting to learn whether or not an intermediate is present and, if so, what its structure is. All methods are experimental, and an intermediate must be detected in one way or another, often by isolation or trapping.

1. *Isolation of an intermediate*. It is sometimes possible to isolate an intermediate from a reaction mixture by stopping the reaction after a short time or by the use of very mild conditions. For example, in the *Neber rearrangement* (reaction **18-12**) the intermediate **1** (an azirene)[43] has been isolated. If it can be shown that the isolated compound gives the same product when subjected to the reaction conditions, and at a rate no slower than the starting compound, this constitutes strong evidence that the reaction involves that intermediate, although it is not conclusive, since the compound may arise by an alternate path and by coincidence give the same product.



Neber rearrangement **1**

2. *Detection of an intermediate*. In many cases an intermediate cannot be isolated but can be detected by normal IR, ReactIR,[44] NMR,[45] or other spectra.[46] The detection by Raman spectra of NO_2^+ was regarded as strong evidence that this is an intermediate in the nitration of benzene (see **11-2**). Free radical and triplet intermediates can often be detected by ESR and by CIDNP (see Chapter 5). Free radicals (as well as radical ions and EDA complexes) can also be detected by a method that does not rely on spectra. In this method a double-bond compound is added to the reaction mixture, and its fate traced.[47] One possible result is *cis–trans* conversion. For example, *cis*-stilbene is isomerized to the *trans* isomer in the presence of RS• radicals, by this mechanism:



cis-Stilbene *trans*-Stilbene

[42] For a discussion, see Martin, R.B. *J. Chem. Educ.* ***1985***, *62*, 789.
[43] See Gentilucci, L.; Grijzen, Y.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* ***1995***, *36*, 4665.
[44] ReactIR uses mid-range infrared spectroscopy for the identification and monitoring of critical reaction species and follows the changes in the reaction on a second-by-second basis. For applications, see Stead, D.; Carbone, G.; O'Brien, P.; Campos, K.R.; Coldham, I; Sanderson, A. *J. Am. Chem. Soc.* ***2010***, *132*, 7260; Rutherford, J.L.; Hoffmann, D.; Collum, D.B. *J. Am. Chem. Soc.* ***2002***, *124*, 264.
[45] See Fernández, I.; Fernández-Valle, M.E.; Martínez-Álvarez, R.; Molero-Vílchez, D.; Pardo, Z.D.; Sáez-Barajas, E.; Sánchez, Á.; Herrera, A. *J. Org. Chem.* ***2014***, *79*, 8086.
[46] See Parker, V.D. *Adv. Phys. Org. Chem.* ***1983***, *19*, 131; Sheridan, R.S. *Org. Photochem.* ***1987***, *8*, 159.
[47] For a review, see Todres, Z.V. *Tetrahedron* ***1987***, *43*, 3839.

Since the *trans* isomer is more stable than the *cis*, the reaction does not go the other way, and the detection of the isomerized product is evidence for the presence of the RS• radicals.

3. *Trapping of an intermediate*. In some cases, the suspected intermediate is known to be one that reacts in a given way with a certain compound. The intermediate can then be trapped by running the reaction in the presence of that compound. For example, benzynes (Sec. 13.A.iii) react with dienes in the *Diels-Alder reaction* (**15-56**). In any reaction where a benzyne is a suspected intermediate, the addition of a diene and the detection of the *Diels-Alder* adduct indicate that the benzyne was probably present.
4. *Addition of a suspected intermediate*. If a certain intermediate is suspected, and if it can be obtained by other means, then under the same reaction conditions it should give the same products. This kind of experiment can provide conclusive negative evidence: if the correct products are not obtained, the suspected compound is not an intermediate. However, if the correct products are obtained, this is not conclusive since they may arise by coincidence. The *von Richter reaction* (**13-31**) provides a good example here too. For many years, it had been assumed that an aryl cyanide was an intermediate, since cyanides are hydrolyzed to carboxylic acids (**16-4**). Indeed, *p*-chlorobenzonitrile was shown to give *p*-chlorobenzoic acid under normal *von Richter* conditions.[48] However, when the experiment was repeated with 1-cyanonaphthalene, no 1-naphthoic acid was obtained, although 2-nitronaphthalene gave 13% 1-naphthoic acid under the same conditions.[49] This proved that 2-nitronaphthalene must have been converted to 1-naphthoic acid by a route that does not involve 1-cyanonaphthalene. It also showed that even the conclusion that *p*-chlorobenzonitrile was an intermediate in the conversion of *m*-nitrochlorobenzene to *p*-chlorobenzoic acid must now be suspect, since it is not likely that the mechanism would substantially change in going from the naphthalene to the benzene system.

6.J.iii. The Study of Catalysis[50]

Many organic reactions are slow in the absence of a catalyst. Acid-catalyzed reactions are prevalent. Once it is known that a reaction is subject to catalysis, much information about the mechanism of a reaction can be obtained from a knowledge of which substances catalyze the reaction, which inhibit it, and which do neither. Of course, just as a mechanism must be compatible with the products, so must it be compatible with its catalysts. In general, *catalysts perform their actions by providing an alternate pathway for the reaction* in which $\Delta G^{\ddagger}$ is less than it would be without the catalyst. Catalysts do not change ΔG.

[48] Bunnett, J.F.; Rauhut, M.M.; Knutson, D.; Bussell, G.E. *J. Am. Chem. Soc.* ***1954***, *76*, 5755.
[49] Bunnett, J.F.; Rauhut, M.M. *J. Org. Chem.* ***1956***, *21*, 944.
[50] See Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, ***1969***; Bender, M.L. *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, Wiley, NY, ***1971***; Coenen, J.W.E. *Recl. Trav. Chim. Pays-Bas*, ***1983***, *102*, 57; and in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, the articles by Keeffe, J.R.; Kresge, A.J. pp. 747–790; Haller, G.L.; Delgass, W.N. pp. 951–979.

6.J.iv. Isotopic Labeling[51]

Molecules that have been isotopically labeled can be used to trace the path of the reaction, which may provide much useful mechanistic information. For example, in the reaction

$$\overset{*}{\mathrm{RCOO}}^- + \mathrm{BrCN} \longrightarrow \overset{*}{\mathrm{RCN}}$$

does the CN group in the product come from the CN in the BrCN? The use of ^{14}C supplied the answer, since $R^{14}CO_2^-$ gave *radioactive* RCN.[52] This surprising result saved a lot of labor, since it ruled out a mechanism involving the replacement of CO_2 by CN (see reaction **16-88**). Other radioactive isotopes are also frequently used as tracers, but even stable isotopes can be used. An example is the hydrolysis of esters.

Which bond of the ester is broken, the acyl—O bond or the alkyl—O bond? The answer is found by the use of $H_2{}^{18}O$. If the acyl—O bond breaks, the labeled oxygen will appear in the acid; otherwise it will be in the alcohol (see **16-58**). Although neither compound is radioactive, the one that contains ^{18}O can be determined by submitting both to mass spectrometry. In a similar way, deuterium can be used as a label for hydrogen. In this case, mass spectrometry is not the only option since IR and ^1H and ^{13}C NMR[53] spectra can be used to determine when deuterium has been substituted for hydrogen. It is noted that electrospray ionization mass spectrometry has been employed in the study of mechanisms and in research into catalysis.[54]

In the labeling technique, it is not generally necessary to use completely labeled compounds. Partially labeled material is usually sufficient.

6.J.v. Stereochemical Evidence[55]

If the products of a reaction are capable of existing in more than one stereoisomeric form, the form that is obtained may give information about the mechanism.[56] For example, Walden[57] discovered that (+)-malic acid gives (−)-chlorosuccinic acid when treated with PCl_5 and the (+) enantiomer when treated with $SOCl_2$, showing that the mechanisms of these apparently similar conversions could not be the same (Sec. 10.A.i and Sec. 10.D). Much useful information has been obtained about nucleophilic substitution, elimination, rearrangement, and addition reactions from this type of experiment. The isomers involved

[51] See Wentrup, C. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger. A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 613–661; Collins, C.J. *Adv. Phys. Org. Chem.* ***1964***, *2*, 3. See also, the series *Isotopes in Organic Chemistry*.

[52] Douglas, D.E.; Burditt, A.M. *Can. J. Chem.* ***1958***, *36*, 1256.

[53] For a review, see Hinton, J.; Oka, M.; Fry, A. *Isot. Org. Chem.* ***1977***, *3*, 41.

[54] Schröder, D. *Acc. Chem. Res.* ***2012***, *45*, 1521.

[55] See Billups, W.E.; Houk, K.N.; Stevens, R.V. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 663–746; Eliel, E.L. *Stereochemistry of Carbon Compounds*, McGraw-Hill, NY, ***1962***; Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***.

[56] Bonnet, L.; Larrégaray, P.; Duguay, B.; Rayez, J.-C.; Che, D.C.; Kasai, T. *Bull. Chem. Soc. Jpn.* ***2007***, *80*, 707.

[57] Walden, P. *Ber.* ***1896***, *29*, 136; ***1897***, *30*, 3149; ***1899***, *32*, 1833.

need not be enantiomers. Thus, the fact that *cis*-but-2-ene treated with $KMnO_4$ gives *meso*-butane-2,3-diol and not the racemic mixture is evidence that the two OH groups attack the double bond from the same side (see reaction **15-44**).

6.J.vi. Kinetic Evidence[58]

The rate of a homogeneous reaction[59] is the rate of disappearance of a reactant or appearance of a product. The rate nearly always changes with time, since it is usually proportional to concentration and the concentration of reactants decreases with time. However, the rate is not always proportional to the concentration of all reactants. In some cases, a change in the concentration of a reactant produces no change at all in the rate, while in other cases the rate may be proportional to the concentration of a substance (a catalyst) that does not even appear in the stoichiometric equation. A study of which reactants affect the rate often tells a good deal about the mechanism.

If the rate is proportional to the change in concentration of only one reactant (**A**), the *rate law* (the rate of change of concentration of A with time *t*) is

$$\text{rate} = \frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}]$$

where *k* is the *rate constant* for the reaction.[60] There is a minus sign because the concentration of **A** decreases with time. A reaction that follows such a rate law is called a *first-order reaction*. The units of *k* for a first-order reaction are s^{-1}.

The rate of a *second-order reaction* is proportional to the concentration of two reactants, or to the square of the concentration of one:

$$\text{rate} = \frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}][\mathbf{B}]$$

or

$$\text{rate} = \frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}]^2$$

For a second-order reaction the units are L mol^{-1} s^{-1} or some other units expressing the reciprocal of concentration or pressure per unit time interval.

Similar expressions can be written for third-order reactions.

A reaction whose rate is proportional to [**A**] and to [**B**] is said to be first order in **A** and in **B**, and second order overall.

A reaction rate can be measured in terms of any reactant or product, but the rates so determined are not necessarily the same. For example, if the stoichiometry of a reaction is

$$2\mathbf{A} + \mathbf{B} \rightarrow \mathbf{C} + \mathbf{D}$$

[58] See Connors, K.A. *Chemical Kinetics*, VCH, NY, ***1990***; Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics*, Wiley, NY, ***1984***; Drenth, W.; Kwart, H. *Kinetics Applied to Organic Reactions*, Marcel Dekker, NY, ***1980***; Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, ***1970***, pp. 53–100; Gardiner Jr., W.C. *Rates and Mechanisms of Chemical Reactions*, W.A. Benjamin, NY, ***1969***; Leffler, J.E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*, Wiley, NY, ***1963***; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, ***1969***, pp. 555–614.

[59] A homogeneous reaction occurs in one phase. Heterogeneous kinetics have been studied much less.

[60] Colins, C.C.; Cronin, M.F.; Moynihan, H.A.; McCarthy, D.G. *J. Chem. Soc., Perkin Trans. 1* ***1997***, 1267.

then, on a molar basis, **A** must disappear twice as fast as **B**, so that $-d[\mathbf{A}]/dt$ and $-d[\mathbf{B}]/dt$ are not equal but the former is twice as large as the latter.

The rate law of a reaction is an experimentally determined fact. The rate law leads to an understanding of the *molecularity*, which may be defined as the number of molecules that come together to form the activated complex. It is obvious that if it is known how many (and which) molecules take part in the activated complex, a good deal is known about the mechanism. The experimentally determined rate order is not necessarily the same as the molecularity. Any reaction, no matter how many steps are involved, has only one rate law, but each step of the mechanism has its own molecularity.

For reactions that take place in one step (reactions without an intermediate) the order is the same as the molecularity. A first-order, one-step reaction is always unimolecular; a one-step reaction that is second order in **A** always involves two molecules of **A**; if it is first order in **A** and first order in **B**, then a molecule of **A** reacts with one of **B**, and so on.

For reactions that take place in more than one step, the order *for each step* is the same as the molecularity *for that step*. This fact enables us to predict the rate law for any proposed mechanism, although the calculations may get lengthy at times.[61] If any one step of a mechanism is considerably slower than all the others (this is usually the case), the rate of the overall reaction is essentially the same as that of the slow step, which is consequently called the *rate-determining* step.[62]

For reactions that take place in two or more steps, two broad cases can be distinguished:

1. The first step is slower than any subsequent step and is consequently rate determining. In such cases, the rate law simply includes the reactants that participate in the slow step. For example, if the reaction $\mathbf{A} + 2\mathbf{B} \rightarrow \mathbf{C}$ has the mechanism

$$\mathbf{A} + \mathbf{B} \xrightarrow{\text{Slow}} \mathbf{I}$$
$$\mathbf{I} + \mathbf{B} \xrightarrow{\text{Fast}} \mathbf{C}$$

where **I** is an intermediate, the reaction is second order, with the rate law

$$\text{rate} = \frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}][\mathbf{B}]$$

2. When the first step is not rate determining, determination of the rate law is usually much more complicated. For example, consider the mechanism

$$\mathbf{A} + \mathbf{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{I}$$
$$\mathbf{I} + \mathbf{B} \xrightarrow{k_2} \mathbf{C}$$

[61] For a discussion of how order is related to *molecularity* in many complex situations, see Szabó, Z.G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 2, Elsevier, NY, ***1969***, pp. 1–80.

[62] Many chemists prefer to use the term *rate-limiting step or rate-controlling step* for the slow step, rather than *rate-determining step*. See the definitions in Gold, V.; Loening, K.L.; McNaught, A.D.; Sehmi, P. *IUPAC Compendium of Chemical Terminology,* Blackwell Scientific Publications, Oxford, ***1987***, p. 337. For a discussion of rate-determining steps, see Laidler, K.J. *J. Chem. Educ.* ***1988***, *65*, 250.

where the first step is a rapid attainment of equilibrium, followed by a slow reaction to give **C**. The rate of disappearance of **A** is

$$\text{rate} = \frac{-d[\mathbf{A}]}{dt} = k_1[\mathbf{A}]\,[\mathbf{B}] - k_{-1}[\mathbf{I}]$$

Both terms must be included because A is being formed by the reverse reaction as well as being used up by the forward reaction. This equation is of very little help as it stands since the concentration of the intermediate cannot be measured. However, the combined rate law for the formation and disappearance of **I** is

$$\text{rate} = \frac{-d[\mathbf{A}]}{dt} = k_1[\mathbf{A}][\mathbf{B}] - k_{-1}[\mathbf{I}] - k_2[\mathbf{I}][\mathbf{B}]$$

This equation is of little help unless the assumption is made that *the concentration of **I** does not change with time*, since it is an intermediate that is used up (going either to **A** + **B** or to **C**) as fast as it is formed. This assumption, called the assumption of the *steady state*,[63] enables $d[\mathbf{I}]/dt$ to be set equal to zero and hence to solve for [**I**] in terms of the measurable quantities [**A**] and [**B**]:

$$[\mathbf{I}] = \frac{k_1[\mathbf{A}][\mathbf{B}]}{k_2[\mathbf{B}] + k_{-1}}$$

Inserting this value for [**I**] into the original rate expression gives

$$\frac{-d[\mathbf{A}]}{dt} = \frac{k_1 k_2[\mathbf{A}][\mathbf{B}]^2}{k_2[\mathbf{B}] + k_{-1}}$$

Note that this rate law is valid whatever the values of k_1, k_{-1}, and k_2. However, our original hypothesis was that the first step was faster than the second, or that

$$k_1[\mathbf{A}][\mathbf{B}] \gg k_2[\mathbf{I}][\mathbf{B}]$$

Since the first step is an equilibrium

$$k_1[\mathbf{A}][\mathbf{B}] = k_{-1}[\mathbf{I}]$$

this gives

$$k_{-1}[\mathbf{I}] \gg k_2[\mathbf{I}][\mathbf{B}]$$

Canceling [**I**] gives

$$k_{-1} \gg k_2[\mathbf{B}]$$

[63] For a discussion, see Raines, R.T.; Hansen, D.E. *J. Chem. Educ.* ***1988***, *65*, 757.

Neglecting $k_2[\mathbf{B}]$ in comparison with k_{-1} gives

$$\frac{-d[\mathbf{A}]}{dt} = \frac{k_1 k_2}{k_{-1}}[\mathbf{A}][\mathbf{B}]^2$$

The overall rate is thus third order: first order in **A** and second order in **B**. Incidentally, if the first step is rate determining (as was the case in the preceding paragraph), then

$$k_2[\mathbf{B}] \gg k_{-1}$$

and

$$\frac{-d[\mathbf{A}]}{dt} = k_1[\mathbf{A}][\mathbf{B}]$$

which is the same rate law deduced from the rule that where the first step is rate determining, the rate law includes the reactants that participate in that step.

It is possible for a reaction to involve **A** and **B** in the rate-determining step, although only [**A**] appears in the rate law. This occurs when a large excess of **B** is present, say 100 times the molar quantity of **A**. In this case the complete reaction of **A** uses up only 1 equivalent of **B**, leaving 99 equivalents. It is not easy to measure the change in concentration of **B** with time in such a case, and it is seldom attempted, especially when **B** is also the solvent. Since [**B**], for practical purposes, does not change with time, the reaction appears to be first order in **A** although actually both **A** and **B** are involved in the rate-determining step. This is often referred to as a *pseudo-first-order* reaction. Pseudo-order reactions can also come about when one reactant is a catalyst whose concentration does not change with time because it is replenished as fast as it is used up and when a reaction is conducted in a medium that keeps the concentration of a reactant constant, for example, in a buffer solution where H^+ or ^-OH is a reactant. Pseudo-first-order conditions are frequently used in kinetic investigations for convenience in experimentation and calculations.

What is actually being measured is the change in concentration of a product or a reactant with time. Many methods have been used to make such measurements.[64] The choice of a method depends on its convenience and its applicability to the reaction being studied. Among the most common methods are the following.

1. *Periodic or continuous spectral readings*. In many cases, the reaction can be carried out in the cell while it is in the instrument. Then all that is necessary is that the instrument be read, periodically or continuously. Among the methods used are IR and UV spectroscopy, polarimetry, NMR, and ESR.[65]
2. *Quenching and analyzing*. A series of reactions can be set up and each stopped in some way (perhaps by suddenly lowering the temperature or adding an inhibitor)

[64] See Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics*, Wiley, NY, ***1984***. See Batt, L. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics,* Vol. 1, Elsevier, NY, ***1969***, pp. 1–111.
[65] For a review of ESR to measure kinetics, see Norman, R.O.C. *Chem. Soc. Rev.* ***1979***, *8*, 1.

after a different amount of time has elapsed. The materials are then analyzed by spectral readings, titrations, chromatography, polarimetry, or any other method.

3. *Removal of aliquots at intervals*. Each aliquot is then analyzed, as in method 2.
4. *Measurement of changes in total pressure, for gas-phase reactions*.[66]
5. *Calorimetric methods*. The output or absorption of heat can be measured at time intervals.

Special methods exist for kinetic measurements of very fast reactions.[67]

A graph is usually obtained that shows the change in concentration with time. Interpretation[68] is required to obtain a rate law and a value of k. If a reaction obeys simple first- or second-order kinetics, the interpretation is generally not difficult. For example, for a concentration at the start $= A_o$, the first-order rate law

$$\frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}] \text{ or } \frac{-d[A]}{[A]} = k\,dt$$

can be integrated between the limits $t = 0$ and $t = t$ to give

$$-\ln \frac{[\mathbf{A}]}{A_o} = kt \text{ or } \ln [\mathbf{A}] = -kt + \ln A_o$$

Therefore, if a plot of ln [**A**] against t is linear, the reaction is first order and k can be obtained from the slope.

For first-order reactions, it is customary to express the rate not only by the rate constant k, but also by the *half-life*, which is the time required for one-half of any given quantity of a reactant to be used up. Since the half-life t_2^1 is the time required for [**A**] to reach **A**o/2:

$$\ln \frac{\mathbf{A}_o}{2} = kt_{1/2} + \ln \mathbf{A}_o$$

so that

$$t_{1/2} = \frac{\ln \left[\frac{\mathbf{A}_o}{\mathbf{A}_o/2}\right]}{k} = \frac{\ln 2}{k} = \frac{0.693}{k}$$

[66] See le Noble, W.J. *Prog. Phys. Org. Chem.* ***1967***, *5*, 207; Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* ***1985***, 1; Matsumoto, K.; Sera, A. *Synthesis* ***1985***, 999.

[67] See Connors, K.A. *Chemical Kinetics*, VCH, NY, ***1990***, pp. 133–186; Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics,* Wiley, NY, ***1984***, pp. 247–327; Krüger, H. *Chem. Soc. Rev.* ***1982***, *11*, 227; Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 2, Wiley, NY, ***1986***. See also, Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 24, Elsevier, NY, ***1983***.

[68] See Connors, K.A. *Chemical Kinetics*, VCH, NY, ***1990***, pp. 17–131; Ritchie, C.D. *Physical Organic Chemistry*, 2nd ed., Marcel Dekker, NY, ***1990***, pp. 1–35; Zuman, P.; Patel, R.C. *Techniques in Organic Reaction Kinetics,* Wiley, NY, ***1984***; Margerison, D. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics,* Vol. 1, Elsevier, NY, ***1969***, pp. 343–421; Moore, J.W.; Pearson, R.G. *Kinetics and Mechanism*, 3rd ed., Wiley, NY, ***1981***, pp. 12–82; in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, the articles by Bunnett, J.F. pp. 251–372, Noyes Pub., pp. 373–423, Bernasconi, C.F. pp. 425–485, Wiberg, K.B. pp. 981–1019.

For the general case of a reaction first order in **A** and first order in **B**, second order overall, integration is complicated, but it can be simplified if equimolar amounts of **A** and **B** are used, so that $\mathbf{A}_o = \mathbf{B}_o$. In this case

$$\frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}][\mathbf{B}]$$

is equivalent to

$$\frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}]^2 \quad \text{or} \quad \frac{-d[\mathbf{A}]}{[\mathbf{A}]^2} = k\,dt$$

Integrating as before gives

$$\frac{1}{[\mathbf{A}]} - \frac{1}{\mathrm{A}_o} = kt$$

Thus, under equimolar conditions, if a plot of $1/[\mathbf{A}]$ against t is linear, the reaction is second order with a slope of k. It is obvious that the same will hold true for a reaction second order in **A**.[69]

Although many reaction-rate studies do give linear plots, which are easily interpreted, the results in many other studies are not so simple. In some cases a reaction may be first order at low concentrations but second order at higher concentrations. In other cases fractional orders are obtained, and even negative orders. The interpretation of complex kinetics often requires much skill and effort. Even where the kinetic data are relatively simple, there is often a problem in interpreting the data because of the difficulty of obtaining sufficiently precise measurements.[70]

Nuclear magnetic resonance (NMR) spectra can be used to obtain kinetic information in a completely different manner from that mentioned above. This method, which involves the study of NMR line shapes,[71] depends on the fact that NMR spectra have an inherent time factor: if a proton changes its environment less rapidly than $\sim 10^3$ times per second, an NMR spectrum shows a separate peak for each position the proton assumes. For example, if the rate of rotation around the C—N bond of *N*,*N*-dimethylacetamide is slower than 10^3 rotations per second, the two *N*-methyl groups appear as separate signal with different chemical shifts indicating that they are not equivalent, one being *cis* to the oxygen and the other *trans* to the acyl methyl group. However, if the environmental change takes place more rapidly than $\sim 10^3$ times per second, only one signal is found, at a chemical shift that is the weighted average of the two individual positions. In many cases, two or more signals are found at low temperatures, but as the temperature is increased, the lines coalesce because the interconversion rate increases with temperature and passes the 10^3 per second mark. From studies of the way line shapes change with temperature it is often possible to calculate rates of reactions and of conformational changes. This method is not limited to

[69] See Margerison, D. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics,* Vol. 1, Elsevier, NY, ***1969***, p. 361.

[70] See Hammett, L.P. *Physical Organic Chemistry,* 2nd ed., McGraw-Hill, NY, ***1970***, pp. 62–70.

[71] See Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, NY, ***1985***; Fraenkel, G. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 2, Wiley, NY, ***1986***, pp. 547–604; Roberts, J.D. *Pure Appl. Chem.* ***1979***, *51*, 1037; Binsch, G. *Top. Stereochem.* ***1968***, *3*, 97.

changes in proton line shapes but can also be used for other atoms that give NMR spectra and for ESR spectra (Sec. 5.C.i).

Several types of mechanistic information can be obtained from kinetic studies.

1. Information can be obtained from the order of a reaction. Which molecules and how many take part in the rate-determining step may be determined. Such knowledge is very useful and often essential in elucidating a mechanism. For any mechanism that can be proposed for a given reaction, a corresponding rate law can be calculated by the methods discussed in the beginning of this section. If the experimentally obtained rate law fails to agree with this, the proposed mechanism is wrong. However, it is often difficult to relate the order of a reaction to the mechanism, especially when the order is fractional or negative. It is frequently the case that two or more proposed mechanisms for a reaction are kinetically indistinguishable, that is, they predict the same rate law.
2. Probably the most useful data obtained kinetically are the rate constants themselves. They are important since they can relate the effect on the rate of a reaction of changes in the structure of the reactants[72] (see Chapter 9), the solvent,[73] the ionic strength, the addition of catalysts, and so on.
3. If the rate is measured at several temperatures, in most cases a plot of ln k against $1/T$ (T stands for absolute temperature) is nearly linear[74] with a negative slope, and fits the equation

$$\ln\ k = \frac{-E_a}{RT} + \ln\ A$$

where R is the gas constant and A is a constant called the *frequency factor*. This permits the calculation of E_a, which is the *Arrhenius activation energy* of the reaction. $\Delta H^{\ddagger}$ can then be obtained by

$$E_a = \Delta H^{\ddagger} + RT$$

It is also possible to use these data to calculate $\Delta S^{\ddagger}$ by the formula[75]

$$\frac{\Delta S^{\ddagger}}{4.576} = \log\ k - 10.753 - \log\ T + \frac{E_a}{4.576T}$$

for energies in calorie units. For joule units the formula is

$$\frac{\Delta S^{\ddagger}}{19.15} = \log\ k - 10.753 - \log\ T + \frac{E_a}{19.15T}$$

One then obtains $\Delta G^{\ddagger}$ from $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$.

[72] Madzhidov, T.I.; Polishchuk, P.G.; Nugmanov, R.I. *Russ. J. Org. Chem.* ***2014***, *50*, 459.

[73] For a discussion of organic reaction rate acceleration by immediate solvent evaporation, see Orita, A.; Uehara, G.; Miwa, K.; Otera, J. *Chem. Commun.* ***2006***, 4729.

[74] See Blandamer, M.J.; Burgess, J.; Robertson, R.E.; Scott, J.M.W. *Chem. Rev.* ***1982***, *82*, 259.

[75] See Bunnett, J.F. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, p. 287.

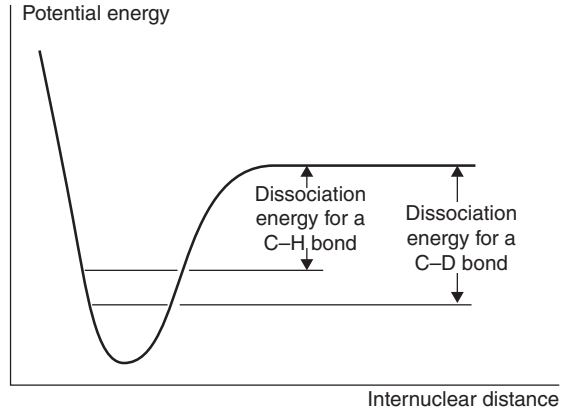


FIGURE 6.4. The C—D bond has a lower zero point than does the corresponding C—H bond; thus the dissociation energy is higher.

6.J.vii. Isotope Effects

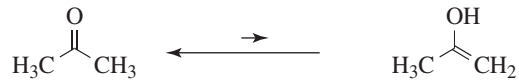
Deuterium isotope effects[76] are observed when a hydrogen atom in a reactant molecule is replaced by deuterium, and a change in rate is expressed by the ratio k_H/k_D. The ground-state vibrational energy (called the zero-point vibrational energy) of a bond depends on the mass of the atoms and is lower when the reduced mass is higher.[77] [Reduced mass is the representation of a two-body system as a single body. It is $(m_A m_B/(m_A + m_B)$, where m is the mass of each atom.] Therefore, D—C, D—O, D—N bonds, and so on, have lower energies in the ground state than the corresponding H—C, H—O, H—N bonds, etc. Complete dissociation of a deuterium bond therefore requires more energy than that for a corresponding hydrogen bond in the same environment (Figure 6.4).

If an H—C, H—O, or H—N bond is not broken at all in a reaction or is broken in a non-rate-determining step, substitution of deuterium for hydrogen causes no change in the rate (see below for an exception to this statement), but if the bond is broken in the rate-determining step, the rate must be lowered by the substitution.

This provides a valuable diagnostic tool for determination of mechanism. For example, in the bromination of acetone (reaction **12-4**)

$$CH_3COCH_3 + Br_2 \longrightarrow CH_3COCH_2Br$$

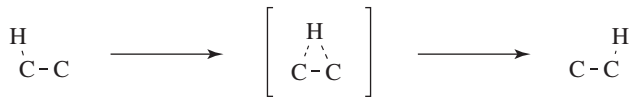
the fact that the rate is independent of the bromine concentration led to the postulate that the rate-determining step was prior tautomerization of the acetone:



[76] See Melander, L.; Saunders Jr., W.H. *Reaction Rates of Isotopic Molecules*, Wiley, NY, ***1980***. See Saunders Jr., W.H. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions*, 4th ed. (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), pt. 1, Wiley, NY, ***1986***, pp. 565–611; Bell, R.P. *Chem. Soc. Rev.* ***1974***, *3*, 513. Also see Kwart, H. *Acc. Chem. Res.* ***1982***, *15*, 401; Thibblin, A.; Ahlberg, P. *Chem. Soc. Rev.* ***1989***, *18*, 209. See also, the series *Isotopes in Organic Chemistry.*

[77] The reduced mass μ of two atoms connected by a covalent bond is $\mu = m_1 m_2/(m_1 + m_2)$.

In turn, the rate-determining step of the tautomerization involves cleavage of a C—H bond (see **12-3**). Thus there should be a substantial isotope effect if deuterated acetone is brominated.[78] In fact, k_H/k_D was found to be ~7.[79] Deuterium isotope effects usually range from 1 (no isotope effect at all) to ~7 or 8, although in a few cases, larger[80] or smaller values have been reported.[81] Values of $k_H/k_D < 1$ are called *inverse isotope effects*. Isotope effects are greatest when, in the transition state, the hydrogen is symmetrically bonded to the atoms between which it is being transferred.[82] Also, calculations show that isotope effects are at a maximum when the hydrogen atom in the transition state is on the straight line connecting the two atoms between which it is being transferred, and that for sufficiently nonlinear configurations they decrease to $k_H/k_D = 1–2$.[83] Of course, in open systems there is no reason for the transition state to be nonlinear, but this is not the case in many intramolecular mechanisms, e.g., in a 1,2 migration of a hydrogen.



Transition state

To measure isotope effects it is not always necessary to prepare deuterium-enriched starting compounds. It can also be done by measuring the change in deuterium concentration at specific sites between a compound containing deuterium in natural abundance and the reaction product, using a high-field NMR instrument.[84]

The substitution of tritium for hydrogen gives isotope effects that are numerically larger.

Isotope effects have also been observed with other elements, but they are much smaller, ~1.02–1.10. For example, k_{12C}/k_{13C} for the reaction of methoxide with benzyl bromide is 1.053.[85]

$$Ph^*CH_2Br + CH_3O^- \xrightarrow{CH_3OH} Ph^*CH_2OCH_3$$

Although they are small, heavy-atom isotope effects can be measured quite accurately and are often very useful.[86]

[78] For Cl kinetic isotope effects, see Świderek, K.; Paneth, P. *J. Org. Chem.* ***2012***, *77*, 5120.

[79] Reitz, O.; Kopp, J. *Z. Phys. Chem. Abt. A* ***1939***, *184*, 429.

[80] For an example of a reaction with a deuterium isotope effect of 24.2, see Lewis, E.S.; Funderburk, L.H. *J. Am. Chem. Soc.* ***1967***, *89*, 2322. The high isotope effect in this case has been ascribed to *tunneling* of the proton: See Kresge, A.J.; Powell, M.F. *J. Am. Chem. Soc.* ***1981***, *103*, 201; Caldin, E.F.; Mateo, S.; Warrick, P. *J. Am. Chem. Soc.* ***1981***, *103*, 202. For arguments that high isotope effects can be caused by factors other than tunneling, see Thibblin, A. *J. Phys. Org. Chem.* ***1988***, *1*, 161; Kresge, A.J.; Powell, M.F. *J. Phys. Org. Chem.* ***1990***, *3*, 55. For a review of tunneling in organic reactions, see Greer, E.M.; Kwon, K.; Greer, A.; Doubleday, C. *Tetrahedron.* ***2016***, *72*, 7357.

[81] See Sims, L.B.; Lewis, D.E. *Isot. Org. Chem.* ***1984***, *6*, 161.

[82] Bethell, D.; Hare, G.J.; Kearney, P.A. *J. Chem. Soc., Perkin Trans. 2* ***1981***, 684, and references cited therein. See, however, Motell, E.L.; Boone, A.W.; Fink, W.H. *Tetrahedron* ***1978***, *34*, 1619.

[83] More O'Ferrall, R.A. *J. Chem. Soc. B* ***1970***, 785, and references cited therein.

[84] Pascal, R.A.; Baum, M.W.; Wagner, C.K.; Rodgers, L.R.; Huang, D. *J. Am. Chem. Soc.* ***1986***, *108*, 6477.

[85] Stothers, J.B.; Bourns, A.N. *Can. J. Chem.* ***1962***, *40*, 2007. See also, Ando, T.; Yamataka, H.; Tamura, S.; Hanafusa, T. *J. Am. Chem. Soc.* ***1982***, *104*, 5493.

[86] For a review of carbon isotope effects, see Willi, A.V. *Isot. Org. Chem.* ***1977***, *3*, 237.

Deuterium isotope effects have been found even where it is certain that the C—H bond does not break at all in the reaction. Such effects are called *secondary isotope effects*,[87] as the term *primary isotope effect* is reserved for the type discussed previously. Secondary isotope effects can be divided into α and β effects. In a β secondary isotope effect, substitution of deuterium for hydrogen β to the position of bond breaking slows the reaction. An example is solvolysis of 2-bromopropane to propan-2-ol,where k_H/k_D was found to be 1.34.[88]

$$(CH_3)_2CHBr + H_2O \xrightarrow{k_H} (CH_3)_2CHOH$$
$$(CD_3)_2CHBr + H_2O \xrightarrow{k_D} (CD_3)_2CHOH$$

The cause of β isotope effects has been a matter of much controversy, but they are most likely due to hyperconjugation effects in the transition state. The effects are greatest when the transition state has considerable carbocation character.[89] Although the C—H bond in question is not broken in the transition state, the carbocation is stabilized by hyperconjugation (Sec. 2.M) involving this bond. Because of hyperconjugation, the difference in vibrational energy between the C—H bond and the C—D bond in the transition state is less than it is in the ground state, so the reaction is slowed by substitution of deuterium for hydrogen.

Support for hyperconjugation as the major cause of β isotope effects is the fact that the effect is greatest when D is *anti* to the leaving group[90] (because of the requirement that all atoms in a resonance system be coplanar, planarity of the D—C—C—X system would most greatly increase the hyperconjugation), and the fact that secondary isotope effects can be transmitted through unsaturated systems.[91] There is evidence that at least some β isotope effects are steric in origin[92] (e.g., a CD_3 group has a smaller steric requirement than a CH_3 group) and a field-effect explanation has also been suggested (CD_3 is apparently a better electron donor than CH_3[93]), but hyperconjugation (Sec. 2.M) is the most probable cause in most instances.[94] Part of the difficulty in attempting to explain these effects is their small size, ranging only as high as ~1.5.[95] Another complicating factor is that they can change with temperature. In one case,[96] k_H/k_D was 1.00 ± 0.01 at 0 °C, 0.90 ± 0.01 at 25 °C, and 1.15 ± 0.09 at 65 °C. Whatever the cause, there seems to be a good correlation between β

[87] See Westaway, K.C. *Isot. Org. Chem.* ***1987***, *7*, 275; Sunko, D.E.; Hehre, W.J. *Prog. Phys. Org. Chem.* ***1983***, *14*, 205. See McLennan, D.J. *Isot. Org. Chem.* ***1987***, *7*, 393; Sims, L.B.; Lewis, D.E. *Isot. Org. Chem.* ***1984***, *6*, 161.
[88] Leffek, K.T.; Llewellyn, J.A.; Robertson, R.E. *Can. J. Chem.* ***1960***, *38*, 2171.
[89] Bender, M.L.; Feng, M.S. *J. Am. Chem. Soc.* ***1960***, *82*, 6318; Jones, J.M.; Bender, M.L. *J. Am. Chem. Soc.* ***1960***, *82*, 6322.
[90] DeFrees, D.J.; Hehre, W.J.; Sunko, D.E. *J. Am. Chem. Soc.* ***1979***, *101*, 2323. See also, Siehl, H.; Walter, H. *J. Chem. Soc., Chem. Commun.* ***1985***, 76.
[91] Shiner Jr., V.J.; Kriz Jr., G.S. *J. Am. Chem. Soc.* ***1964***, *86*, 2643.
[92] Carter, R.E.; Dahlgren, L. *Acta Chem. Scand.* ***1970***, *24*, 633; Leffek, K.T.; Matheson, A.F. *Can. J. Chem.* ***1971***, *49*, 439; Sherrod, S.A.; Boekelheide, V. *J. Am. Chem. Soc.* ***1972***, *94*, 5513.
[93] Halevi, E.A.; Nussim, M.; Ron, M. *J. Chem. Soc.* ***1963***, 866; Halevi, E.A.; Nussim, M. *J. Chem. Soc.* ***1963***, 876.
[94] Sunko, D.E.; Szele, I.; Hehre, W.J. *J. Am. Chem. Soc.* ***1977***, *99*, 5000; Kluger, R.; Brandl, M. *J. Org. Chem.* ***1986***, *51*, 3964.
[95] Halevi, E.A.; Margolin, Z. *Proc. Chem. Soc.* ***1964***, 174. A value for k_{CH_3}/k_{CD_3} of 2.13 was reported for one case: Liu, K.; Wu, Y.W. *Tetrahedron Lett.* ***1986***, *27*, 3623.
[96] Halevi, E.A.; Margolin, Z. *Proc. Chem. Soc.* ***1964***, 174.

secondary isotope effects and carbocation character in the transition state, and they are thus a useful tool for probing mechanisms.

The other type of secondary isotope effect results from a replacement of hydrogen by deuterium at the carbon containing the leaving group. These so-called *secondary isotope effects* are varied, with values so far reported[97] ranging from 0.87 to 1.26.[98] These effects are also correlated with carbocation character. Nucleophilic substitutions that do not proceed through carbocation intermediates (S_N2 reactions) have an isotope effect near unity.[99] Those that do involve carbocations (S_N1 reactions) have higher isotope effects, which depend on the nature of the leaving group.[100] The accepted explanation for α isotope effects is that one of the bending C—H vibrations is affected by the substitution of D for H more or less strongly in the transition state than in the ground state.[101] Depending on the nature of the transition state, this may increase or decrease the rate of the reaction. The α isotope effects on S_N2 reactions can vary with concentration,[102] an effect attributed to a change from a free nucleophile to one that is part of an ion pair[103] (Sec. 10.G.ii). This illustrates the use of secondary isotope effects as a means of studying transition-state structure. The γ secondary isotope effects have also been reported.[104]

Another kind of isotope effect is the *solvent isotope effect*.[105] Reaction rates often change when the solvent is changed from H_2O to D_2O or from ROH to ROD. These changes may be due to any of three factors or a combination of all of them.

1. The solvent may be a reactant. If an O—H bond of the solvent is broken in the rate-determining step, there will be a primary isotope effect. If the molecules involved are D_2O or D_3O^+ there may also be a secondary effect caused by the O—D bonds that are not breaking.
2. The substrate molecules may become labeled with deuterium by rapid hydrogen exchange, and then the newly labeled molecule may become cleaved in the rate-determining step.
3. The extent or nature of solvent–solute interactions may be different in the deuterated and nondeuterated solvents; this may change the energies of the transition state and hence the activation energy of the reaction. These are secondary isotope effects. Two physical models for this third factor have been constructed.[106]

It is obvious that in many cases the first and third factors at least, and often the second, are working simultaneously. Attempts have been made to separate them.[107]

[97] See Caldwell, R.A.; Misawa, H.; Healy, E.F.; Dewar, M.J.S. *J. Am. Chem. Soc.* ***1987***, *109*, 6869.
[98] See Harris, J.M.; Hall, R.E.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1971***, *93*, 2551.
[99] For reported exceptions, see Tanaka, N.; Kaji, A.; Hayami, J. *Chem. Lett.* ***1972***, 1223; Westaway, K.C. *Tetrahedron Lett.* ***1975***, 4229.
[100] Shiner Jr., V.J.; Neumann, A.; Fisher, R.D. *J. Am. Chem. Soc.* ***1982***, *104*, 354 and references cited therein.
[101] Streitwieser Jr., A.; Jagow, R.H.; Fahey, R.C.; Suzuki, S. *J. Am. Chem. Soc.* ***1958***, *80*, 2326.
[102] Westaway, K.C.; Waszczylo, Z.; Smith, P.J.; Rangappa, K.S. *Tetrahedron Lett.* ***1985***, *26*, 25.
[103] Westaway, K.C.; Lai, Z. *Can. J. Chem.* ***1988***, *66*, 1263.
[104] Werstiuk, N.H.; Timmins, G.; Cappelli, F.P. *Can. J. Chem.* ***1980***, *58*, 1738.
[105] See Alvarez, F.J.; Schowen, R.L. *Isot. Org. Chem.* ***1987***, *7*, 1; Kresge, A.J.; More O'Ferrall, R.A.; Powell, M.F. *Isot. Org. Chem.* ***1987***, *7*, 177; Schowen, R.L. *Prog. Phys. Org. Chem.* ***1972***, *9*, 275.
[106] Bunton, C.A.; Shiner Jr., V.J. *J. Am. Chem. Soc.* ***1961***, *83*, 42, 3207, 3214; Swain, C.G.; Thornton, E.R. *J. Am. Chem. Soc.* ***1961***, *83*, 3884, 3890. See also, Mitton, C.G.; Gresser, M.; Schowen, R.L. *J. Am. Chem. Soc.* ***1969***, *91*, 2045.
[107] More O'Ferrall, R.A.; Koeppl, G.W.; Kresge, A.J. *J. Am. Chem. Soc.* ***1971***, *93*, 9.

The methods described in this chapter are not the only means of determining mechanisms. A detailed examination of the literature, coupled with well-planned experiments, is the best way to devise an approach to the mechanism of a given reaction.

6.K. CATALYST DEVELOPMENT

Both homogeneous catalysts[108] and heterogeneous catalysts[109] are well established as useful reagents/methods in organic chemical reactions. Brønsted acids are used for catalysis.[110] With the revolution in transition metal-catalyzed reactions over the last 30–40 years, as well as the use of non-transition metal catalysis in organic synthesis, there is a large area of research that involves catalyst development. Myriad transition metal catalysts in many reactions as well as nonmetal catalysts have been developed.[111] This area is vast, and far too large to do more than a survey of recent developments.

Many transition metals have been used in organic catalysis. Palladium catalysts are the mainstay of the *Heck reaction* (**13-13**), the *Suzuki-Miyara reaction* (**13-11**), the *Sonogashira reaction* (**13-14**), the *Tsuji Trost reaction* (**10-60**), and many more. The role of palladium in the surface catalysis of coupling reactions has been discussed.[112] A homogeneous Pd/Cu catalyst has been developed for continuous recycling and used for cross-coupling reactions.[113] Palladium- and Ni-catalyzed reactions using bidentate directing groups are important.[114] Palladium nanoparticles have been used.[115]

Rhodium catalysts are the mainstay of the most used olefin metathesis catalysts (**18-37**).[116] Several dirodium catalysts have been developed, including the *Davies catalyst*[117] [Rh_2(*S*-DOSP)$_2$ and Doyle and co-workers[118] developed several important rhodium catalysts, including the *Doyle catalysts* that are widely used in cyclopropanation and C—H insertion reactions.

[108] van Leeuwen, P.W.N.M.; Chadwick, J.C. *Homogeneous Catalysts. Activity—Stability—Deactivation*, Wiley-VCH, Weinheim, ***2011.*** Šebesta, R. *Enantioselective Homogeneous Supported Catalysis*, Royal Society of Chemistry, Cambridge, ***2011.***

[109] See Ross, J.R.H. *Heterogeneous Catalysis. Fundamentals and Applications*, Elsevier, Amsterdam, ***2012***. Thomas, J.M.; Thomas, W.J. *Principles and Practice of Heterogeneous Catalysis. Second, Completely Revised Version*, Wiley-VCH, Weinheim ***2014***.

[110] See Aziz, H.R.; Singleton, D.A. *J. Am. Chem. Soc.* ***2017***, *139*, 5965. Rueping, M.; Nachtsheim, B.J.; Ieawsuwan, W.; Atodiresei, J. *Angew. Chem. Int. Ed.* ***2011***, *50*, 6706.

[111] Triflic acid can be inadvertently generated from metal triflates and act to catalyze reactions. See Dang, T.T.; Boeck, F.; Hintermann, L. *J. Org. Chem.* ***2011***, *76*, 9353.

[112] Shao, L.; Zhang, B.; Zhang, W.; Hong, S.Y.; Schlögl, R.; Su, D.S. *Angew. Chem. Int. Ed.* ***2013***, *52*, 2114. Also see Wei, C.S.; Davies, G.H.M.; Soltani, O.; Albrecht, J.; Gao, Q.; Pathirana, C.; Hsiao, Y.; Tummala, S.; Eastgate, M.D. *Angew. Chem. Int. Ed.* ***2013***, *52*, 5822.

[113] Basavaraju, S.S.K.C.; Singh, A.K.; Kim, D.P. *Org. Lett.* ***2014***, *16*, 3974.

[114] Yang, X.; Shan, G.; Wang, L.; Rao, Y. *Tetrahedron Lett.* ***2016***, *57*, 819.

[115] Yamada, Y.M.A.; Yuyama, Y.; Sato, T.; Fujikawa, S.; Uozumi, Y. *Angew. Chem. Int. Ed.* ***2014***, *53*, 127.

[116] Vougioukalakis, G.C.; Grubbs, R.H. *Chem. Rev.* ***2010***, *110*, 1746; Samojłowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev.* ***2009***, *109*, 3708.

[117] Davies, H.M.L.; Hansen, T.; Churchill, M.R. *J. Am. Chem. Soc.* ***2000***, *122*, 3063; Davies, H.M.L.; Hansen, T. *J. Am. Chem. Soc.* ***1997***, *119*, 9075. Also see Davies, H.M.L. *Aldrichimica Acta* ***1997***, *30*, 107.

[118] Colacot, T.J. *Proc. Indian Acad. Sci. (Chem. Sci.)* ***2000***, *112*, 197; Doyle, M.P. *Pure & Appl. Chem.* ***1998***, *70*, 1123; Doyle, M.P.; Protopopova, M.N. *Tetrahedron,* ***1998***, *54*, 7919; Martin, S.F.; Spaller, M.R.; Liras, L.; Hartman, B. *J. Am. Chem. Soc.* ***1994***, *116*, 4493; Doyle, M.P.; Kalinin, A.V. *J. Org. Chem.* ***1996***, *61*, 2179; Doyle, M.P.; Dyatkin, A.B.; Roos, G.H.P.; Cañas, F.; Pierson, D.A.; van Basten, A.; Mueller, P.; Polleux, P. *J. Am. Chem. Soc.* ***1994***, *116*, 4507.

Rhenium carbonyl complexes have been used to catalyze organic reactions.[119] Gold catalysts are increasingly important.[120] Cationic Au catalysts have been reported,[121] as well as chiral Au catalysts.[122] Nickel catalysts are well known.[123] (Poly)olefin-supported recoverable/reusable Cr(III)-salen catalysts are known.[124] Recycling an osmium catalyst using a chemoentrapment approach has been reported.[125] An asymmetric Mukaiyama aldol reaction was reported in aqueous media as reported using cupric triflate and bis(oxazolidine) catalyst.[126] Low-valent Co catalysis has been discussed.[127] Aldehydes react with $CrCl_2$ in the presence of a Ni catalyst.[128] (*R*)-BINOL-Titanium catalysts have been used in solvents such as toluene or CH_2Cl_2 (where BINOL is 1,1'-bi-2-naphthol).[129]

A thermally stable and magnetically recyclable catalyst system has been developed: porous silica covered Fe_3O_4•CeO_2.[130] Substituent effects on the catalytic activity of bipyrrolidine–iron catalyst has been evaluated.[131] A C_2-symmetric chiral bis(oxazoline)–Fe(III) complex has been used.[132]

There is considerable research on metal-free catalysis,[133] sometimes called carbocatalysis,[134] and also called organocatalysis,[135] and there are many variations.[136] There is

[119] Kuninobu, Y.; Takai, K. *Chem. Rev.* ***2011***, *111*, 1938.

[120] Shahzad, S.A.; Sajid, M.A.; Khan, Z.A.; Canseco-Gonzalez, D. *Synth. Commun.* ***2017***, *47*, 735. For a discussion of immobilization of Au-nanoparticles on C@P4CP core-shell microspheres, see Li, J.; Hunag, Z.; Yang, M.; Tan, L.; Zhang, X.; Gao, H.; Tang, Y.; Ma, Q.; Wang, G. *New J. Chem.* ***2015***, 2949. Dual Au-catalysis is discussed in Hashmi, A.S.K. *Acc. Chem. Res.* ***2014***, *47*, 864.

[121] Malhotra, D.; Mashuta, M.S.; Hammond, G.B.; Xu, B. *Angew. Chem. Int. Ed.* ***2014***, *53*, 4456.

[122] Pradal, A.; Toullec, P.Y.; Michelet, V. *Synthesis* ***2011***, *43*, 1501.

[123] For gauze-supported catalysts, see Fow K.L.; Ganapathi, M.; Stassen, I.; Fransaer, J.; De Vos, D.E. *Chem. Commun.* ***2013***, *49*, 8498.

[124] Bergbreiter, D.E.; Hobbs, C.; Hongfa, C. *J. Org. Chem.* ***2011***, *76*, 523.

[125] Kim, S.; Chung, J.; Kim, B.M. *Tetrahedron Lett.* ***2011***, *52*, 1363.

[126] Kobayashi, S.; Nagayama, S.; Busujima, T. *Chem. Lett.* ***1999***, 71; *Tetrahedron* ***1999***, *55*, 8739.

[127] Gao, K.; Yoshikai, N. *Acc. Chem. Res.* ***2014***, *47*, 1208.

[128] Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* ***1986***, *108*, 6048.

[129] Mikami, K.; Matsukawa, S.; Kayaki, Y.; Ikariya, T. *Tetrahedron Lett.* ***2000***, *41*, 1931.

[130] Li, X.; Dapeng, X.-W.; Song, S.; Zhang, H. *Chem. Commun.* ***2014***, *50*, 7198.

[131] Olivo, G.; Lanzalunga, O.; Mandolini, L.; Di Stefano, S. *J. Org. Chem.* ***2013***, *78*, 11508. For a discussion of chiral Fe catalysts, see Gopalaiah, K. *Chem. Rev.* ***2013***, *113*, 3248; Bauer, I.; Knölker, H.-J. *Chem. Rev.* ***2015***, *115*, 3170.

[132] Corey, E.J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* ***1991***, *113*, 728.

[133] North, M. (ed.) *Sustainable Catalysis. Without Metals or Other Endangered Elements, Part 1 and 2*, RSC Publishing, ***2016***.

[134] Chua, C.K.; Pumera, M. *Chem. Eur. J.* ***2015***, *21*, 12550; Su, D.S.; Wen, G.; Wu, S.; Peng, F.; Schlögl, R. *Angew. Chem. Int. Ed.* ***2017***, *56*, 936.

[135] Glorius F. (ed.), *N-Heterocyclic Carbenes in Transition Metal Catalysis; Topics in Organimetallic Chemistry, Vol. 21*, Springer-Verlag, Berlin/Heidelberg, ***2007***; Nolan, S.P. (ed.) *N-Heterocyclic Carbenes in Synthesis*, Wiley-VCH, NY, ***2006***; Nair, V.; Vellalath, S.; Babu, B.P. *Chem. Soc. Rev.* ***2008***, *37*, 2691; Enders, D.; Nemeier, O.; Henseler, A. *Chem. Rev.* ***2007***, *107*, 5606; Marion, N.; Diez-Gonxalez, S.; Nolan, S.P. *Angew. Chem. Int. Ed.* ***2007***, *46*, 2988; Dalko, P.I. (ed.) *Comprehensive Enantioselective Organocatalysis*, 3 Volumes, Wiley-VCH, Weinheim, ***2013***. Torres, R.R. (ed.) *Stereoselective Organocatalysis. Bond Formation Methodologies and Activation Modes*, Wiley, Hoboken, ***2013***. Hernández, J.G.; Juaristi, E. *Chem. Commun.* ***2012***, *48*, 5396; Renzi, P.; Bella, M. *Chem. Commun.* ***2012***, *48*, 6881. See Panov, I.; Drabina, P.; Hanusek, J.; Sedlák, M. *Tetrahedron: Asymmetry* ***2011***, *22*, 215. Nugent, T.C.; Sadiq, A.; Bibi, A.; Heine, T.; Zeonjuk, L.-L.; Vankova, N.; Bassil, B.S. *Chem. Eur. J.* ***2012***, *18*, 4088. For SOMO activation with enantioselective organocatalysts, see Mečiarová, M.; Tisovský, P.; Šebesta, R. *New J. Chem.* ***2016***, 4855.

[136] For the use of nontoxic Bi2O3 as a photocatalyst, see Riente, P.; Adams, A.M.; Albero, J.; Palomares, E.; Pericàs, M.A. *Angew. Chem. Int. Ed.* ***2014***, *53*, 9613. For sulfenate anions as organocatalysts, see Zhang, M.; Jia, T.; Yin, H.; Carroll, P.J.; Schelter, E.J.; Walsh, P.J. *Angew. Chem. Int. Ed.* ***2014***, *53*, 10755. For α,

significant work on developing molecular catalysts by computer.[137] Recycling asymmetric catalysts is an important area of research.[138] Asymmetric catalysis[139] is perhaps the most important area of research, and physical organic parameters have been used to correlate asymmetric catalyst performance.[140] Additive effects have been observed in asymmetric catalysis.[141]

There are many examples of organocatalysts. Oxaborolidines derived from amino alcohols of (1*R*)-camphor have been used as catalysts.[142] Chiral oxazaborolidines are an important class of catalysts.[143] Protected proline and abrine esters (L-abrine is *N*-methyl-L-tryptophan) and related compounds have been used as chiral catalysts.[144] Asymmetric phosphazenes have been developed as organocatalysts[145] for aldol condensation reactions (**16-34**). Chiral 2-aminobensimidazole derivatives have been developed as bifunctional organocatalysts.[146] Aliphatic oxocarbenium ions have been used for asymmetric catalysis.[147] A review is available for Cinchona alkaloids and their derivatives as important catalysts for asymmetric synthesis.[148] Hypervalent iodine catalysts have been used for intermolecular enantioselective reactions.[149]

A *biocatalyst* is a substance, such as an enzyme or hormone, that initiates or increases the rate of a chemical reaction.[150] Biocatalysts continue to be an important area of research. A recyclable biocatalyst,[151] decorated magnetic nonabeads, has been prepared for use in aqueous media.[152] There is a discussion of the structure–activity relationship

β-unsaturated acylammonium salts, see Vellalath, S.; Romo, D. *Angew. Chem. Int. Ed.* ***2016***, *55*, 13934. For *S*-benzyl isothiouronium chloride, see Nguyen, O.P.B.; Kim, T.H. *Synthesis* ***2012***, *44*, 1977. For guanidine, see Selig, P. *Synthesis* ***2013***, *45*, 703. For poly(dopamine), see Mrówczyński, R.; Bunge, A.; Liebscher, J. *Chem. Eur. J.* ***2014***, *20*, 8647. For β-carbonyl phenyltetrazolesulfones, see Zweifel, T.; Nielsen, M.; Overgaard, J.; Jacobsen, C.B.; Jørgensen, K.A. *Eur. J. Org. Chem.* ***2011***, 47. For chiral bis-dilanols and diols, see Beemelmanns, C.; Husmann, R.; Whelligan, D.K.; Özçubukçu, S.; Bolm, C. *Eur. J. Org. Chem.* ***2012***, 3373. For functionalized prolinamides, see Orlandi, M.; Benaglia, M.; Raimondi, L.; Celentano, G. *Eur. J. Org. Chem.* ***2013***, 2346. For diarylprolinol silyl ether systems, see Jensen, L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K.A. *Acc. Chem. Res.* ***2012***, *45*, 248.

[137] Dupuis, M. *Acc. Chem. Res.* ***2015***, *48*, 248.

[138] Moberg, C. *Acc. Chem. Res.* ***2016***, *49*, 2736. For a discussion of recyclable Pd catalysts, see Molnár, Á. *Chem. Rev.* ***2011***, *111*, 2251.

[139] Moberg, C. *Isr. J. Chem.* ***2012***, *52*, 653.

[140] Harper, K.C.;. Sigman, M.S. *J. Org. Chem.* ***2013***, *78*, 2813.

[141] Hong, L.; Sun, W.; Yang, D.; Li, G.; Wang, R. *Chem. Rev.* ***2016***, *116*, 4006.

[142] Santhi, V.; Rao, J.M. *Tetrahedron: Asymmetry* ***2000***, *11*, 3553.

[143] For cycloaddition catalysts, see Reddy, K.M.; Bhimireddy, E.; Thirupathi, B.; Breitler, S.; Yu, S. Corey, E.J. *J. Am. Chem. Soc.* ***2016***, *138*, 2443. Also see Corey, E.J.; Imwinkelried, R.; Pikul, S.; Xiang, Y.B. *J. Am. Chem. Soc.* ***1989***, *111*, 5493.

[144] Ahrendt, K.A.; Borths, C.J.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2000***, *122*, 4243.

[145] Simón, L.; Paton, R.S. *J. Org. Chem.* ***2015***, *80*, 2756.

[146] Lee, M.; Zhang, L.; Park, Y.; Park, H.-g. *Tetrahedron* ***2012***, *68*, 1452.

[147] Lee, S.; Kaib, P.S.J.; List, B. *J. Am. Chem. Soc.* ***2017***, *139*, 2156.

[148] Yeboah, E.M.O.; Yeboah, S.O.; Singh, G.S. *Tetrahedron* ***2011***, *67*, 1725.

[149] Haubenreisser, S.; Wöste, T.H.; Martínez, C.; Ishihara, K.; Muñiz, K. *Angew. Chem. Int. Ed.* ***2016***, *55*, 413.

[150] Reetz, M.T. *J. Am. Chem. Soc.* ***2013***, *135*, 12480. See Czekster, C.M.; Ledewig, H.; McMahon, S.A.; Naismith, J.H. *Nature Communications* ***2017***, *8*, 1045; Anthonsen, T. *Reactions Catalyzed by Enzymes* in Adlercreutz, P.; Straathof, A.J.J. *Applied Biocatalysis* (2nd ed.), Taylor & Francis, Boca Raton, FL, ***2000***, pp. 18–59. Faber, K. *Biotransformations in Organic Chemistry* (6th ed.), Springer, Berlin, ***2011***.

[151] Faber, K.; Fessner, W.-D.; Nicholas, J.; Turner, N.J. (eds) *Biocatalysis in Organic Synthesis. Science of Synthesis, Vol. 1–3*, Georg Thieme, Stuttgart, ***2015.*** MacDonald, C.B.J.; Tobin, M.F.; Morrison, A.E.; Tait, M.E.; D'Cunha, G.B.; MacQuarrie, S.L. *Aust. J. Chem.* ***2015***, *68*, 396.

[152] Sim, Y.K.; Jung, S.; Lim, J.Y.; Kim, J.; Kim, S.-H.; Song, B.K.; Kim, B.T.; Lee, H.; Park, S. *Tetrahedron Lett.* ***2011***, *52*, 1041.

and catalyst activation pathway for air-stable catalysts used for C—C or C—N coupling.[153]

Frustrated Lewis pairs have been used for catalysis.[154] Lewis acids are, in general, excellent catalysts[155] for many reactions, including the Diels-Alder reaction (**15-56**).[156] Lewis acid-assisted hydrogen bond donor catalysis is known.[157] Titanocene/zinc catalytic platforms have been used for redox and Lewis acid relay catalysis for the development of multicomponent coupling reactions.[158] The mechanistic role of chiral counterions has been discussed.[159] Shibasaki catalysts, especially involving lanthanides, have been developed for use in asymmetric synthetic chemistry.[160] Ureates were formed by the reaction of ureas with *n*-BuLi and they activate SmI_2 toward the reduction of several organohalides.[161]

Covalent organic frameworks, formed from multidentate organic building blocks through covalent bonds, are a relatively new class of porous crystalline materials.[162] Myriad organic functionality have been employed for these frameworks. Homochiral two-dimensional frameworks have been developed for heterogeneous asymmetric catalysis.[163] Chiral phosphine–alkene ligands have been used with a (cyclopentadienyl)manganese(I) scaffold.[164] Pyradazine has been examined as a possible scaffold for nucleophilic catalysis.[165] 2,5-Siamniobixyclo[2.2.2]octane has been used as a scaffold via salen–metal complexes.[166]

There are phosphinite-functionalized, imidazolyl-P (PCP)-pincer (phosphorus–carbon–phosphorus) complexes of Ni^{II}.[167] Note that a pincer ligand is a type of chelating agent that binds tightly to three adjacent coplanar sites. A chiral, bis(imidazolidine)-derived NCN-type palladium pincer complex has been developed.[168] Porphyrin-based PCP pincer complexes are known.[169] Phosphite ligands have been used for asymmetric catalysis.[170] Bicyclic phosphorus ligands have been developed for use in ionic liquids.[171] Ligand development is

[153] Seechurn, C.C.C.J.; Parisel, S.L.; Colacot, T.J. *J. Org. Chem.* ***2011***, *76*, 7918.
[154] Manuel, A. *Synlett* ***2014***, *25*, 1519.
[155] For enantiodivergent catalysis in water, see Aplander, K.; Lindström, U.M.; Wennerberg, J. *Synthesis* ***2012***, *44*, 848.
[156] Yates, P.; Eaton, P. *J. Am. Chem. Soc.* ***1960***, *82*, 4436; Fray, E.I.; Robinson, R. *J. Am. Chem. Soc.* ***1961***, *83*, 249.
[157] So, S.S.; Burkett, J.A.; Mattson, A.E. *Org. Lett.* ***2011***, *13*, 716.
[158] Gianino, J.B.; Campos, C.A.; Lepore, A.J.; Pinkerton, D.M.; Ashfeld, B.L. *J. Org. Chem.* ***2014***, *79*, 12083.
[159] Jindal, G.; Sunoj, R.B. *J. Org. Chem.* ***2014***, *79*, 7600.
[160] Gröger, H. *Eur. J. Org. Chem.* ***2016***, 4116.
[161] McDonald, C.E.; Ramsey, J.D.; McAtee, C.C.; Mauck, J.R.; Hale, E.M.; Cumens, J.A. *J. Org. Chem.* ***2016***, *81*, 5903.
[162] Côte, A.P.; Benin, A.I.; Ockwig, N.W.; O'Keeffe, M.; Matzger, A.J.; Yaghi, O.M. *Science* ***2005***, *310*, 1166; Kandambeth, S.; Mallick, A.; Lukose, B.; Mane, M.; Heine, T.; Banerjee, R. *J. Am. Chem. Soc.* ***2012***, *134*, 19524; Uribe-Romo, F.J.; Hunt, J.R.; Furukawa, H.; Klöck, C.; O'Keeffe, M.; Yaghi, O.M. *J. Am. Chem. Soc.* ***2009***, *131*, 4570; Bunck, D.N.; Dichtel, W.R. *J. Am. Chem. Soc.* ***2013***, *135*, 14952; Spitler, E.L.; Dichtel, W.R. *Nat. Chem.* ***2010***, *2*, 672; Fang, Q.; Zhuang, Z.; Gu, S.; Kaspar, R.B.; Zheng, J.; Wang, J.; Qiu, S.; Yan, Y. *Nat. Commun.* ***2014***, *5*, 4503; Beaudoin, D.; Maris, T.; Wuest, J.D. *Nat. Chem.* ***2013***, *5*, 830.
[163] Wang, X.; Han, X.; Zhang, J.; Wu. X.; Liu, Y.; Cui, Y. *J. Am. Chem. Soc.* ***2016***, *138*, 12332.
[164] Kamikawa, K.; Tseng, Y.-Y.; Jian, J.-H.; Takahashi, T.; Ogasawara, M. *J. Am. Chem. Soc.* ***2017***, *139*, 1545. Khusnutdinov, R.I.; Bayguzina, A.R.; Dzhemilev, U.M. *Russ. J. Org. Chem.* ***2012***, *48*, 309.
[165] Tamaki, A.; Kojima, S.; Yamamoto, Y. *J. Org. Chem.* ***2016***, *81*, 8710.
[166] White, J.D.; Shaw, S. *Org. Lett.* ***2011***, *13*, 2488.
[167] Vabre, B.; Canac, Y.; Lepetit, C.; Duhayon, C.; Chauvin, R.; Zargarian, D. *Chem. Eur. J.* ***2015***, *21*, 17403.
[168] Arai, T.; Oka, I.; Morihata, T.; Awata, A.; Masu, H. *Chem. Eur. J.* ***2013***, *19*, 1554.
[169] Fujimoto, K.; Yoneda, T.; Yorimitsu, H.; Osuka, A. *Angew. Chem. Int. Ed.* ***2014***, *53*, 1127.
[170] van Leeuwen, P.W.N.M.; Kamer, P.C.J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* ***2011***, *111*, 2077.
[171] Escárcega-Bobadilla, M.V.; Teuma, E.; Masdeu-Bultó, A.M.; Gómez, M. *Tetrahedron* ***2011***, *67*, 421.

an important area of research. Imidazole-based chiral ligands are important.[172] Rotaxane ligands have been developed.[173] A chiral P,π-dihydrobenzooxaphosphole ligand has been developed for asymmetric catalysts.[174] TADDOL-derived phosphonites, phosphites, and phosphoramidites have been used in asymmetric catalysis.[175]

[172] For biaryl P,N-ligands, see Cardoso, F.S.P.; Abboud, K.A.; Aponick, A. *J. Am. Chem. Soc.* ***2013***, *135*, 14548.
[173] For [2]rotaxanes, see Hoekman, S.; Kitching, M.O.; Leigh, D.A.; Papmeyer, M.; Roke, D. *J. Am. Chem. Soc.* ***2015***, *137*, 7656. With a chiral rotaxane, see Cakmak, Y.; Erbas-Cakmak, S.; Leigh, D.A. *J. Am. Chem. Soc.* ***2016***, *138*, 1749.
[174] Sieber, J.D.; Chennamadhavuni, D.; Fandrick, K.R.; Qu, B.; Han, Z.S.; Savoie, J.; Ma, S.; Samankumara, L.P.; Grinberg, N.; Lee, H.; Song, J.J.; Senanayake, C.H. *Org. Lett.* ***2014***, *16*, 5494.
[175] Lam, H.W. *Synthesis* ***2011***, *43*, 2011.

CHAPTER 7

Irradiation Processes and Techniques that Influence Reactions in Organic Chemistry

Most reactions carried out in organic chemistry laboratories take place between molecules, all of which are in their ground electronic states. In a *photochemical reaction*,[1] however, a reacting molecule has been previously promoted to an electronically excited state by absorption of light. A molecule in an excited state must lose its extra energy in some manner; it cannot remain in the excited state for long. The subject of electronic spectra is closely related to photochemistry. A chemical reaction is not the only possible means of relinquishing the extra energy in a photochemical process. In this chapter, electronically excited states and the processes of promotion to these states will be discussed. Reactions of such molecules are called photoreactions. There are enantioselective organocatalytic photoreactions,[2] but they will not be discussed here.[3] Two other methods are available to facilitate chemical reactions: sonochemistry and microwave chemistry. Although the physical processes involved are not the same excitation processes observed in photochemistry, irradiation with ultrasound or with microwaves have a significant influence on chemical reactivity, and both are widely used. For that reason, they are included in this chapter. Two relatively new techniques are also included, which are flow reactor chemistry and mechanochemistry, which are increasingly important in organic reactions.

[1] See Michl, J.; Bonačić-Koutecký, V. *Electronic Aspects of Organic Photochemistry*, Wiley, NY, ***1990***; Scaiano, J.C. *Handbook of Organic Photochemistry*, 2 vols., CRC Press, Boca Raton, FL, ***1989***; Coxon, J.M.; Halton, B. *Organic Photochemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1987***; Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***, *Introduction to Organic Photochemistry*, Wiley, NY, ***1986***; Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, ***1984***; Margaretha, P. *Preparative Organic Photochemistry*, *Top. Curr. Chem.* ***1982***, *103*; Turro, N.J. *Modern Molecular Photochemistry*, W.A. Benjamin, NY, ***1978***; Rohatgi-Mukherjee. K.K. *Fundamentals of Photochemistry*, Wiley, NY, ***1978***; Barltrop, J.A.; Coyle, J.D. *Principles of Photochemistry*, Wiley, NY, ***1978***; Scaiano, J.; Johnston, L.J. *Org. Photochem.* ***1989***, *10*, 309. For a history of photochemistry, see Roth, H.D. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1193; Braslavsky, S.E.; Houk, K.N. *Pure Appl. Chem.* ***1988***, *60*, 1055. See also the series *Advances in Photochemistry*, *Organic Photochemistry*, and *Excited States*. For a discussion of microflow (Sec. 4.D) photochemistry, see Aida, S.; Terao, K.; Nishiyama, Y.; Kakiuchi, K.; Oelgemöller, M. *Tetrahedron Lett.* ***2012***, *53*, 5578.

[2] *Chemical Photocatalysis*, König, B. (ed.), De Gruyter, Berlin, ***2013***.

[3] Wessig, P. *Angew. Chem. Int. Ed.* ***2006***, *45*, 2168.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

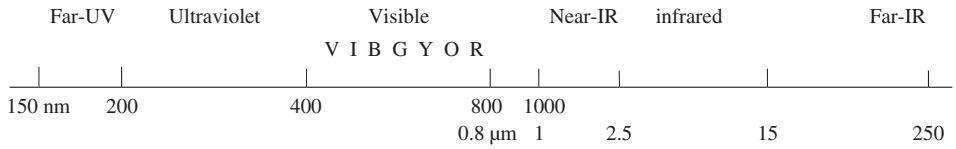


FIGURE 7.1. The UV, visible, and IR portions of the electromagnetic spectrum.

7.A. PHOTOCHEMISTRY[4]

7.A.i. Excited States and the Ground State

Electrons can move from the ground-state energy level of a molecule to a higher level (i.e., an unoccupied orbital of higher energy) if outside energy is supplied.[5] In a photochemical process, this energy is in the form of light. Light of any wavelength has an energy value associated with it given by $E = h\nu$, where ν is the frequency of the light (ν = velocity of light c divided by the wavelength λ) and h is Planck's constant. Since the energy levels of a molecule are quantized, the amount of energy required to raise an electron in a given molecule from one level to a higher one is a fixed quantity. Only light with exactly the frequency corresponding to this amount of energy will cause the electron to move to the higher level. If light of another frequency (too high or too low) is sent through a sample, it will pass out without a loss in intensity, since the molecules will not absorb it. However, if light of the correct frequency is passed into a sample, molecules will use that energy for electron promotion, and the light that leaves the sample will be diminished in intensity or altogether gone. A *spectrophotometer* is an instrument that allows light of a given frequency to pass through a sample and that detects (by means of a phototube) the amount of light that has been transmitted, that is, not absorbed. A spectrophotometer compares the intensity of the transmitted light with that of the incident light. Automatic instruments gradually and continuously change the frequency, and an automatic recorder plots a graph of absorption versus frequency or wavelength.

The energy of electronic transitions corresponds to light in the visible, UV, and far-UV regions of the spectrum (Figure 7.1). Absorption positions are normally expressed in wavelength units, usually nanometers (nm).[6] If a compound absorbs in the visible, it is colored, possessing a color complementary to that absorbed.[7] Thus a compound absorbing in the violet has a yellow color. Organic chemists study the far-UV region less often than the visible or ordinary UV regions because special vacuum instruments are required, owing to the fact that oxygen and nitrogen absorb in the UV, far-UV, and visible.

From these considerations it would seem that an electronic spectrum should consist of one or more sharp peaks, each corresponding to the transfer of an electron from one electronic level to another. Under ordinary conditions the peaks are seldom sharp. In order to understand why, it is necessary to realize that molecules are constantly vibrating and rotating and that these motions are also quantized. A molecule at any time is not

[4] Zimmerman, H.E. *Pure Appl. Chem.* ***2006***, *78*, 2193.
[5] Bao, J.; Weber, P.M. *J. Am. Chem. Soc.* ***2011***, *133*, 4164.
[6] Formerly, millimicrons (mμ) were frequently used; numerically they are the same as nanometers.
[7] For monographs, see Zollinger, H. *Color Chemistry*, VCH, NY, ***1987***; Gordon, P.F.; Gregory, P. *Organic Chemistry in Color*, Springer, NY, ***1983***; Griffiths, J. *Color and Constitution of Organic Molecules*, Academic Press, NY, ***1976***. See also, Fabian, J.; Zahradník, R. *Angew. Chem. Int. Ed.* ***1989***, *28*, 677.

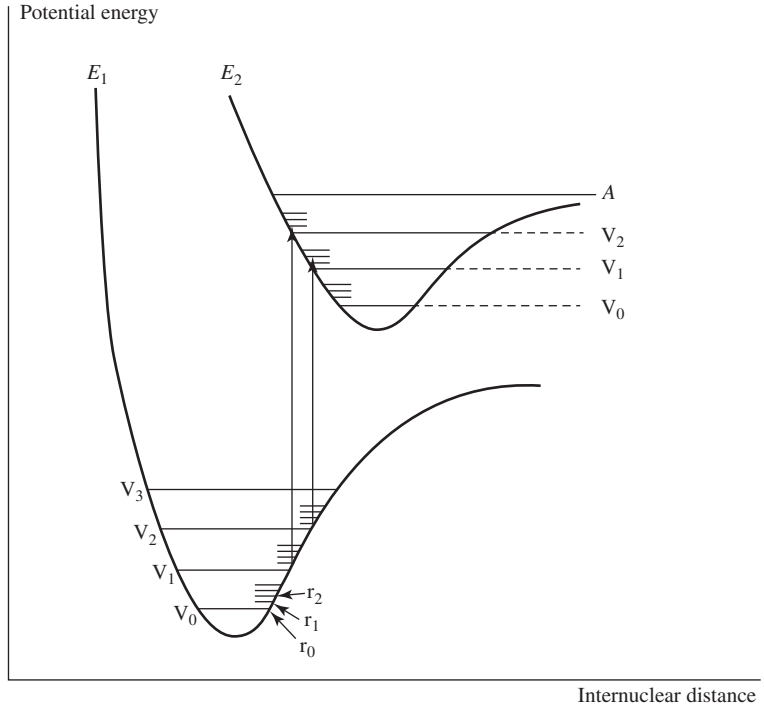


FIGURE 7.2. Energy curves for a diatomic molecule. Two possible transitions are shown. When an electron has been excited to the point marked *A*, the molecule may cleave (Sec. 7.A.v).

only in a given electronic state but also in a given vibrational and rotational state. The difference between two adjacent vibrational levels is much smaller than the difference between adjacent electronic levels, and the difference between adjacent rotational levels is smaller still. A typical situation is shown in Figure 7.2. When an electron moves from one electronic level to another, it moves from a given vibrational and rotational level within that electronic level to some vibrational and rotational level at the next electronic level. A given sample contains a large number of molecules, and even if all of them are in the ground electronic state, they are still distributed among the vibrational and rotational states (though the ground vibrational state V_0 is most heavily populated). This means that not just one wavelength of light will be absorbed but a number of them close together, with the most probable transition causing the most intense peak. But in molecules containing more than a few atoms there are so many possible transitions and these are so close together that what is observed is a relatively broad band.

The height of the peak depends on the number of molecules making the transition and is proportional to log ε, where ε is the *extinction coefficient*. The extinction coefficient can be expressed by

$$\varepsilon = E/cl$$

where c is the concentration in moles per liter, l is the cell length in centimeters, and $E = \log I_0/I$, where I_0 is the intensity of the incident light and I of the transmitted light. The wavelength is usually reported as λ_{max}, meaning that this is the top of the peak. Purely

vibrational transitions, such as between V_0 and V_1 of E_1, which require much less energy, are found in the IR region and are the basis of IR spectra. Purely rotational transitions are found in the far-IR and microwave (beyond the far-IR) regions.

An UV or visible absorption peak is caused by the promotion of an electron in one orbital (usually a ground-state orbital) to a higher orbital. Normally the amount of energy necessary to make this transition depends mostly on the nature of the two orbitals involved and much less on the rest of the molecule. Therefore, a simple functional group such as the C═C double bond always causes absorption in the same general area. A group that causes absorption is called a *chromophore*. A balanced linear equation for the extended Woodward UV rules have been reported for conjugated ketones.[8] The Woodward-Fieser rules are several sets of empirically derived rules which attempt to predict the wavelength of the absorption maximum (λ_{max}) in the ultraviolet–visible spectra of organic compounds.[9]

7.A.ii. Singlet and Triplet States: "Forbidden" Transitions

In most organic molecules, all electrons in the ground state are paired, with each member of a pair possessing opposite spin as demanded by the *Pauli principle*. When one of a pair of electrons is promoted to an orbital of higher energy, the two electrons no longer share an orbital, and the promoted electron may, in principle, have the same spin as its former partner or have the opposite spin. As seen in Chapter 5, a molecule in which two unpaired electrons have the same spin is called a *triplet*,[10] while one in which all spins are paired is a *singlet*. Thus, at least in principle, for every excited singlet state there is a corresponding triplet state. In most cases, the triplet state has a lower energy than the corresponding singlet, which is in accord with *Hund's rule*. Therefore, a different amount of energy, and hence a different wavelength, is required to promote an electron from the ground state (which is almost always a singlet) to an excited singlet than to the corresponding triplet state.

It would thus seem that promotion of a given electron in a molecule could result either in a singlet or a triplet excited state depending on the amount of energy added. However, this is often not the case because transitions between energy levels are governed by selection rules, which state that certain transitions are "forbidden." There are several types of "forbidden" transitions, two of which are more important than the others.

1. *Spin-forbidden transitions*. If the spin of an electron changes, transitions are not allowed, because a change from one spin to the opposite involves a change in angular momentum and such a change would violate the law of conservation of angular momentum. Therefore, singlet–triplet and triplet–singlet transitions are forbidden, whereas singlet–singlet and triplet–triplet transitions are allowed.
2. *Symmetry-forbidden transitions*. Among the transitions in this class are those in which a molecule has a center of symmetry. In such cases, a $g \rightarrow g$ or $u \rightarrow u$ transition (Sec. 1.A) is "forbidden," while a $g \rightarrow u$ or $u \rightarrow g$ transition is allowed.

The word "forbidden" is in quotation marks because these transitions are not actually forbidden but only highly improbable. In most cases, promotions from a singlet ground state

[8] Kang, Y.; Kang, F.-A. *Tetrahedron Lett.* ***2012***, *53*, 1928.
[9] Woodward, R.B. *J. Am. Chem. Soc.* ***1941***, *63*, 1123; Fieser, L.F.; Fieser, M.; Rajagopalan, S. *J. Org. Chem.* ***1948***, *13*, 800; Silverstein, R.M.; Bassler, G.C.; Morrill, T. *Spectrophotometric Identification of Organic Compounds*, 5th ed., Wiley, NY, ***1991***, Tables 7.5 and 7.6, pp. 299–300.
[10] See Kurreck, H. *Angew. Chem. Int. Ed.* ***1993***, *32*, 1409.

TABLE 7.1 Ultraviolet absorption[14] of $CH_3—(CH{=}CH)_n—CH_3$ for some values of *n*

n	nm
2	227
3	263
6	352
9	413

to a triplet excited state are so improbable that they cannot be observed, and it is safe to state that in most molecules only singlet–singlet promotions take place. However, this rule does break down in certain cases, most often when a heavy atom (e.g., iodine) is present in the molecule, in which case it can be shown from spectra that singlet–triplet promotions are occurring.[11] Symmetry-forbidden transitions can frequently be observed, though usually with low intensity.

7.A.iii. Types of Excitation

When an electron in a molecule is promoted (normally only one electron in any molecule), it usually goes into the lowest available vacant orbital, though promotion to higher orbitals is also possible. For most organic molecules, there are consequently four types of electronic excitation:

1. $\sigma \rightarrow \sigma^*$. Alkanes, which have no *n* or π electrons, can be excited only in this way.[12]
2. $n \rightarrow \sigma^*$. Alcohols, amines,[13] ethers, and so on can also be excited in this manner.
3. $\pi \rightarrow \pi^*$. This pathway is open to alkenes as well as to aldehydes, carboxylic esters, and so on.
4. $n \rightarrow \pi^*$. Aldehydes, ketones, carboxylic esters, and so on can undergo this promotion as well as the other three.

The four excitation types above are listed in what is normally the order of decreasing energy. Thus light of the highest energy (in the far-UV) is necessary for $\sigma \rightarrow \sigma^*$ excitation, while $n \rightarrow \pi^*$ promotions are caused by ordinary UV light. However, the order may sometimes be altered in some solvents.

In buta-1,3-diene (and other compounds with two conjugated double bonds) there are two π and two π^* orbitals (Sec. 2.C). The energy difference between the higher π (χ_2) and the lower π^* (χ_3) orbital is less than the difference between the π and π^* orbitals of ethene. Therefore, 1,3-butadiene requires less energy than ethene, and thus light of a higher wavelength, to promote an electron. This is a general phenomenon, and it may be stated that, in general, *the more conjugation in a molecule*, *the more the absorption is displaced toward higher wavelengths* (see Table 7.1).[14] When a chromophore absorbs at a certain wavelength and the substitution of one group for another causes absorption at a longer

[11] See Koziar, J.C.; Cowan, D.O. *Acc. Chem. Res.* ***1978***, *11*, 334.
[12] An *n* electron is one in an unshared pair.
[13] See Malkin, Yu.N.; Kuz'min, V.A. *Russ. Chem. Rev.* ***1985***, *54*, 1041.
[14] Bohlmann, F.; Mannhardt, H. *Chem. Ber.* ***1956***, *89*, 1307.

TABLE 7.2 Some UV peaks of substituted benzenes (solvent is in parentheses)[a]

	Primary band		Secondary band	
Substituted benzene	λ_{max}, nm	ε_{max}	λ_{max}, nm	ε_{max}
PhH (hexane)	204	7 900	256	200
PhCl	210	7 600	265	240
PhOH	210.5	6 200	270	1 450
PhOMe	217	6 400	269	1 480
PhCN	224	13 000	271	1 000
PhCOOH	230	10 000	270	800
$PhNH_2$	230	8 600	280	1 430
PhO^-	235	9 400	287	2 600
PhAc	240	13 000	278	1 100
PhCHO	244	15 000	280	1 500
$PhNO_2$	252	10 000	280	1 000

[a]Note how auxochromes shift and usually intensify the peaks.[16]
Reprinted with permission from Silverstein, R.M.; Bassler, G.C. *Spectrometric Identification of Organic Compounds*, 2nd ed., Wiley, NY, ***1967***, pp. 164–165, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. Copyright © ***1967*** by Wiley-VCH Verlag.

wavelength, a *bathochromic shift* is said to have occurred. The opposite kind of shift is called *hypsochromic*.

Of the four excitation types listed above, the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ are far more important in organic photochemistry than the other two. Compounds containing C═O groups can be excited in both ways, giving rise to at least two peaks in the UV.

As seen above, a *chromophore* is a group that causes a molecule to absorb light. Examples of chromophores in the visible or UV are C═O, N═N,[15] Ph, and NO_2. Some chromophores in the far-UV (beyond 200 nm) are C═C, C≡C, Cl, and OH.

An *auxochrome* is a group that displaces (through resonance) and usually intensifies the absorption of a chromophore present in the same molecule. Groups such as Cl, OH, and NH_2 are generally regarded as auxochromes since they shift (usually bathochromically) the UV and visible bands of chromophores such as Ph or C═O (see Table 7.2).[16]

Since auxochromes are themselves chromophores (to be sure, generally in the far-UV), it is sometimes difficult to decide which group in a molecule is an auxochrome and which a chromophore. For example, in acetophenone (PhCOMe) is the chromophore Ph or C═O? In such cases the distinction becomes practically meaningless.

7.A.iv. Nomenclature and Properties of Excited States

An excited state of a molecule can be regarded as a distinct chemical species, different from the ground state of the same molecule and from other excited states. It is obvious that some method of naming excited states is required. Unfortunately, there are several methods in use, depending on whether one is primarily interested in photochemistry, spectroscopy,

[15] For a review of the azo group as a chromophore, see Rau, H. *Angew. Chem. Int. Ed.* **1973**, *12*, 224. Also see Liu, Z.; Yan, X.; Li, L.; Wu, G. *J. Phys. Org. Chem.* ***2017***, *30*, e3631.

[16] These values are from Silverstein, R.M.; Bassler, G.C. *Spectrometric Identification of Organic Compounds*, 2nd ed., Wiley, NY, ***1967***, pp. 164–165. Also see Jaffé, H.H.; Orchin, M. *Theory and Applications of Ultraviolet Spectroscopy*, Wiley, NY, ***1962***, p. 257.

or molecular-orbital theory.[17] One of the most common methods simply designates the original and newly occupied orbitals, with or without a superscript to indicate singlet or triplet. Thus the singlet state arising from promotion of a π to a π* orbital in ethylene would be the $^1(\pi,\pi^*)$ state or the π,π* singlet state. Another very common method can be used even in cases where one is not certain which orbitals are involved. The lowest-energy excited state is called S_1, the next S_2, and so on, and triplet states are similarly labeled T_1, T_2, T_3, and so on. In this notation the ground state is S_0. Other notational systems exist, but this book shall discuss only the two types just mentioned.

The properties of excited states are not easy to measure because of their generally short lifetimes and low concentrations, but enough work has been done for us to know that they often differ from the ground state in geometry, dipole moment, and acid or base strength.[18] For example, acetylene, which is linear in the ground state, has a *trans* geometry in the excited state, having carbon atoms with approximate sp^2 hybridization in the $^1(\pi,\pi^*)$ state.[19] Similarly, the $^1(\pi,\pi^*)$ and the $^3(\pi,\pi^*)$ states of ethylene have a perpendicular and not a planar geometry,[20] and the $^1(n,\pi^*)$ and $^3(n,\pi^*)$ states of formaldehyde are both pyramidal.[21] Triplet species tend to stabilize themselves by distortion, which relieves interaction between the unpaired electrons. Obviously, if the geometry is different, the dipole moment will probably differ also and the change in geometry and electron distribution often results in a change in acid or base strength.[22] For example, the S_1 state of 2-naphthol is a much stronger acid ($pK = 3.1$) than the ground state (S_0) of the same molecule ($pK = 9.5$).[23]

7.A.v. Photolytic Cleavage

As stated above, when a molecule absorbs a quantum of light it is promoted to an excited state. Actually, that is not the only possible outcome. Because the energy of visible and UV light is of the same order of magnitude as that of covalent bonds,[24a] another possibility is that the molecule may cleave into two parts, a process known as *photolysis*. There are three situations that can lead to cleavage:

1. The promotion may bring the molecule to a vibrational level so high that it lies above the right-hand portion of the E_2 curve (line *A* in Figure 7.2). In such a case the excited molecule cleaves at its first vibration.
2. Even where the promotion is to a lower vibrational level, one that lies wholly within the E_2 curve (e.g., V_1 or V_2), the molecule may still cleave. As Figure 7.2 shows,

[17] See Pitts Jr., J.N.; Wilkinson, F.; Hammond, G.S. *Adv. Photochem.* ***1963***, *1*, 1; Porter, G.B.; Balzani, V.; Moggi, L. *Adv. Photochem.* ***1974***, *9*, 147; Braslavsky, S.E.; Houk, K.N. *Pure Appl. Chem.* ***1988***, *60*, 1055.

[18] For reviews of the structures of excited states, see Zink, J.I.; Shin, K.K. *Adv. Photochem.* ***1991***, *16*, 119; Innes, K.K. *Excited States* ***1975***, *2*, 1; Hirakawa, A.Y.; Masamichi, T. *Vib. Spectra Struct.* ***1983***, *12*, 145.

[19] Ingold, C.K.; King, G.W. *J. Chem. Soc.* ***1953***, 2702, 2704, 2708, 2725, 2745. For a review of acetylene photochemistry, see Coyle, J.D. *Org. Photochem.* ***1985***, *7*, 1.

[20] Merer, A.J.; Mulliken, R.S. *Chem. Rev.* ***1969***, *69*, 639.

[21] Garrison, B.J.; Schaefer III, H.F.; Lester Jr., W.A. *J. Chem. Phys.* ***1974***, *61*, 3039; Streitwieser Jr., A.; Kohler, B. *J. Am. Chem. Soc.* ***1988***, *110*, 3769. For reviews of excited states of formaldehyde, see Buck, H.M. *Recl. Trav. Chim. Pays-Bas* ***1982***, *101*, 193, 225; Moule, D.C.; Walsh, A.D. *Chem. Rev.* ***1975***, *75*, 67.

[22] See Ireland, J.F.; Wyatt, P.A.H. *Adv. Phys. Org. Chem.* ***1976***, *12*, 131.

[23] Weller, A. *Z. Phys. Chem. (Frankfurt am Main)* ***1955***, *3*, 238, *Discuss. Faraday Soc.* ***1959***, *27*, 28.

[24] (a) Lovering, E.G.; Laidler, K.J. *Can. J. Chem.* ***1960***, *38*, 2367; (b) Lubitz, W.; Lendzian, F.; Bittl, R. *Acc. Chem. Res.* ***2002***, *35*, 313.

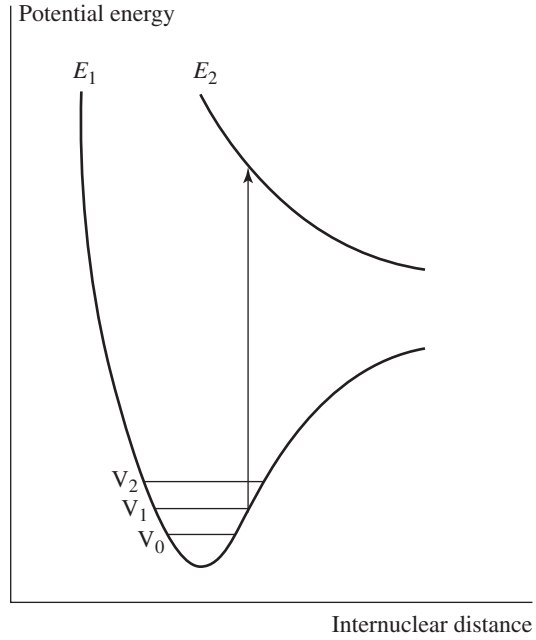


FIGURE 7.3. Promotion to a dissociative state results in bond cleavage.

equilibrium distances are greater in excited states than in the ground state. The *Franck-Condon principle* states that promotion of an electron takes place much faster than a single vibration (promotion takes $\sim 10^{-15}$ s; a vibration $\sim 10^{-12}$ s). Therefore, when an electron is suddenly promoted, even to a low vibrational level, the distance between the atoms is essentially unchanged and the bond finds itself in a compressed condition like a pressed-in spring; this condition may be relieved by an outward surge that is sufficient to break the bond.

3. In some cases, the excited state is entirely dissociative (Figure 7.3), that is, there is no distance where attraction outweighs repulsion, and the bond must cleave. An example is the hydrogen molecule, where a $\sigma \rightarrow \sigma^*$ promotion always results in cleavage.

A photolytic cleavage can break the molecule into two smaller molecules or into two free radicals (Sec. 7.A.vii). Cleavage into two ions, though known, is rare. Once free radicals are produced by a photolysis, they behave like free radicals produced in any other way (Chapter 5) except that they may be in excited states, and this can cause differences in behavior.[24b]

7.A.vi. The Fate of the Excited Molecule: Physical Processes

When a molecule has been photochemically promoted to an excited state, it does not remain in the excited state for long. Most promotions are from the S_0 to the S_1 state. As seen previously, promotions from S_0 to triplet states are "forbidden." Promotions to S_2 and higher singlet states take place, but in liquids and solids these higher states usually drop very rapidly to the S_1 state ($\sim 10^{-13}$ to $\sim 10^{-11}$ s). The energy lost when an S_2 or S_3 molecule drops to S_1 is given up in small increments to the environment by collisions with neighboring molecules. Such a process is called an *energy cascade*. In a similar manner, the initial excitation and the

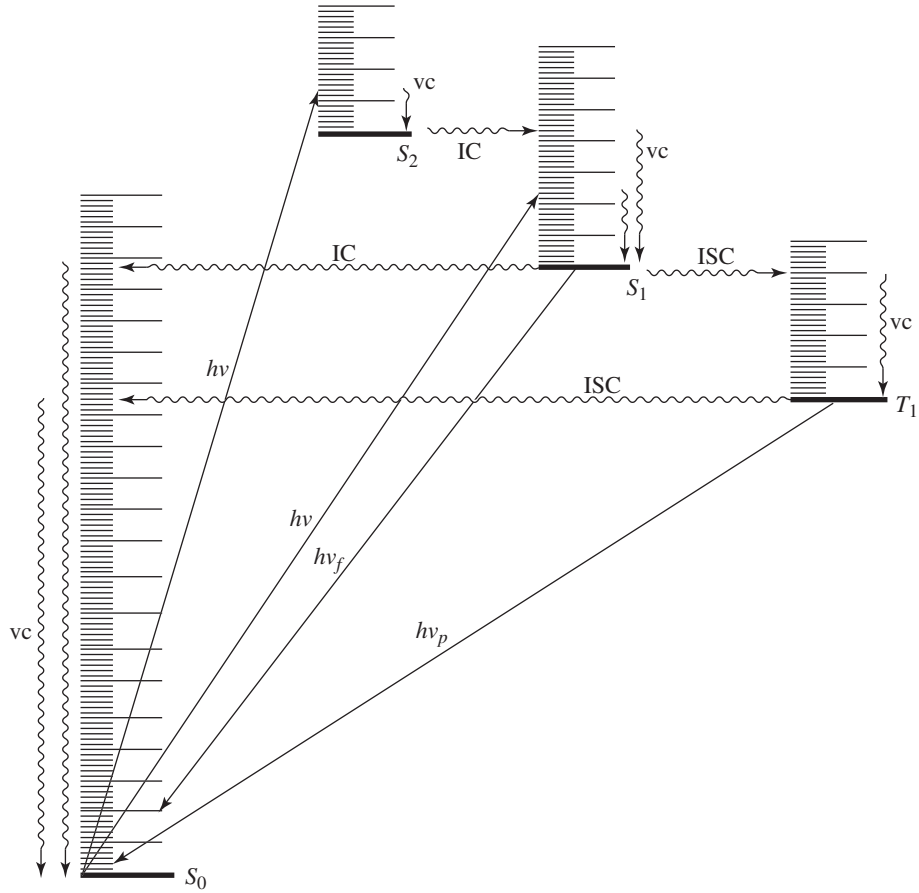


FIGURE 7.4. Modified Jablonski diagram showing transitions between excited states and the ground state. Radiative processes are shown by straight lines, radiationless processes by wavy lines. vc = vibrational cascade; $h\nu_f$ = fluorescence; $h\nu_p$ = phosphorescence.

decay from higher singlet states initially populate many of the vibrational levels of S_1, but these also cascade, down to the lowest vibrational level of S_1. Therefore, in most cases, the lowest vibrational level of the S_1 state is the only important excited singlet state.[25] This state can undergo various physical and chemical processes. In the following list, we describe the physical pathways open to molecules in the S_1 and excited triplet states. These pathways are also shown in a modified *Jablonski diagram* (Figure 7.4) and in Table 7.3.

1. A molecule in the S_1 state can cascade down through the vibrational levels of the S_0 state and thus return to the ground state by giving up its energy in small increments to the environment, but this is generally quite slow because the amount of energy is large. The process is called *internal conversion* (**IC**, see Figure 7.4). Because it is slow, most molecules in the S_1 state adopt other pathways.[26]

[25] See Turro, N.J.; Ramamurthy, V.; Cherry, W.; Farneth, W. *Chem. Rev.* ***1978***, *78*, 125.

[26] See Lin, S.H. *Radiationless Transitions*, Academic Press, NY, ***1980***. For reviews, see Kommandeur, J. *Recl. Trav. Chim. Pays-Bas* ***1983***, *102*, 421; Freed, K.F. *Acc. Chem. Res.* ***1978***, *11*, 74.

TABLE 7.3 Physical processes undergone by excited molecules[a]

$S_0 + h\nu \rightarrow S_1^v$	Excitation
$S_1^v \rightsquigarrow S_1 + \Delta$	Vibrational relaxation
$S_1 \rightarrow S_1 + h\nu$	Fluorescence
$S_1 \rightsquigarrow S_0 + \Delta$	Internal conversion
$S_1 \rightsquigarrow T_1^v$	Intersystem crossing
$T_1^v \rightsquigarrow T_1 + \Delta$	Vibrational relaxation
$T_1 \rightarrow S_0 + h\nu$	Phosphorescence
$T_1 \rightsquigarrow S_0 + \Delta$	Intersystem crossing
$S_1 + A_{(S_0)} \rightarrow S_0 + A_{(S_1)}$	Singlet–singlet transfer (photosensitization)
$T_1 + A_{(S_0)} \rightarrow S_0 + A_{(T_1)}$	Triplet–triplet transfer (photosensitization)

[a]The superscript v indicates vibrationally excited state: excited states higher than S_1 or T_1 are omitted.

2. A molecule in the S_1 state can drop to some low vibrational level of the S_0 state all at once by giving off the energy in the form of light. This process, which generally happens within 10^{-9} s, is called *fluorescence*. This pathway is not very common either (because it is relatively slow), except for small molecules, for example, diatomic, and rigid molecules, for example, aromatic. For most other compounds, fluorescence is very weak or undetectable. For compounds that do fluoresce, the fluorescence emission spectra are usually the approximate mirror images of the absorption spectra. This comes about because the fluorescing molecules all drop from the lowest vibrational level of the S_1 state to various vibrational levels of S_0, while excitation is from the lowest vibrational level of S_0 to various levels of S_1 (Figure 7.5). The only peak in common is the one that results from transitions between the lowest vibrational levels of the two states (called the 0-0 peak). In solution, even the 0-0 peak may be noncoincidental because the two states are solvated differently. Fluorescence nearly always arises from a $S_1 \rightarrow S_0$ transition, although azulene (Sec. 2.I.iii) and its simple derivatives are exceptions,[27] emitting fluorescence from $S_2 \rightarrow S_0$ transitions.

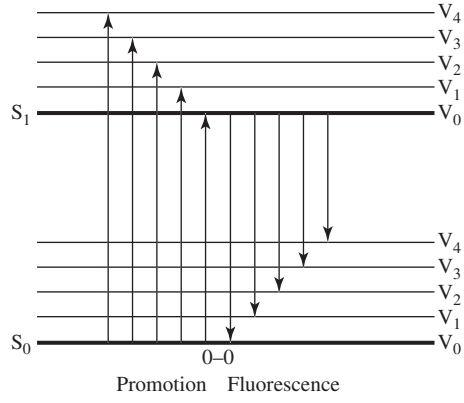


FIGURE 7.5. Promotion and fluorescence between S_1 and S_0 states.

[27] For other exceptions, see Sugihara, Y.; Wakabayashi, S.; Murata, I.; Jinguji, M.; Nakazawa, T.; Persy, G.; Wirz, J. *J. Am. Chem. Soc.* ***1985***, *107*, 5894, and references cited therein. See also, Turro, N.J.; Ramamurthy, V.; Cherry, W.; Farneth, W. *Chem. Rev.* ***1978***, *78*, 125 (pp. 126–129).

Because of the possibility of fluorescence, any chemical reactions of the S_1 state must take place very fast, or fluorescence will occur before they can happen.

3. Most molecules (but by no means all) in the S_1 state can undergo an *intersystem crossing* (ISC, see Figure 7.4) to the lowest triplet state T_1.[28] An important example is benzophenone, of which approximately 100% of the molecules that are excited to the S_1 state cross over to the T_1.[29] Intersystem crossing from singlet to triplet is of course a "forbidden" pathway, since the angular-momentum problem (Sec. 7.A.ii) must be taken care of, but this often takes place by compensations elsewhere in the system. Intersystem crossings take place without loss of energy. Since a singlet state usually has a higher energy than the corresponding triplet, this means that energy must be given up. One way for this to happen is for the S_1 molecule to cross to a T_1 state at a high vibrational level and then for the T_1 to cascade down to its lowest vibrational level (see Figure 7.4). This cascade is very rapid (10^{-12} s). When T_2 or higher states are populated, they too rapidly cascade to the lowest vibrational level of the T_1 state.
4. A molecule in the T_1 state may return to the S_0 state by giving up heat (intersystem crossing) or light (this is called *phosphorescence*).[30] Of course, the angular-momentum difficulty exists here, so that both intersystem crossing and phosphorescence are very slow ($\approx 10^{-3}$ to 10^{1} s). This means that T_1 states generally have much longer lifetimes than S_1 states. When they occur in the same molecule, phosphorescence is found at lower frequencies than fluorescence (because of the higher difference in energy between S_1 and S_0 than between T_1 and S_0) and is longer lived (because of the longer lifetime of the T_1 state).
5. If nothing else happens to it first, a molecule in an excited state (S_1 or T_1) may transfer its excess energy all at once to another molecule in the environment, in a process called *photosensitization*.[31] The excited molecule (which we will call D for donor) thus drops to S_0 while the other molecule (A for acceptor) becomes excited:

$$D^* + A \longrightarrow A^* + D$$

Thus there are *two* ways for a molecule to reach an excited state: by absorption of a quantum of light or by transfer from a previously excited molecule.[32] The donor D is also called a *photosensitizer*. This energy transfer is subject to the *Wigner spin-conservation rule*, which is actually a special case of the law of conservation of momentum we encountered previously. According to the Wigner rule, the total electron spin does not change after the energy transfer. For example, when a triplet species interacts with a singlet these are some allowed possibilities:[33]

[28] See Li, R.; Lim, E.C. *Chem. Phys.* ***1972***, *57*, 605; Sharf, B.; Silbey, R. *Chem. Phys. Lett.* ***1970***, *5*, 314; Schlag, E.W.; Schneider, S.; Fischer, S.F. *Annu. Rev. Phys. Chem.* ***1971***, *22*, 465 (p. 490). There is evidence that ISC can also occur from the S_2 state of some molecules: Samanta, A. *J. Am. Chem. Soc.* ***1991***, *113*, 7427; Ohsaku, M.; Koga, N.; Morokuma, K. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 71.

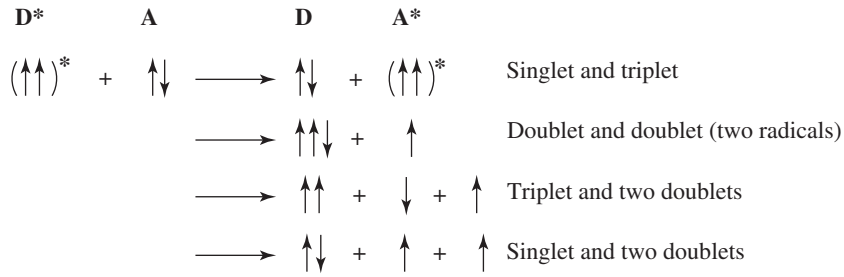
[29] Moore, W.M.; Hammond, G.S.; Foss, R.P. *J. Am. Chem. Soc.* ***1961***, *83*, 2789.

[30] See Lower, S.K.; El-Sayed, M.A. *Chem. Rev.* ***1966***, *66*, 199. For a review of physical and chemical processes of triplet states see Wagner, P.J.; Hammond, G.S. *Adv. Photochem.* ***1968***, *5*, 21.

[31] See Albini, A. *Synthesis*, ***1981***, 249; Turro, N.J.; Dalton, J.C.; Weiss, D.S. *Org. Photochem.* ***1969***, *2*, 1. Ionic liquids may be soluble photosensitizers. See Hubbard, S.C.; Jones, P.B. *Tetrahedron* ***2005***, *61*, 7425.

[32] In certain cases excited states can be produced directly in ordinary reactions. See White, E.H.; Miano, J.D.; Watkins, C.J.; Breaux, E.J. *Angew. Chem. Int. Ed.* ***1974***, *13*, 229.

[33] For another table, see Calvert, J.G.; Pitts Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***, p. 89.



In all these cases, the products have three electrons spinning "up" and the fourth "down" (as do the starting molecules). However, formation of, say, two triplets (↑↓ + ↓↓) or two singlets (↑↓ + ↑↓), whether ground states or excited, would violate the rule.

In the two most important types of photosensitization, both of which are in accord with the Wigner rule, a triplet excited state generates another triplet and a singlet generates a singlet:

$$D_{T1} + A_{So} \longrightarrow A_{T1} + D_{So} \qquad \text{Triplet-triplet transfer}$$
$$D_{S1} + A_{So} \longrightarrow A_{S1} + D_{So} \qquad \text{Singlet-triplet transfer}$$

Singlet–singlet transfer can take place over relatively long distances, e.g., 40 Å, but triplet transfer normally requires a collision between the molecules.[34] Both types of photosensitization can be useful for creating excited states when they are difficult to achieve by direct irradiation. Photosensitization is therefore an important method for carrying out photochemical reactions when a molecule cannot be brought to the desired excited state by direct absorption of light. Triplet–triplet transfer is especially important because triplet states are usually much more difficult to prepare by direct irradiation than singlet states (often impossible) and because triplet states, having longer lifetimes, are much more likely than singlets to transfer energy by photosensitization. Photosensitization can also be accomplished by electron transfer.[35]

In choosing a photosensitizer,[36] one should avoid a compound that absorbs in the same region as the acceptor because the latter will then compete for the light.[37] For examples of the use of photosensitization to accomplish reactions, see **15-58**, **15-59**.

1. An excited species can be quenched. Quenching is the deactivation of an excited molecular entity intermolecularly by an external environmental influence (e.g., a quencher), or intramolecularly by a substituent through a nonradiative process.[38] When the external environmental influence (quencher) interferes with the behavior of the excited state after its formation, the process is referred to as dynamic quenching. Common mechanisms include energy transfer, charge transfer, and so

[34] See Bennett, R.G.; Schwenker, R.P.; Kellogg, R.E. *J. Chem. Phys.* ***1964***, *41*, 3040; Ermolaev, V.L.; Sveshnikova, E.B. *Opt. Spectrosc. (USSR)* ***1964***, *16*, 320.
[35] See Kavarno, G.J.; Turro, N.J. *Chem. Rev.* ***1986***, *86*, 401; Mariano, P.S. *Org. Photochem.* ***1987***, *9*, 1.
[36] For a discussion of pyrylogens as an electron-transfer sensitizer, see Clennan, E.L.; Liao, C.; Ayokosok, E. *J. Am. Chem. Soc.* ***2008***, *130*, 7552.
[37] See Engel, P.S.; Monroe, B.M. *Adv. Photochem.* ***1971***, *8*, 245.
[38] Verhoeven, J.W. *Pure Appl. Chem.* ***1996***, *68*, 2223 (see p. 2268).

on. When the environmental influence inhibits the excited state formation the process is referred to as static quenching. A quencher is defined as a molecular entity that deactivates (quenches) an excited state of another molecular entity, either by energy transfer, electron transfer, or by a chemical mechanism.[38]

An example is the rapid triplet quenching of aromatic ketone triplets[39] by amines, which is well known.[40] Alkyl and aryl thiols and thioethers also serve as quenchers in this system.[41] In this latter case, the mechanism involves electron transfer from the sulfur atom to the triplet ketone, and this is supported by theoretical calculations.[42] Aromatic ketone triplets are quenched by phenols, and the photochemical reaction between aromatic ketones and phenols is efficient only in the presence of an acid catalyst.[43] Indirect evidence has been provided for involvement of the hydrogen-bonded triplet exciplex and for the role of electron transfer in this reaction.[44]

7.A.vii. The Fate of the Excited Molecule: Chemical Processes

Although both excited singlet and triplet species can undergo chemical reactions, they are much more common for triplets, simply because these generally have much longer lifetimes. Excited singlet species, in most cases, have a lifetime of $<10^{-10}$ s and undergo one of the physical processes already discussed before they have a chance to react chemically. Therefore, photochemistry is largely the chemistry of triplet states.[45] Table 7.4[46] lists many of the possible chemical pathways that can be taken by an excited molecule.[47]

The first four of these are unimolecular reactions; the others are bimolecular. In the case of bimolecular reactions it is rare for two excited molecules to react with each other (because the concentration of excited molecules at any one time is generally low); reactions are between an excited molecule and an unexcited molecule of either the same or another species.

The reactions listed in Table 7.4 are primary processes. Secondary reactions often follow, since the primary products are frequently radicals or carbenes; even if they are ordinary molecules, they are often in upper vibrational levels and so have excess energy. In almost all cases the primary products of photochemical reactions are in their ground states, though exceptions are known.[48] Of the reactions listed in Table 7.4, the most common

[39] See Samanta, S.; Mishra, B.K.; Pace, T.C.S.; Sathyamurthy, N.; Bohne, C.; Moorthy, J.N. *J. Org. Chem.* ***2006***, *71*, 4453.

[40] See Aspari, P.; Ghoneim, N.; Haselbach, E.; von Raumer, M.; Suppan, P.; Vauthey, E. *J. Chem. Soc., Faraday Trans.* ***1996***, *92*, 1689; Cohen, S.G.; Parola, A.; Parsons Jr., G.H. *Chem. Rev.* ***1973***, *73*, 141; von Raumer, M.; Suppan, P.; Haselbach, E. *Helv. Chim. Acta* ***1997***, *80*, 719.

[41] Inbar, S.; Linschitz, H.; Cohen, S.G. *J. Am. Chem. Soc.* ***1982***, *104*, 1679; Bobrowski, K.; Marciniak, B.; Hug, G.L. *J. Photochem. Photobiol. A: Chem.* ***1994***, *81*, 159; Wakasa, M.; Hayashi, H. *J. Phys. Chem.* ***1996***, *100*, 15640.

[42] Marciniak, B.; Bobrowski, K.; Hug, G.L. *J. Phys. Chem.* ***1993***, *97*, 11937.

[43] Becker, H.-D. *J. Org. Chem.* ***1967***, *32*, 2115; 2124; 2140.

[44] Lathioor, E.C.; Leigh, W.J.; St. Pierre, M.J. *J. Am. Chem. Soc.* ***1999***, *121*, 11984.

[45] See Wagner, P.J.; Hammond, G.S. *Adv. Photochem.* ***1968***, *5*, 21. For other reviews of triplet states, see *Top. Curr. Chem.* ***1975***, Vols. 54 and 55.

[46] Adapted from Calvert, J.G.; Pitts Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***, p. 367.

[47] For a different kind of classification of photochemical reactions, see Dauben, W.G.; Salem, L.; Turro, N.J. *Acc. Chem. Res.* ***1975***, *8*, 41. For reviews of photochemical reactions where the molecules are geometrically constrained, see Ramamurthy, V. *Tetrahedron* ***1986***, *42*, 5753; Ramamurthy, V.; Eaton, D.F. *Acc. Chem. Res.* ***1988***, *21*, 300; Turro, N.J.; Cox, G.S.; Paczkowski, M.A. *Top. Curr. Chem.* ***1985***, *129*, 57.

[48] Turro, N.J.; Lechtken, P.; Lyons, A.; Hautala, R.T.; Carnahan, E.; Katz, T.J. *J. Am. Chem. Soc.* ***1973***, ***95***, 2035.

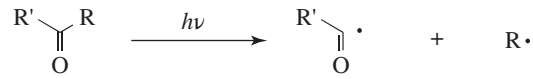
TABLE 7.4 Primary photochemical reactions[a] of an excited molecule A—B—C[46]

Reactions	Reaction type	Example number
(A—B—C) → A—B• + C•	Simple cleavage into radicals[49]	1
(A—B—C) → E + F	Decomposition into molecules	2
(A—B—C) → A—C—B	Intramolecular rearrangement	3
(A—B—C) → A—B—C'	Photoisomerization	4
(A—B—C) + RH → A—B—C—H + R•	Hydrogen-atom abstraction	5
(A—B—C) → $(ABD)_2$	Photodimerization	6
(A—B—C) + A → ABC + A*	Photosensitization	7

[a]Examples are given in the text; the most common are 1, 2, and, in the presence of a suitable acceptor molecule, 7.

are cleavage into radicals (1), decomposition into molecules (2), and (in the presence of a suitable acceptor molecule) photosensitization (7), which we have already discussed. The following are some specific examples of reaction categories 1 to 6. Other examples are discussed in Part 2 of this book.[50]

Category 1 *Simple cleavage into radicals*.[51] Aldehydes and ketones absorb in the 230 to 330 nm region. This is assumed to result from an $n \rightarrow \pi^*$ singlet–singlet transition. The excited aldehyde or ketone can then cleave.[52]



When applied to ketones, this is called *Norrish Type I cleavage* or often just *Type I cleavage*. In a secondary process, the acyl radical R'—CO• can then lose CO to give R'• radicals.[53] Another example of a category 1 process is cleavage of Cl_2 to give two Cl atoms. Other bonds that are easily cleaved by photolysis are the O—O bonds of peroxy compounds and the C—N bonds of aliphatic azo compounds R—N=N—R.[54] The latter is an important source

[49] See DeLuca, L.; Giacomelli, G.; Porcu, G.; Taddei, M. *Org. Lett.* ***2001***, *3*, 855.

[50] See Ninomiya, I.; Naito, T. *Photochemical Synthesis*, Academic Press, NY, ***1989***; Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***; Schönberg, A. *Preparative Organic Photochemistry*, Springer, Berlin, ***1968***.

[51] For reviews, see Jackson, W.M.; Okabe, H. *Adv. Photochem.* ***1986***, *13*, 1; Kresin, V.Z.; Lester Jr., W.A. *Adv. Photochem.* ***1986***, *13*, 95.

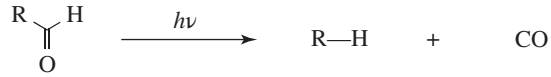
[52] See Formosinho, S.J.; Arnaut, L.G. *Adv. Photochem.* ***1991***, *16*, 67; Newton, R.F. in Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***, pp. 39–60; Lee, E.K.C.; Lewis, R.S. *Adv. Photochem.* ***1980***, *12*, 1; Coyle, J.D.; Carless, H.A.J. *Chem. Soc. Rev.* ***1972***, *1*, 465; Bérces, T. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 5; Elsevier, NY, ***1972***, pp. 277–380; Turro, N.J.; Dalton, J.C.; Dawes, K.; Farrington, G.; Hautala, R.; Morton, D.; Niemczyk, M.; Shore, N. *Acc. Chem. Res.* ***1972***, *5*, 92; Wagner, P.J. *Top. Curr. Chem.* ***1976***, *66*, 1. Also see Weiss, D.S. *Org. Photochem.* ***1981***, *5*, 347; Rubin, M.B. *Top. Curr. Chem.* ***1985***, *129*, 1; ***1969***, *13*, 251; Childs, R.F. *Rev. Chem. Intermed.* ***1980***, *3*, 285. C=S compounds, see Coyle, J.D. *Tetrahedron* ***1985***, *41*, 5393; Ramamurthy, V. *Org. Photochem.* ***1985***, *7*, 231. C=N compounds, see Mariano, P.S. *Org. Photochem.* ***1987***, *9*, 1.

[53] See Shen, L.; Fang, W.H. *J. Org. Chem.* ***2011***, *76*, 773.

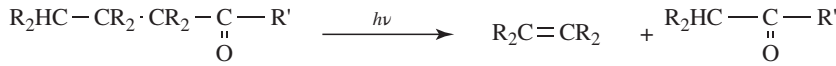
[54] See Adam, W.; Oppenländer, T. *Angew. Chem. Int. Ed.* ***1986***, *25*, 661; Dürr, H.; Ruge, B. *Top. Curr. Chem.* ***1976***, *66*, 53; Drewer, R.J. in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 935–1015.

of radicals R•, since the other product is the very stable N_2. Homoallyl ketones have been prepared from cyclopentanones via a Norrish Type I reaction.[55]

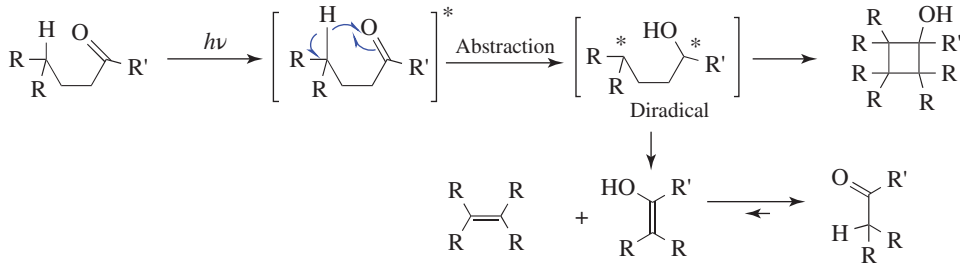
Category 2 *Decomposition into molecules*. Aldehydes (though not generally ketones) can also cleave in this manner:



This is an extrusion reaction (see Chapter 17). In another example of a process in category 2, aldehydes and ketones with a γ hydrogen can cleave in still another way (a β-elimination, see Chapter 17):



This reaction, called *Norrish Type II cleavage*,[56] involves intramolecular abstraction of the γ hydrogen followed by cleavage of the resulting diradical[57] (a secondary reaction) to give an enol that tautomerizes to the aldehyde or ketone product.[58]



Both singlet and triplet n,π^* states undergo the reaction.[59] The intermediate diradical can also cyclize to a cyclobutanol, which is often a side product. Carboxylic esters, anhydrides, and other carbonyl compounds can also give this reaction.[60] The photolysis of ketene to CH_2 (Sec. 5.D.ii) is still another example of a reaction in category 2. Both singlet and triplet CH_2 are generated, the latter in two ways:

[55] Okada, M.; Yamada, K.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Ryu, I. *J. Org. Chem.* ***2015***, *80*, 9365.

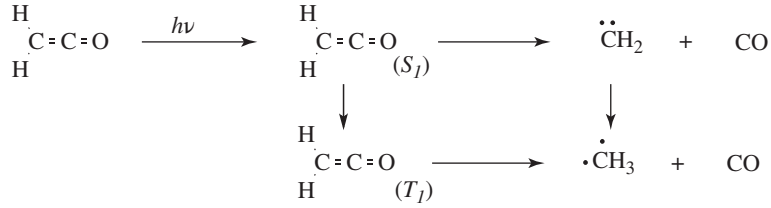
[56] See Wagner, P.J. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 381–444; *Acc. Chem. Res.* ***1971***, *4*, 168. See Niu, Y.; Christophy, E.; Hossenlopp, J.M. *J. Am. Chem. Soc.* ***1996***, *118*, 4188 for a new view of Norrish Type II elimination.

[57] See Wilson, R.M. *Org. Photochem.* ***1985***, *7*, 339 (pp. 349–373); Scaiano, J.C.; Lissi, E.A.; Encina, M.V. *Rev. Chem. Intermed.* ***1978***, *2*, 139. Also see Wagner, P.J. *Acc. Chem. Res.* ***1989***, *22*, 83.

[58] This mechanism was proposed by Yang, N.C.; Yang, D.H. *J. Am. Chem. Soc.* ***1958***, *80*, 2913. The diradical intermediate has been trapped: Wagner, P.J.; Zepp, R.G. *J. Am. Chem. Soc.* ***1972***, *94*, 287; Wagner, P.J.; Kelso, P.A.; Zepp, R.G. *J. Am. Chem. Soc.* ***1972***, *94*, 7480; Adam, W.; Grabowski, S.; Wilson, R.M. *Chem. Ber.* ***1989***, *122*, 561. See also, Caldwell, R.A.; Dhawan, S.N.; Moore, D.E. *J. Am. Chem. Soc.* ***1985***, *107*, 5163.

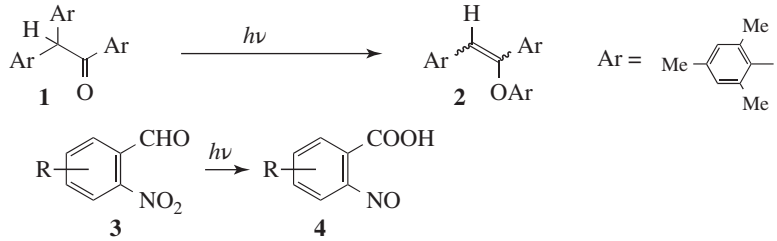
[59] See Casey, C.P.; Boggs, R.A. *J. Am. Chem. Soc.* ***1972***, *94*, 6457.

[60] For a review of the photochemistry of carboxylic acids and acid derivatives, see Givens, R.S.; Levi, N. in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1; Wiley, NY, ***1979***, pp. 641–753.

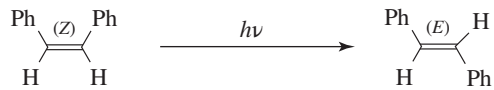


Reactions are known where *both* Norrish Type I and Norrish Type II reactions compete, and the substituents on and nature of the substrate will determine which leads to the major product.[61]

Category 3 *Intramolecular rearrangement*. Two examples are the rearrangement of the trimesityl compound **1** to the enol ether **2**,[62] and irradiation of *o*-nitrobenzaldehydes (**3**) to give *o*-nitrosobenzoic acids (**4**).[63]



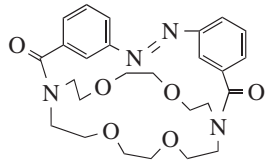
Category 4 *Photoisomerization*. The most common reaction in this category is photochemical *cis–trans* isomerization.[64] For example, *cis*-stilbene can be converted to the *trans* isomer,[65] and the photoisomerization of *O*-methyl oximes is known.[66]



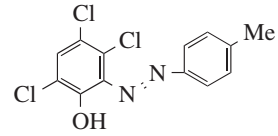
The isomerization takes place because the excited states, both S_1 and T_1, of many alkenes have a perpendicular instead of a planar geometry (7.A.iv), so *cis–trans* isomerism disappears upon excitation. When the excited molecule drops back to the S_0 state, either isomer can be formed. A useful example is the photochemical conversion of *cis*-cyclooctene to the much less stable *trans* isomer.[67] Another interesting example of this isomerization involves

[61] Hwu, J.R.; Chen, B.-L.; Huang, L.W.; Yang, T.-H. *J. Chem. Soc., Chem. Commun.* ***1995***, 299.
[62] Wagner, P.J.; Zhou, B. *J. Am. Chem. Soc.* ***1988***, *110*, 611.
[63] See Morrison, H.A. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, ***1969***, pp. 165–213; Kaupp, G. *Angew. Chem. Int. Ed.* ***1980***, *19*, 243. See also, Yip, R.W.; Sharma, D.K. *Res. Chem. Intermed.* ***1989***, *11*, 109.
[64] See Charlton, J.L. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 25–89; Saltiel, J.; Chang, D.W.L.; Saltiel, J.; D'Agostino, J.; Megarity, E.D.; Metts, L.; Neuberger, K.R.; Wrighton, M.; Zafiriou, O.C. *Org. Photochem.* ***1979***, *3*, 1. Also see Leigh, W.J.; Srinivasan, R. *Acc. Chem. Res.* ***1987***, *20*, 107; Steinmetz, M.G. *Org. Photochem.* ***1987***, *8*, 67; Adam, W.; Oppenländer, T. *Angew. Chem. Int. Ed.* ***1986***, *25*, 661; Johnson, R.P. *Org. Photochem.* ***1985***, *7*, 75.
[65] For photoisomerization of stilbenes, see Waldeck, D.H. *Chem. Rev.* ***1991***, *91*, 415.
[66] Kawamura, Y.; Takayama, R.; Nishiuchi, M.; Tsukayama, M. *Tetrahedron Lett.* ***2000***, *41*, 8101.
[67] Deyrup, J.A.; Betkouski, M. *J. Org. Chem.* ***1972***, *37*, 3561.

azo crown ethers. The crown ether **5**, in which the N=N bond is *anti*, preferentially binds NH_4^+, Li^+, and Na^+, but the *syn* isomer preferentially binds K^+ and Rb^+ (Sec. 3.C.ii). Thus, ions can be selectively put in or taken out of solution merely by turning a light source on or off.[68]

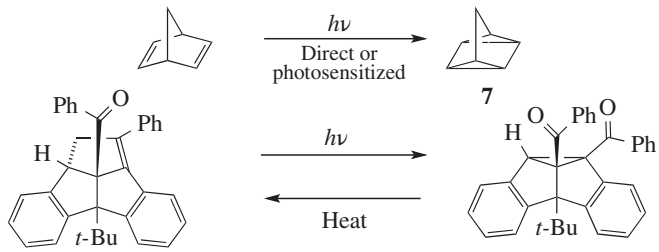


5



6

In another example, the *trans* azo compound **6** is converted to its *cis* isomer when exposed to light. In this case[69] the *cis* isomer is a stronger acid than the *trans*. The *trans* isomer is dissolved in a system containing a base, wherein a liquid membrane separates two sides, one of which is illuminated, the other kept dark. On the illuminated side, the light converts the *trans* isomer to the *cis*. The *cis* isomer, being a stronger acid, donates its proton to the base, converting *cis* ArOH to *cis* ArO^-. This ion migrates to the dark side, where it rapidly reverts to the *trans* ion, which reacquires a proton. Because each cycle forms one H_3O^+ ion in the illuminated compartment and one ^-OH ion in the dark compartment, the process reverses the normal reaction whereby these ions neutralize each other.[70] Thus the energy of light is used to do chemical work.[71] Another example of a category 4 reaction is the conversion of bicyclo[2.2.1]hept-2,5-diene to **7**.[64] The thermal isomerization of dibenzosemibullvalene **9** to the corresponding dibenzodihydropentalenofuran **8** in quantitative yield was known,[72] but in another example of a category 4 reaction the photochemical isomerization of **8** to **9** has now been reported.[73] Photoisomerization of hydantoin derivatives characterized their use as photoswitches.[74]



[68] Akabori, S.; Kumagai, T.; Habata, Y.; Sato, S. *J. Chem. Soc., Perkin Trans. 1* ***1989***, 1497; Shinkai, S.; Yoshioka, A.; Nakayama, H.; Manabe, O. *J. Chem. Soc., Perkin Trans. 2* ***1990***, 1905. For a review, see Shinkai, S.; Manabe, O. *Top. Curr. Chem.* ***1984***, *121*, 67.

[69] Haberfield, P. *J. Am. Chem. Soc.* ***1987***, *109*, 6177.

[70] Haberfield, P. *J. Am. Chem. Soc.* ***1987***, *109*, 6178.

[71] See Beer, P.D. *Chem. Soc. Rev.* ***1989***, *18*, 409. For an example not involving a macrocycle, see Feringa, B.L.; Jager, W.F.; de Lange, B.; Meijer, E.W. *J. Am. Chem. Soc.* ***1991***, *113*, 5468.

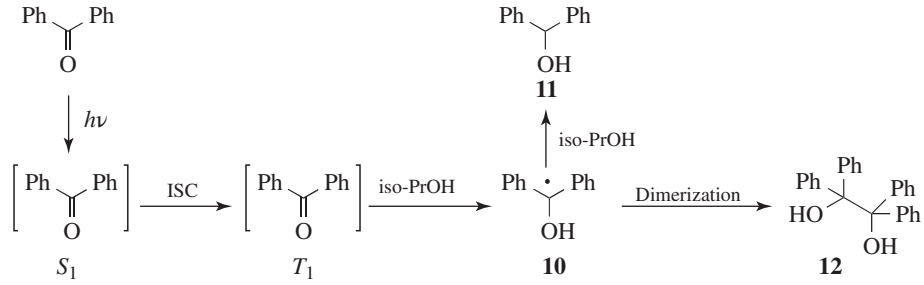
[72] Sajimon, M.C.; Ramaiah, D.; Muneer, M.; Rath, N.P.; George, M.V. *J. Photochem. Photobiol. A Chem.* ***2000***, *136*, 209.

[73] Sajimon, M.C.; Ramaiah, D.; Thomas, K.G.; George, M.V. *J. Org. Chem.* ***2001***, *66*, 3182.

[74] Martínez-López, D.; Yu, M.-L.; García-Iriepa, C.; Campos, P.J.; Manuel Frutos, L.; Golen, J.A.; Sivappa Rasapalli, S.; Sampedro, D. *J. Org. Chem.* ***2015***, *80*, 3929.

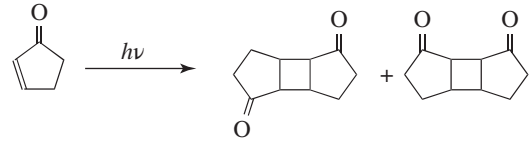
These examples illustrate that the use of photochemical reactions can make it very easy to obtain compounds that would be difficult to get in other ways. Reactions similar to these are discussed at **15-59**.

Category 5 *Hydrogen atom abstraction*. When benzophenone is irradiated in isopropyl alcohol, the initially formed S_1 state crosses to the T_1 state, which abstracts hydrogen from the solvent to give the radical **10**. Radical **10** then abstracts another hydrogen to give benzhydrol (**11**) or dimerizes to benzpinacol (**12**):



An example of intramolecular abstraction has already been given (see category 2 in this section).

Category 6 *Photodimerization*. An example is dimerization of cyclopentenone:[75]



See reaction **15-63** for a discussion of this and similar reactions. It is noted that photoredox catalysis has been achieved under microflow conditions (Sec. 7.D).[76] The use of photochemically generated intermediates in synthesis has been discussed.[77]

7.A.viii. The Determination of Photochemical Mechanisms[78]

The methods used for the determination of photochemical mechanisms are largely the same as those used for organic mechanisms in general (Chapter 6): product identification, isotopic tracing, the detection and trapping of intermediates, and kinetics. There are, however, a few new factors: (i) there are generally many products in a photochemical reaction, as many as 10 or 15; (ii) in measuring kinetics, there are more variables, since it is possible to study the effect of the intensity or the wavelength of light on the rate; (iii) in the detection of

[75] Eaton, P.E. *Acc. Chem. Res.* ***1968***, *1*, 50. For a review of the photochemistry of α,β-unsaturated ketones, see Schuster, D.I. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, ***1989***, pp. 623–756.
[76] Neumann, M.; Zeitler, K. *Org. Lett.* ***2012***, *14*, 2658.
[77] Albini, A.; Fagnoni, M. *Photochemically-Generated Intermediates in Synthesis*, Wiley, Hoboken, ***2013***.
[78] For a review, see Calvert, J.G.; Pitts Jr., J.N. *Photochemistry*, Wiley, NY, ***1966***, pp. 580–670.

intermediates by spectra the technique of *flash photolysis* can be used, which can detect extremely short-lived intermediates.

In addition to these methods, there are two additional techniques.

1. *The use of emission (fluorescence and phosphorescence) as well as absorption spectroscopy.* From these spectra both the presence of as well as the energy and lifetime of singlet and triplet excited states can often be calculated.
2. *The study of quantum yields.* The *quantum yield* is the fraction of absorbed light that goes to produce a particular result. There are several types. A *primary quantum yield* for a particular process is the fraction of molecules absorbing light that undergo that particular process. Thus, if 10% of all the molecules that are excited to the S_1 state cross over to the T_1 state, the primary quantum yield for that process is 0.10. However, primary quantum yields are often difficult to measure. A *product quantum yield* (usually designated Φ) for a product P that is formed from a photoreaction of an initially excited molecule A can be expressed as

$$\Phi = \frac{\text{number of molecules of P formed}}{\text{number of quanta absorbed by A}}$$

Product quantum yields are much easier to measure. The number of quanta absorbed can be determined by an instrument called an *actinometer*, which is actually a standard photochemical system whose quantum yield is known. An example of the information that can be learned from quantum yields is the following. If the quantum yield of a product is finite and invariant with changes in experimental conditions, it is likely that the product is formed in a primary rate-determining process. Another example: in some reactions, the product quantum yields are found to be well over 1 (perhaps as high as 1000). Such a finding indicates a chain reaction (see Sec. 14.A.i for a discussion of chain reactions).

7.B. SONOCHEMISTRY

Sonochemistry (chemical events induced by exposure to ultrasound) occupies an important place in organic chemistry.[79] The chemical effects of high-intensity ultrasound were extensively studied in aqueous solutions for many years,[80] but are now applied to a variety of organic solvents. Sonochemistry has been used in green solvents and under solvent-free conditions.[81] The origin of sonochemistry is acoustic cavitation: the creation, growth, and implosive collapse of gas vacuoles in solution by the sound field. Acoustic cavitation is the phenomenon by which intense ultrasonic waves induce the formation, oscillation, and implosion of gas bubbles in liquids.[82] Liquids irradiated with high-power ultrasound

[79] Mason, T.J. (ed.) *Advances in Sonochemistry*, JAI Press, NY, ***1990–1994***; Vols. 1–3, Price, G.J. (ed.) *Current Trends in Sonochemistry*, Royal Society of Chemistry, Cambridge, ***1992***; Suslick, K.S. *Science* ***1990***, *247*, 1439; Suslick, K.S. *Ultrasound: Its Chemical, Physical, and Biological Effects*, VCH, NY, ***1988***; Young, F.R. *Cavitation*, McGraw-Hill, NY, ***1989***; Brennen, C.E. *Cavitation and Bubble Dynamics*, Oxford University Press, Oxford, ***1995***; Anbar, M. *Science* ***1968***, *161*, 1343. For a discussion of ultrasound in the chemistry of heterocycles, see Cella, R.; Stefani, H.A. *Tetrahedron* ***2009***, *65*, 2619.

[80] Apfel, R.E. in Edmonds, P. *Methods in Experimental Physics*, Academic Press, New York, ***1981***, Vol. 19; Makino, K.; Mossoba, M.M.; Riesz, P. *J. Am. Chem. Soc.* ***1982***, *104*, 3537.

[81] Lupacchini, M.; Mascitti, A.; Giachi, G.; Tonucci, L.; d'Alessandro, N.; Martinez, J.; Colacino, E. *Tetrahedron.* ***2017***, *73*, 609.

[82] Stottlemeyer, T.R.; Apfel, R.E. *J. Acoust. Soc. Am.* ***1997***, *102*, 1413.

undergo chemical decomposition and emit light.[83] These phenomena occur near the end of the collapse of bubbles expanded many times their equilibrium sizes. Chemistry (sonochemistry), light emission (sonoluminescence), and cavitation noise often accompany the process of acoustic cavitation.[84]

Sonochemistry generates gas vacuoles *in situ*. The collapse of gas vacuoles generates transient hot spots with local temperatures of several thousand K, and pressures of hundreds of atmospheres. A sonochemical hot spot forms where the gas-phase and liquid-phase reaction zones have effective temperatures of 5200 and 1900 K, respectively.[85] The high temperatures and pressures that are achieved in the bubbles during the quasiadiabatic collapse[86] lead to the generation of chemistry and to the emission of light, most probably coming from molecular excited states and molecular recombination. Note that work has been done which shows that the commonly held view that bubbles are filled with saturated gas is inconsistent with a realistic estimate of condensation rates.[87] The alternative view of extensive solvent vapor supersaturation in bubbles uniformly heated to a few thousand K, depending on the conditions, is in accord with sonochemical rates and products.[88]

There is a correlation between sonochemical and sonoluminescence measurements, which is usually not observed. Sonoluminescence is the consequence that both the sonochemical production (under air) of oxidizing species, and the emission of light reflect the variations of the primary sonochemical acts, which are themselves due to variations of the number of "active" bubbles.[89] Pulsed ultrasound in the high-frequency range (>1 MHz) is extensively used in medical diagnosis, and the effects of pulsed ultrasound in the 20 kHz range using an immersed titanium horn has been reported.[90]

The chemical effects of ultrasound have been studied for >50 years,[91] and were applied to colloid chemistry in the 1940s.[92] Modern interest in the chemical uses of ultrasound involves chemistry in both homogeneous[93] and heterogeneous[94] systems. Organic solvents, such as alkanes, support acoustic cavitation and the associated sonochemistry, and this leads to carbon–carbon bond cleavage and radical rearrangements, with the peak temperatures reached in such cavities controlled by the vapor pressure of the solvent.[95]

[83] Suslick, K.S.; Crum, L.A. in *Sonochemistry and Sonoluminescence, Handbook of Acoustics*, Crocker, M.J. (ed.), Wiley, NY, ***1998***, Chapter 23; Leighton, T.G. *The Acoustic Bubble*, Academic Press, London, ***1994***, Chapter 4; Brennen, C.E. *Cavitation and Bubble Dynamics*, Oxford University Press, ***1995***, Chapters 1–4; Hua, I.; Hoffmann, M.R. *Environ. Sci. Technol.* ***1997***, *31*, 2237.

[84] Suslick, K.S.; Didenko, Y.T.; Fang, M.M.; Hyeon, T.; Kolbeck, K.J.; McNamara III, W.B.; Mdleleni, M.M.; Wong, M. *Philos. Trans. R. Soc. London A* ***1999***, *357*, 335. For problems of sonochemistry and cavitation, see Margulis, M.A. *Ultrasonics Sonochemistry* ***1994***, *1*, S87.

[85] Suslick, K.S.; Hammerton, D.A.; Cline Jr., R.E. *J. Am. Chem. Soc.* ***1986***, *108*, 5641.

[86] Didenko, Y.T.; McNamara III, W.B.; Suslick, K.S. *J. Am. Chem. Soc.* ***1999***, *121*, 5817.

[87] Colussi, A.J.; Hoffmann, M.R. *J. Phys. Chem. A* ***1999***, *103*, 11336.

[88] Colussi, A.J.; Weavers, L.K.; Hoffmann, M.R. *J. Phys. Chem. A* ***1998***, *102*, 6927.

[89] Segebarth, N.; Eulaerts, O.; Reisse, J.; Crum, L.A.; Matula, T.J. *J. Phys. Chem. B* ***2002***, *106*, 9181.

[90] Dekerckheer, C.; Bartik, K.; Lecomte, J.-P.; Reisse, J. *J. Phys. Chem. A* ***1998***, *102*, 9177.

[91] Elpiner, I. E. *Ultrasound: Physical, Chemical, and Biological Effects*, Consultants Bureau, NY, ***1964***.

[92] Sollner, K. *Chem. Rev.* ***1944***, *34*, 371.

[93] Suslick, K.S.; Schubert, P.F.; Goodale, J.W. *J. Am. Chem. Soc.* ***1981***, *103*, 7342; Sehgal, C.; Yu, T.J.; Sutherland, R.G.; Verrall, R.E. *J. Phys. Chem.* ***1982***, *86*, 2982.

[94] Han, B.-H.; Boudjouk, P. *J. Org. Chem.* ***1982***, *47*, 5030; Boudjouk, P.; Han, B.-H.; Anderson, K.R. *J. Am. Chem. Soc.* ***1982***, *104*, 4992; Boudjouk, P.; Han, B.-H. *J. Catal.* ***1983***, *79*, 489; Regen, S.L.; Singh, A. *J. Org. Chem.* ***1982***, *47*, 1587; Kegelaers, Y.; Eulaerts, O.; Reisse, J.; Segebarth, N. *Eur. J. Org. Chem.* ***2001***, 3683.

[95] Suslick, K.S.; Gawienowski, J.J.; Schubert, P.F.; Wang H.H. *J. Phys. Chem.* ***1983***, *87*, 2299.

It is often difficult to compare the sonochemical results reported from different laboratories (the reproducibility problem in sonochemistry).[96] The sonochemical power irradiated into the reaction system can be different for different instruments. Several methods are available to estimate the amount of ultrasonic power entered into a sonochemical reaction,[96] the most common being calorimetry. This experiment involves measurement of the initial rate of a temperature rise produced when a system is irradiated by power ultrasound. It has been shown that calorimetric methods combined with the Weissler reaction can be used to standardize the ultrasonic power of individual ultrasonic devices.[97]

Sonochemistry has been used to facilitate or assist many organic reactions,[98] and there are other applications.[99] The scope of reactions studied is beyond this work, but some representative examples will be listed. Ultrasound has been used to promote lithiation of organic compounds,[100] for the generation of carbenes,[101] and reactions of metal carbonyls where sonochemical ligand dissociation has been observed, which often produces multiple CO substitution.[102] The influence of ultrasound on phase-transfer catalyzed thioether synthesis has been studied.[103]

Sonochemistry has been applied to acceleration of the *Reformatsky reaction*,[104] *Diels-Alder reactions*,[105] the arylation of active methylene compounds,[106] nucleophilic aromatic substitution of haloarenes,[107] and to hydrostannation and tin hydride reduction.[108] Other sonochemical applications involve the reaction of benzyl chloride and nitrobenzene,[109] an $S_{RN}1$ reaction in liquid ammonia at room temperature,[110] and *Knoevenagel condensation* of aromatic aldehydes.[111] Iodination of aliphatic hydrocarbons can be accelerated,[112] and oxyallyl cations have been prepared from α,α'-diiodoketones using sonochemistry.[113] Sonochemistry has been applied to the preparation of carbohydrate compounds.[114] When

[96] Mason, T.J. *Practical Sonochemistry: User's Guide to Applications in Chemistry and Chemical Engineering*, Ellis Horwood, West Sussex, ***1991***, pp. 43–46; Broeckaert, L.; Caulier, T.; Fabre, O.; Maerschalk, C.; Reisse, J.; Vandercammen, J.; Yang, D.H.; Lepoint, T.; Mullie, F. *Current Trends in Sonochemistry*, Price, G.J. (ed.), Royal Society of Chemistry, Cambridge, ***1992***, p. 8; Mason, T.J.; Lorimer, J.P.; Bates, D.M.; Zhao, Y. *Ultrasonics Sonochemistry* ***1994***, *1*, S91; Mason, T.J.; Lorimer, J.P.; Bates, D.M. *Ultrasonics* ***1992***, *30*, 40.

[97] Kimura, T.; Sakamoto, T.; Leveque, J.-M.; Sohmiya, H.; Fujita, M.; Ikeda, S.; Ando, T. *Ultrasonics Sonochemistry* ***1996***, *3*, S157.

[98] Luche, J.-L. *Synthetic Organic Sonochemistry*, Plenum Press, NY, ***1998***; Luche, J.-L. *Ultrasonics Sonochemistry* ***1996***, *3*, S215.

[99] Adewuyi, Y.G. *Ind. Eng. Chem. Res.* ***2001***, *40*, 4681.

[100] Boudjouk, P.; Sooriyakumaran, R.; Han, B.H. *J. Org. Chem.* ***1986***, *51*, 2818, and Ref. 1 therein.

[101] Regen, S.L.; Singh, A. *J. Org. Chem.* ***1982***, *47*, 1587.

[102] Suslick, K.S.; Goodale, J.W.; Schubert, P.F.; Wang, H.H. *J. Am. Chem. Soc.* ***1983***, *105*, 5781.

[103] Wang, M.-L.; Rajendran, V. *J. Mol. Catalysis A: Chemical* ***2005***, *244*, 237.

[104] Han, B.H.; Boudjouk, P. *J. Org. Chem.* ***1982***, *47*, 5030.

[105] Nebois, P.; Bouaziz, Z.; Fillion, H.; Moeini, L.; Piquer, Ma.J.A.; Luche, J.-L.; Riera, A.; Moyano, A.; Pericàs, M.A. *Ultrasonics Sonochemistry* ***1996***, *3*, 7.

[106] Mečiarová, M., Kiripolský, M.; Toma, Š. *Ultrasonics Sonochemistry* ***2005***, *12*, 401.

[107] Mečiarová, M.; Toma, S.; Magdolen, P. *Ultrasonics Sonochemistry* ***2003***, *10*, 265.

[108] Nakamura, E.; Machii, D.; Inubushi, T. *J. Am. Chem. Soc.* ***1989***, *111*, 6849.

[109] Vinatoru, M.; Stavrescua, R.; Milcoveanu, A.B.; Toma, M.; Mason, T.J. *Ultrasonics Sonochemistry* ***2002***, *9*, 245.

[110] Manzo, P.G.; Palacios, S.M.; Alonso, R.A. *Tetrahedron Lett.* ***1994***, *35*, 677.

[111] McNulty, J.; Steere, J.A.; Wolf, S. *Tetrahedron Lett.* ***1998***, *39*, 8013.

[112] Kimura, T.; Fujita, M.; Sohmiya, H.; Ando, T. *Ultrasonics Sonochemistry* ***2002***, *9*, 205.

[113] Montaña, A.M.; Grima, P.M. *Tetrahedron Lett.* ***2001***, *42*, 7809.

[114] Kardos, N.; Luche, J.-L. *Carbohydrate Res.* ***2001***, *332*, 115.

sonochemistry is an important feature of a chemical reaction, this fact will be noted in the reactions presented in Chapters 10–19.

7.C. MICROWAVE CHEMISTRY

In 1986 independent work by Gedye and co-workers[115] as well as Majetich and Giguere[116] reported the use of microwave irradiation for organic reactions. Gedye described four different types of reactions, including the hydrolysis of benzamide to benzoic acid under acidic conditions, and all reactions showed significant rate enhancements when compared to the same reactions done at reflux conditions.[117] Majetich, Giguere and co-workers reported rate enhancements for microwave-promoted *Diels-Alder*, *Claisen*, and ene reactions.[116] Many publications[118] have appeared that describe chemical synthesis promoted by microwave irradiation, including many review articles[119] and books.[120]

Microwaves are electromagnetic waves (Sec. 7.A.i) and there are electric and magnetic field components. Charged particles start to migrate or rotate as the electric field is applied,[121] which leads to further polarization of polar particles. Because the concerted forces applied by the electric and magnetic components of microwaves are rapidly changing in direction ($2.4 \times 10^9\ s^{-1}$), warming occurs.[121] In general, the most common frequencies used for microwave dielectric heating[122] are 918 MHz and 2.45 GHz[123] (wavelengths of 33.3 and 12.2 cm, respectively), which are in the region between the IR and radiowave wavelengths in the electromagnetic spectrum. For chemical reactions done with microwave irradiation, rapid heating is usually observed,[124] and if a solvent is used superheating of that solvent is always observed.[122] Agitation is usually important.[125] In the early days of microwave chemistry, reactions were often done in open vessels, but also in sealed Teflon or glass vessels using unmodified domestic household ovens.[126] Dielectric heating is direct so if the reaction matrix has a sufficiently large dielectric loss tangent, and contains molecules

[115] Gedye, R.N.; Smith, F.E.; Westaway, K.C. *Can. J. Chem.* ***1987***, *66*, 17.
[116] Giguere, R.J.; Bray, T.; Duncan, S.M.; Majetich, G. *Tetrahedron Lett.* ***1986***, *27*, 4945.
[117] Taken from Horeis, G.; Pichler, S.; Stadler, A.; Gössler, W.; Kappe, C.O. *Microwave-Assisted Organic Synthesis – Back to the Roots*, Fifth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-5), ***2001*** (http://www.mdpi.org/ecsoc-5.htm). Chen, P.-K.; Rosana, M.R.; Dudley, G.B.; Stiegman, A.E. *J. Org. Chem.* ***2014***, *79*, 7425.
[118] Kappe, C.O. *Angew. Chem. Int. Ed.* ***2004***, *43*, 6250.
[119] Majetich, G.; Karen, W. in Kingston, H.M.; Haswell, S.J. *Microwave-Enhanced Chemistry: Fundamentals, Sample Preparation, and Applications*, American Chemical Society, Washington, DC, ***1997***, p 772; Bose, A.K.; Manhas, M.S.; Banik, B.K.; Robb, E.W. *Res. Chem. Intermed.* ***1994***, *20*, 1; Majetich, G.; Hicks, R. *Res. Chem. Intermed.* ***1994***, *20*, 61; Strauss, C.R.; Trainor, R.W. *Aust. J. Chem.* ***1995***, *48*, 1665; Caddick, S. *Tetrahedron* ***1995***, *51*, 10403; Mingos, D M.P. *Res. Chem. Intermed.* ***1994***, *20*, 85; Berlan, J. *Rad. Phys. Chem.* ***1995***, *45*, 581; Fini, A.; Breccia, A. *Pure Appl. Chem.* ***1999***, *71*, 573.
[120] Kingston, H.M.; Haswell, S.J. *Microwave-Enhanced Chemistry. Fundamentals, Sample Preparation, and Applications*, American Chemical Society, Washington, DC, ***1997***; Loupy, A. *Microwaves in Organic Synthesis*, Wiley-VCH, Weinheim, ***2002***; Hayes, B.L. *Microwave Synthesis: Chemistry at the Speed of Light*, CEM Publishing, Matthews, NC, ***2002***; Lidström, P., Tierney, J.P. *Microwave-Assisted Organic Synthesis*, Blackwell Scientific, ***2005***; Kappe, C.O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, Weinheim, ***2005***; *Microwave Heating as a Tool for Sustainable Chemistry.* Leadbeater, N.E. (ed.) CRC Press, Boca Raton, FL. ***2010***.
[121] Galema, S.A. *Chem. Soc. Rev.* ***1997***, *26*, 233.
[122] Gabriel, C.; Gabriel, S.; Grant, E.H.; Halstead, B.S.J.; Mingos, D.M.P. *Chem. Soc. Rev.* ***1998***, *27*, 213.
[123] This frequency is usually applied in domestic microwave ovens.
[124] See Hoogenboom, R.; Wilms, T.F.A.; Erdmenger, T.; Schubert, U.S. *Austr. J. Chem.* ***2009***, *62*, 236.
[125] Moseley, J.D.; Lenden, P.; Thomson, A.D.; Gilday, J.P. *Tetrahedron Lett.* ***2007***, *48*, 6084.
[126] Caddick, S. *Tetrahedron* ***1995***, *51*, 10403.

possessing a dipole moment, a solvent is not required. The use of dry-reaction microwave chemistry is increasingly popular.[127]

Microwave dielectric heating was initially categorized by thermal effects and nonthermal effects.[128] "Thermal effects are those which are caused by the different temperature regime which can be created due to microwave dielectric heating. Nonthermal effects are effects[129] which are caused by effects specifically inherent to the microwaves and are not caused by different temperature regimes."[121] Some researchers claimed special effects[130] in microwave chemistry, such as lowering of Gibbs energy of activation, but later study under careful temperature control indicated no special rate effects.[131] When conventional microwave ovens were used, temperature control was difficult, particularly when reactions were carried out in closed reaction vessels. The main contributing factor to any rate acceleration caused by microwave dielectric heating seems to be due to a thermal effect. The thermal effect may be due to a faster initial heating rate or to the occurrence of local regions with higher temperatures.[121]

Conventional microwave ovens are used less often for microwave chemistry today. Microwave reactors for chemical synthesis are commercially available and widely used in academia and in industry. These instruments have built-in magnetic stirring, direct temperature control of the reaction mixture, shielded thermocouples or IR sensors, and the ability to control temperature and pressure by regulating microwave output power.

The applications of microwave chemistry to organic chemistry are literally too numerous to mention.[132] A few representative examples will be given to illustrate the scope and utility. The combined use of microwaves and ultrasound is important in process chemistry and organic synthesis.[133] Microwave chemistry is widely used in synthesis,[134] including organocatalyzed asymmetric reactions.[135] Examples include the *Heck reaction* (**13-10**),[136] the *Suzuki reaction* (**13-12**),[137] the *Sonogashira reaction* (**13-13**),[138] *Ullman type couplings*

[127] Varma, R.S. *Green Chem.* ***1999***, 43; Kidawi, M. *Pure Appl. Chem.* ***2001***, *73*, 147; Varma, R.S. *Pure Appl. Chem.* ***2001***, *73*, 193.

[128] Langa, F.; de la Cruz, P.; de la Hoz, A.; Díaz-Ortiz, A.; Díez-Barra, E. *Contemp. Org. Synth.* ***1997***, *4*, 373. Also see Schmink, J.R.; Leadbeater, N.E. *Org. Biomol. Chem.* ***2009***, *7*, 3842.

[129] See Kuhnert, N. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1863.

[130] Laurent, R.; Laporterie, A.; Dubac, J.; Berlan, J.; Lefeuvre, S.; Audhuy, M. *J. Org. Chem.* ***1992***, *57*, 7099 and references therein.

[131] Raner, K.D.; Strauss, C.R.; Vyskoc, F.; Mokbel, L. J. *Org. Chem.* ***1993***, *58*, 950, and references cited therein.

[132] Hassan, H.M.A.; Harakeh, S.; Sakkaf, K.A.; Denetiu, J. *Aust. J. Chem.* ***2012***, *65*, 1647.

[133] Cravotto, G.; Cintas, P. *Chem. Eur. J.* ***2007***, *13*, 1902.

[134] See Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* ***2002***, *35*, 717; Nüchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* ***2004***, *6*, 128; Roberts, B.A.; Strauss, C.R. *Acc. Chem. Res.* ***2005***, *38*, 653; Kuznetsov, D.V.; Raev, V.A.; Kuranov, G.L.; Arapov, O.V.; Kostikov, R.R. *Russ. J. Org. Chem.* ***2005***, *41*, 1719. For a discussion of microwave-assisted organic synthesis in near critical water, see Kremsner, J.M.; Kappe, C.O. *Eur. J. Org. Chem.* ***2005***, 3672.

[135] Mossé, S.; Alexakis, A. *Org. Lett.* ***2006***, *8*, 3577.

[136] Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* ***2002***, *35*, 717; Olofsson, K.; Larhed, M. in Lidström, P.; Tierney, J.P. *Microwave-Assisted Organic Synthesis*, Blackwell, Oxford, ***2004***, Chap. 2, Andappan, M.M.S.; Nilsson, P.; Larhed, M. *Mol. Diversity* ***2003***, *7*, 97.

[137] Nuteberg, D.; Schaal, W.; Hamelink, E.; Vrang, L.; Larhed, M. *J. Comb. Chem.* ***2003***, *5*, 456; Miller, S.P.; Morgan, J.B.; Nepveux, F.J.; Morken, J.P. *Org. Lett.* ***2004***, *6*, 131; Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe, C.O.; Van der Eycken, E. *Mol. Diversity* ***2003***, *7*, 125; Gong, Y.; He, W. *Heterocycles* ***2004***, *62*, 851; Leadbeater, N.E.; Marco, M. *J. Org. Chem.* ***2003***, *68*, 888; Bai, L.; Wang, J.-X.; Zhang, Y. *Green Chem.* ***2003***, *5*, 615; Leadbeater, N.E.; Marco, M. *J. Org. Chem.* ***2003***, *68*, 5660.

[138] Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe, C.O.; Van der Eycken, E. *Mol. Diversity* ***2003***, *7*, 125; Gong, Y.; He, W. *Heterocycles* ***2004***, *62*, 851; Leadbeater, N.E.; Marco, M.; Tominack, B.J. *Org. Lett.* ***2003***, *5*, 3919; Appukkuttan, P.; Dehaen, W.; Van der Eycken, E. *Eur. J. Org. Chem.* ***2003***, 4713.

(**13-3**),[139] cycloaddition reactions (**15-58** to **15-66**),[140] dihydroxylation (**15-48**),[141] and the *Mitsunobu reaction* (**10-23**).[142] There are a multitude of other reactions[143] types from earlier literature that can be found in the cited review articles. When microwave chemistry is an important feature of a chemical reaction, this fact will be noted in the reactions presented in Chapters 10–19.

7.D. FLOW CHEMISTRY[144]

Chemical reactions can be done using *flow chemistry*,[145] otherwise known as *microchemistry*[146] or *continuous flow chemistry*,[147] in which pumps move fluid though a tube, where the reaction is done. When more than one tube is used, the fluids contact each other, and in some cases, react. The advantages to this approach are that the reactions are generally faster, the products have fewer side products, scale-up is easier, and there are other advantages. This approach is a rapidly growing area of research. This section will introduce the technique, and applications to individual reactions will be noted for specific reactions, indicated by the section in which that reaction appears. Many reactions have been examined using flow chemistry.[148]

Continuous flow iodination using a controlled liquid–liquid extraction system has been reported.[149] Continuous synthesis and purification has been accomplished by coupling a flow reactor with a simulated moving-bed chromatograph.[150] Site-selective modification of multifunctional molecules has been examined.[151] There are microwave-assisted flow reactions.[152] A flow liquid–liquid extraction system has been developed using open-source

[139] Wu, Y.-J.; He, H.; L'Heureux, A. *Tetrahedron Lett.* ***2003***, *44*, 4217; Lange, J.H.M.; Hofmeyer, L.J.F.; Hout, F.A.S.; Osnabrug, S.J.M.; Verveer, P.C.; Kruse, C.G.; Feenstra, R.W. *Tetrahedron Lett.* ***2002***, *43*, 1101.

[140] See Van der Eycken, E.; Appukkuttan, P.; De Borggraeve, W.; Dehaen, W.; Dallinger, D.; Kappe, C.O. *J. Org. Chem.* ***2002***, *67*, 7904; Pinto, D.C.G.A.; Silva, A.M.S.; Almeida, L.M.P.M.; Carrillo, J.R.; D'az-Ortiz, A.; de la Hoz, A.; Cavaleiro, J.A.S. *Synlett* ***2003***, 1415.

[141] Dupau, P.; Epple, R.; Thomas, A.A.; Fokin, V.V.; Sharpless, K.B. *Adv. Synth. Catal.* ***2002***, *344*, 421.

[142] Raheem, I.T.; Goodman, S.N.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2004***, *126*, 706.

[143] For photoredox-catalyzed, multicomponent reactions, see Rueping, M.; Vila, C. *Org. Lett.* ***2013***, *15*, 2092.

[144] Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 1048–1053.

[145] Wegner, J.; Ceylan, S.; Kirschning, A. *Chem. Commun.* ***2011***, *47*, 4583. McQuade, D.T.; Seeberger, P.H. *J. Org. Chem.* ***2013***, *78*, 6384. Kirschning, A.; Kupracz, L.; Hartwig, J. *Chem. Lett.* ***2012***, *41*, 562. Sachse, A.; Galarneau, A.; Coq, B.; Fajula, F. *New J. Chem.* ***2011***, 259. Reizman, B.J.; Jensen, K.F. *Acc. Chem. Res.* ***2016***, *49*, 1786. Plutschack, M.B.; Pieber, B.; Gilmore, K.; Seeberger, P.H. *Chem. Rev.* ***2017***, *117*, 11796. For a review of reaction screening, see Mohamed, D.K.B.; Yu, X.; Li, J.; Wu, J. *Tetrahedron Lett.* ***2016***, *57*, 3965.

[146] Wiles, C.; Watts, P. *Micro Reaction Technology in Organic Synthesis*, CRC Press, Boca Raton, FL. ***2011***. Yoshida, J. *Basics of Flow Microreactor Synthesis. Springer Briefs in Molecular Sciences Series*, Springer, Berlin, ***2015***. For a discussion of microarrays, see Wu, H.; Ge, J.; Uttamchandani, M.; Yao, S.Q. *Chem. Commun.* ***2011***, *47*, 5664.

[147] Fabry, D.C.; Sugiono, E.; Rueping, M. *Isr J. Chem.* ***2014***, *54*, 341. Morse, P.D.; Beingessner, R.L.; Jamison, T.F. *Isr J. Chem.* ***2017***, *57*, 218. For a discussion of laboratory scale, continuous flow reactions see Browne, D.L.; Baumann, M.; Harji, B.H.; Baxendale, I.R.; Ley, S.V. *Org. Lett.* ***2011***, *13*, 3312. Also see Hartwig, J.; Metternich, J.B.; Nikbin, N.; Kirschning, A.; Ley, S.V. *Org. Biomol. Chem.* ***2014***, *12*, 3611.

[148] Kelly, C.B.; Lee, C.; Leadbeater, N.E. *Tetrahedron Lett.* ***2011***, *52*, 263.

[149] O'Brien, M.; Cooper, D.A.; Dolan, J. *Tetrahedron Lett.* ***2017***, *58*, 829.

[150] O'Brien, A.G.; Horváth, Z.; Lévesque, F.; Lee, J.W.; Seidel-Morgenstern, A.; Seeberger, P.H. *Angew. Chem. Int. Ed.* ***2012***, *51*, 7028.

[151] Fuse, S.; Mifune, Y.; Tanabe, N.; Takahashi, T. *Synlett.* ***2014***, *25*, 2087.

[152] Nishioka, M.; Miyakawa, M.; Sato, K.; Miyazawa, A.; Suzuki, T.M. *Chem. Lett.* ***2013***, *42*, 1096.

technology.[153] Photochemical flow reactions are known.[154] Processing conditions, by means of microreactor technology, have been called "Novel Process Windows."[155]

Several natural products[156] and biologically important and/or commercial molecules[157] have been prepared using flow chemistry. The synthesis of C2 symmetric chiral pybox ligands have been subjected to scaled-up continuous flow synthesis.[158] A "catch-react-release" method has been used.[159] Continuous liquid–liquid separation has been used for the diazotization of amino acids.[160] The method has been used for optimization, scale-up, and library synthesis.[161] Heterogeneous catalyzed reactions have been reported using continuous flow techniques.[162] Continuous flow has been used for the biocatalytic resolution of methyl sulfinylacetates.[163] Phosgene has been generated and used in reactions in a microflow system.[164] A carbon-based molecular cage macrocycle has been prepared by continuous flow synthesis.[165] Organolithium reagents have been used in flow microreactors.[166] Ionic liquid droplet microreactors have been developed for use in catalysis reactions that are not

[153] O'Brien, M.; Kos, P.; Browne, D.L.; Ley, S.V. *Org. Biomol. Chem.* ***2012***, *10*, 7031.

[154] Schuster, E.M.; Wipf, P. *Isr. J. Chem.* ***2014***, *54*, 361. Garlets, Z.J.; Nguyen, J.D.; Stephenson, C.R.J. *Isr. J. Chem.* ***2014***, *54*, 351.

[155] Hessel, V.; Gursel, I.V.; Wang, Q.; Noël, T.; Lang, J. *Chem. Eng. Technol.* ***2012***, *35*, 1184; Hessel, V.; Cortese, B.; de Croon, M.H.J.M. *Chem. Eng. Sci.* ***2011***, *66*, 1426; Razzaq, T.; Kappe, C.O. *Chem. Asian J.* ***2010***, *5*, 1274; Hessel, V. *Chem. Eng. Technol.* ***2009***, *32*, 1655; Hessel, V.; Kralisch, D.; Krtschil, U. *Energy Environ. Sci.* ***2008***, *1*, 467.

[156] For a synthesis of ginkgolide B derivatives, see Qin, Y.; He, W.; Su, M.; Fang, Z.; Gu, J.; Ouyang, P.; Guo. K. *Tetrahedron Lett.* ***2016***, *57*, 1243. For a synthesis of nucleosides, see Sniady, A.; Bedore, M.W.; Jamison, T.F. *Angew. Chem. Int. Ed.* ***2011***, *50*, 2155; Shen, B.; Bedore, M.W.; Snaidy, A.; Jamison, T.F. *Chem. Commun.* ***2012***, *48*, 7444. For terpene synthesis, see Tang, X.; Allemann, R.K.; Wirth, T. *Eur. J. Org. Chem.* ***2017***, 414. For a synthesis of glycine and taurine-conjugated biole salts, see Veioiello, A.; Sardella, R.; Natalini, B.; Pellicciari, R. *Org. Biomol. Chem.* ***2012***, *10*, 4109. For a vitamin D3 synthesis, see Fuse, S.; Mifune, Y.; Tanabe, N.; Takahashi, T. *Org. Biomol. Chem.* ***2012***, *10*, 4109. For the synthesis of alkaloids, see Nakano, Y.; Savage, G.P.; Saubern, S.; Scammells, P.J.; Polyzos, A. *Aust. J. Chem.* ***2013***, *66*, 178.

[157] See O'Brien, A.G.; Lévesque, F.; Seeberger, P.H. *Chem. Commun.* ***2011***, *47*, 2688. For a synthesis of (2*S*)-(−)-3-*exo*-piperazinoisoborneol, see Osorio-Planes, L.; Rodríguez-Escrich, C.; Pericàs, M.A. *Org. Lett.* ***2012***, *14*, 1816. Drug candidateOZ439, see Lau, S.-H.; Galván, A.; Merchant, R.R.; Battilocchio, C.; Souto, J.A.; Berry, M.B.; Ley, S.V. *Org. Lett.* ***2015***, *17*, 3218. For a synthesis of Zyprexa, see Hartwig, J.; Ceylan, S.; Kupracz, K.; Coutable, L.; Kirschning, A. *Angew. Chem. Int. Ed.* ***2013***, *52*, 9813. For a synthesis of Ibuprofen, see Snead, D.R.; Jamison, T.F. *Angew. Chem. Int. Ed.* ***2015***, *54*, 983. For synthetic work toward anti-malarial compounds, see Pieber, B.; Glasnov, T.; Kappe, C.O. *Chem. Eur. J.* ***2015***, *21*, 4368.

[158] Battilocchio, C.; Baumann, M.; Baxendale, I.R.; Biava, M.; Kitching, M.O.; Ley, S.V.; Martin, R.E.; Ohnmacht, S.A.; Tappin, N.D.C. *Synthesis* ***2012***, *44*, 635.

[159] Suzuki, Y.; Laurino, P.; McQuade, D.T.; Seeberger, P.H. *Helv. Chim. Acta* ***2012***, *95*, 2578. For a synthesis of Imatinib base, see Ingham, R.J.; Riva, E.; Nikbin, N.; Baxendale, I.R.; Ley, S.V. *Org. Lett.* ***2012***, *14*, 3920; Hopkins, M.D.; Baxendale, I.R.; Ley, S.R. *Org. Biomol. Chem.* ***2013***, *11*, 1822. See Yang, J.C.; Niu, D.; Karsten, B.P.; Lima, F.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***2016***, *55*, 2531.

[160] Hu, D.X.; O'Brien, M.; Ley, S.V. *Org. Lett.* ***2012***, *14*, 4246.

[161] Yavorskyy, A.; Shvydkiv, O.; Hoffmann, N.; Nolan, K.; Oelgemöller, M. *Org. Lett.* ***2012***, *14*, 4342. Also see Ullah, F.; Zang, Q.; Javed, S.; Porubsky, P.; Neuenswander, B.; Lushington, G.H.; Hanson, P.R.; Organ, M.G. *Synthesis* ***2012***, *44*, 2547. Koolman, H.F.; Kantor, S.; Bogdan, A.R.; Wang, Y.; Pan, J.Y.; Dujuric, S.W. *Org. Biomol. Chem.* ***2016***, *14*, 6591.

[162] Ishitani, H.; Saito, Y.; Tsubogo, T.; Kobayashi, S. *Org. Lett.* ***2016***, *18*, 1346.

[163] Liu, Z.; Burgess, K. *Tetrahedron Lett.* ***2011***, *52*, 6325. See Tamborini, L.; Romano, D.; Pinto, A.; Contente, M.; Iannuzzi, M.C.; Conti, P.; Molinari, F. *Tetrahedron Lett.* ***2013***, *54*, 6090.

[164] Fuse, S.; Tanabe, N.; Takahashi, T. *Chem. Commun.* ***2011***, *47*, 12661.

[165] Kitchin, M.; Konstas, K.; Sumby, C.J.; Czyz, M.L.; Vlente, P.; Hill, M.R.; Polyzos, A.; Doonan, C.J. *Chem. Commun.* ***2012***, *48*, 7444.

[166] Nagaki, A.; Uesugi, Y.; Kim, H.; Yoshida, J. *Chem. Asian J.* ***2013***, *8*, *705*.

at equilibrium.[167] Ketenes have been generated and trapped in flow.[168] Radicals have been generated in a continuous UV-flow microsystem, from organotrifluoroborates by photoredox catalysis.[169]

7.E. MECHANOCHEMISTRY

It is fair to say that most organic reactions are performed as bulk reactions, that is, reagents and substrates are mixed together in solution, then heated and stirred to facilitate the reaction. With the attention paid nowadays to green chemistry,[170] an arcane method[171] has been updated and applied to modern reactions. Indeed, mechanochemistry[172] is used for organic reactions using milling or grinding of reagents without the need for bulk solvents. Different selectivity in some reactions has been noted,[173] such as oxidation with ozone, for mechanochemical reactions when compared to conventional solution reactions.[174] Moisture-sensitive reactions have been reported under mechanochemical conditions.[175] Chlorination of hydrocarbons has been reported using mechanochemistry.[176] Metal-catalyzed reactions have been done using mechanochemistry.[177]

[167] Zhang, M.; Ettelaie, R.; Yan, T.; Zhang, S.; Cheng, F; Binks, B.P.; Yang, H. *J. Am. Chem. Soc.* ***2017***, *139*, 17387.
[168] Henry, C.; Bolien, D.; Ibanescu, B.; Bloodworth, S.; Harrowven, D.C.; Zhang, X.; Craven, A.; Sneddon, H.F.; Whitby, R.J. *Eur. J. Org. Chem.* ***2015***, 1491.
[169] El Achi, N.; Penhoat, M.; Bakkour, Y.; Rolando, C.; Chausset-Boissarie, L. *Eur. J. Org. Chem.* ***2016***, 4284.
[170] Baig, R.B.N.; Varma, R.S. *Chem. Soc. Rev.* ***2012***, *41*, 1559.
[171] Takacs, L. *Chem. Soc. Rev.* ***2013***, *42*, 7649.
[172] James, S.L.; Adams, C.J.; Bolm, C.; Braga, D.; Collier, P.; Friščić, T.; Grepioni, F.; Harris, K.D.M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A.G.; Parkin, I.P.; Shearouse, W.C.; Steed, J.W.; Waddell, D.C. *Chem. Soc. Rev.* ***2012***, *41*, 413. Do, J.-L.; Friščić, T. *ACS Central Science* ***2017***, *3*, 13. Also see Bruns, C.J.; Stoddart, J.F. *The Nature of the Mechanical Bond. From Molecules to Machines*, Wiley, Hoboken, NJ, ***2016***.
[173] Hernández, J.G.; Bolm, C. *J. Org. Chem.* ***2017***, *82*, 4007.
[174] Collom, S.L.; Anastas, P.T.; Beach, E.S.; Crabtree, R.H.; Hazari, N.; Sommer, T.J. *Tetrahedron Lett.* ***2013***, *54*, 2344.
[175] Waddell, D.C.; Clark, T.D.; Mack, J. *Tetrahedron Lett.* ***2012***, *53*, 4510.
[176] Višňovský, J.; Billik, P.; Kubinec, R.; Podolec, P.; Szabó, A.H.; Juriga, M.; Čabala, R.; Kubincová, J.; Blaško, J. *Tetrahedron Lett.* ***2013***, *54*, 7180.
[177] Hernández, J.G.; Friščić, T. *Tetrahedron Lett.* ***2015***, *56*, 4253.

CHAPTER 8

Acids and Bases

Two acid–base theories are used in organic chemistry today: the Brønsted theory and the Lewis theory.[1] These theories are quite compatible and are used for different purposes.[2] However, the Lewis-based idea of electron-donating species (bases) and electron-accepting species (acids) is often the more useful for organic chemistry. Remember also that most organic reactions are not done in an aqueous medium, and a focus on electron transfer rather than proton transfer is far more useful.

8.A. BRØNSTED THEORY

According to this theory, an acid is defined as a *proton donor*[3] and a base as a *proton acceptor*. However, a base must have a pair of electrons available to share with the proton; this is usually present as an unshared pair, but sometimes is in a π orbital. By this definition, an acid–base reaction is the transfer of a proton from an acid to a base. However, protons do not exist free in solution but must be attached to an electron pair. In fact, the acid does not "give up" a proton, but rather the base donates electrons to the proton, "pulling it away" to form the conjugate acid. After removal of the proton, the species remaining (the *conjugate base*) still retains the electron pair to which the proton was formerly attached. The conjugate base, in theory at least, can reacquire a proton and is therefore a base. All acids will generate a conjugate base upon reaction with a suitable base, and all bases will generate a *conjugate acid* by reaction with a suitable acid. All acid–base reactions fit the equation

$$\underset{\text{Acid}_1}{\text{A—H}} + \underset{\text{Base}_2}{\text{B}} \rightleftharpoons \underset{\text{Base}_1}{\text{A}} + \underset{\text{Acid}_2}{\text{B—H}}$$

[1] For monographs on acids and bases, see Stewart, R. *The Proton: Applications to Organic Chemistry*, Academic Press, NY, ***1985***; Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***; Finston, H.L.; Rychtman, A.C. *A New View of Current Acid–Base Theories*, Wiley, NY, ***1982***.

[2] For discussion of the historical development of acid–base theory, see Bell, R.P. *Q. Rev. Chem. Soc.* ***1947***, *1*, 113; Bell, R.P. *The Proton in Chemistry*, 1st ed., Cornell University Press, Ithaca, NY, ***1959***, pp. 7–17.

[3] According to IUPAC terminology (Bunnett, J.F.; Jones, R.A.Y. *Pure Appl. Chem.* ***1988***, *60*, 1115), an acid is a *hydron* donor. IUPAC recommends that the term *proton* be restricted to the nucleus of the hydrogen isotope of mass 1, while the nucleus of the naturally occurring element (which contains about 0.015% deuterium) be called the *hydron* (the nucleus of mass 2 has always been known as the *deuteron*). This accords with the naturally occurring negative ion, which has long been called the *hydride* ion. In this book, however, we will continue to use *proton* for the naturally occurring form, because most of the literature uses this term.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

No charges are shown in this equation, but an acid always has a charge one positive unit higher than that of its conjugate base.

8.A.i. Brønsted Acids

According to the Brønsted definition, *acid strength* may be defined as the tendency to give up a proton and *base strength* as the tendency to accept a proton. All acid–base reactions are reversible, and both an acid and a conjugate acid are present in the equilibrium mixture. In one sense, acid–base reactions occur because the acid and the conjugate acid are not of equal strength (i.e., the equilibrium can be shifted to one side or the other). If an acid, say HCl, is placed in contact with the conjugate base of a weaker acid, say acetate ion, the conjugate acid in this reaction would be acetic acid. Since HCl is a stronger acid than acetic acid, the equilibrium lies well to the right.

$$HCl + CH_3COO^- \rightleftharpoons CH_3COOH + Cl^-$$

As the reaction is written, if the equilibrium lies to the right (higher concentration of acetic acid and a lower concentration of HCl), HCl is the stronger acid. Likewise, acetate is taken to be a stronger base than the chloride ion. If this is a correct statement, treatment of acetic acid with chloride ion should give essentially no reaction, since the weaker acid already has the proton. This is found to be correct.

For a comparison of two different acids, the position of the equilibrium in reaction with a common base allows the relative strengths of acids to be determined.[4] Likewise, the strength of two different bases will be determined by comparing the equilibrium established when they react with a common acid. By definition, the acid and base are always drawn on the left-hand side of the equation, and the conjugate acid and conjugate base are assumed to be on the right-hand side of the equation.

Of course, if the two acids involved are close to each other in strength, a measurable reaction will occur from both sides. This really means that the concentration of acid and base at equilibrium will be close to that of the concentration of the conjugate acid and conjugate base. However, the position of equilibrium will still be over to the side of the weaker acid (unless the acidities are equal within experimental limits). If the concentration of acid and base is higher, the reaction of conjugate acid and conjugate base is more facile, and the compound labeled as the acid is considered to be a weaker acid. If the concentration of the conjugate acid and conjugate base is higher, the reaction of the acid and base is more facile, and the compound labeled as the acid is a stronger acid.

Using these protocols as the definition of acid strength, it is possible to construct a table in which acids are listed in order of acid strength[5] (Table 8.1).[6] The conjugate base is shown next to each acid in Table 8.1. Using the axiom that a strong acid generates a weak conjugate base and a weak acid will generate a strong conjugate base, it is clear that if the acids in such a table are listed in *decreasing* order of acid strength, the bases must be listed in *increasing* order of base strength. The pK_a values[7] in Table 8.1 are most accurate in the middle of the

[4] Although equilibrium is reached in most acid–base reactions extremely rapidly (Sec. 8.B), some are slow (especially those in which the proton is lost from a carbon) and in these cases time must be allowed for the system to come to equilibrium.

[5] For a review of stronger Brønsted acids, see Akiyama, T. *Chem. Rev.* ***2007***, *107*, 5744.

[6] Table 8.1 is a thermodynamic acidity scale and applies only to positions of equilibria. For the distinction between thermodynamic and kinetic acidity, see Sec. 8.B.

[7] For a first principles calculation of pK values in nonaqueous solution, see Ding, F.; Smith, J.M.; Wang, H. *J. Org. Chem.* ***2009***, *74*, 2679.

TABLE 8.1 The pK_a values for many types of acids[a]
The values in boldface are exact values; the others are approximate, especially above 18 and below −2[8]

Acid	Base	Approximate pK_a (relative to water)	References
$HF–SbF_5$	SbF_6^-		9
$FSO_3H–SbF_5–SO_3$			80
$FSO_3H–SbF_5$			80, 9
FSO_3H	FSO_3^-		80
RNO_2H^+	RNO_2	−12	10
$ArNO_2H^+$	$ArNO_2$	−11	10
$HClO_4$	ClO_4^-	−10	11
HI	I^-	−10	11
$RCNH^+$	RCN	−10	12
$R-\overset{\overset{O}{\|}}{C}-H + OH$	$R-\overset{\overset{O}{\|}}{C}-H$	−10	13
H_2SO_4	HSO_4^-		
HBr	Br^-	−9	11
$Ar-\overset{\overset{O}{\|}}{C}-OR^{14} + OH$	$Ar-\overset{\overset{O}{\|}}{C}-OR$	−7.4	10
HCl	Cl^-	−7	11
RSH_2^+	RSH	−7	10
$Ar-\overset{\overset{O}{\|}}{C}-OH^{14} + OH$	$Ar-\overset{\overset{O}{\|}}{C}-OH$	−7	15

(*continued*)

[8] This table gives average values for functional groups. See Brown, H.C.; McDaniel, D.H.; Häflinger, O. in Braude, E.A.; Nachod, F.C. *Determination of Organic Structures by Physical Methods*, Vol. 1, Academic Press, NY, ***1955***; Serjeant, E.P.; Dempsey, B. *Ionisation Constants of Organic Acids in Aqueous Solution,* Pergamon, Elmsford NY, ***1979***; Kortüm, G.; Vogel, W.; Andrussow, K. *Dissociation Constants of Organic Acids in Aqueous Solution*, Butterworth, London, ***1961***. The index in the 1979 volume covers both volumes. Kortüm, G.; Vogel, W.; Andrussow, K. *Pure Appl. Chem.* ***1960***, *1*, 190; Arnett, E.M. *Prog. Phys. Org. Chem.* ***1963***, *1*, 223; Perrin, D.D. *Dissociation Constants of Organic Bases in Aqueous Solution*, Butterworth, London, ***1965***, and Supplement, 1972; Collumeau, A. *Bull. Soc. Chim. Fr.* ***1968***, 5087; Bordwell, F.G. *Acc. Chem. Res.* ***1988***, *21*, 456; Perrin, D.D. *Ionisation Constants of Inorganic Acids and Bases in Aqueous Solution*, 2nd ed., Pergamon, Elmsford NY, ***1982***; *Pure Appl. Chem.* ***1969***, *20*, 133.

[9] Gold, V.; Laali, K.; Morris, K.P.; Zdunek, L.Z. *J. Chem. Soc., Chem. Commun.* ***1981***, 769; Sommer, J.; Canivet, P.; Schwartz, S.; Rimmelin, P. *Nouv. J. Chim.* ***1981***, *5*, 45.

[10] Arnett, E.M. *Prog. Phys. Org. Chem.* ***1963***, *1*, 223 (pp. 324–325).

[11] Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***.

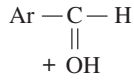
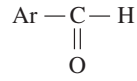
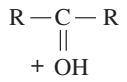
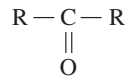
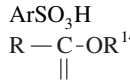
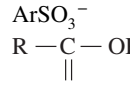
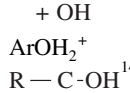
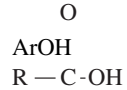
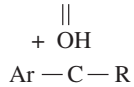
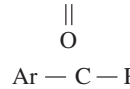
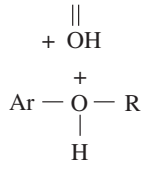
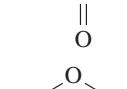
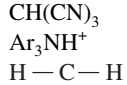
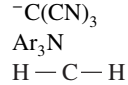
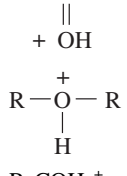
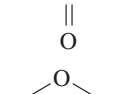
[12] Deno, N.C.; Gaugler, R.W.; Wisotsky, M.J. *J. Org. Chem.* ***1966***, *31*, 1967.

[13] Levy, G.C.; Cargioli, J.D.; Racela, W. *J. Am. Chem. Soc.* ***1970***, *92*, 6238. See, however, Brouwer, D.M.; van Doorn, J.A. *Recl. Trav. Chim. Pays-Bas* ***1971***, *90*, 1010.

[14] Carboxylic acids, esters, and amides are shown in this table to be protonated on the carbonyl oxygen. See Smith, C.R.; Yates, K. *Can. J. Chem.* ***1972***, *50*, 771; Benedetti, E.; Di Blasio, B.; Baine, P. *J. Chem. Soc., Perkin Trans. 2* ***1980***, 500; Homer, R.B.; Johnson, C.D. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 188–197. It has been shown that some amides protonate at nitrogen: see Perrin, C.L. *Acc. Chem. Res.* ***1989***, *22*, 268. For a review of alternative proton sites, see Liler, M. *Adv. Phys. Org. Chem.* ***1975***, *11*, 267.

[15] Stewart, R.; Granger, M.R. *Can. J. Chem.* ***1961***, *39*, 2508.

TABLE 8.1 (*Continued*)

Acid	Base	Approximate pK_a (relative to water)	References
		−7	16
		−7	12, 17, 149
$ArSO_3H$	$ArSO_3^-$	−6.5	18
		−6.5	10
$ArOH_2^+$	ArOH	−6.4	19
		−6	10
		−6	16, 20
		−6	10, 21
$CH(CN)_3$	$^-C(CN)_3$	−5	22
Ar_3NH^+	Ar_3N	−5	23
		−4	24
		−3.5	12, 18, 25
$R_3COH_2^+$	R_3COH	−2	25
$R_2CHOH_2^+$	R_2CHOH	−2	25, 26
$RCH_2OH_2^+$	RCH_2OH	−2	12, 22, 23
H_3O^+	H_2O	0 (−1.74)	27, 77

[16] Yates, K.; Stewart, R. *Can. J. Chem.* ***1959***, *37*, 664; Stewart, R.; Yates, K. *J. Am. Chem. Soc.* ***1958***, *80*, 6355.
[17] Lee, D.G. *Can. J. Chem.* ***1970***, *48*, 1919.
[18] Cerfontain, H.; Koeberg-Telder, A.; Kruk, C. *Tetrahedron Lett.* ***1975***, 3639.
[19] Arnett, E.M.; Wu, C.Y. *J. Am. Chem. Soc.* ***1960***, *82*, 5660; Koeberg-Telder, A.; Lambrechts, H.J.A.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1983***, *102*, 293.
[20] Fischer, A.; Grigor, B.A.; Packer, J.; Vaughan, J. *J. Am. Chem. Soc.* ***1961***, *83*, 4208.
[21] Arnett, E.M.; Wu, C.Y. *J. Am. Chem. Soc.* ***1960***, *82*, 4999.
[22] Boyd, R.H. *J. Phys. Chem.* ***1963***, *67*, 737.
[23] Arnett, E.M.; Quirk, R.P.; Burke, J.J. *J. Am. Chem. Soc.* ***1970***, *92*, 1260.
[24] McTigue. P.T.; Sime, J.M. *Aust. J. Chem.* ***1963***, *16*, 592.
[25] Deno, N.C.; Turner, J.O. *J. Org. Chem.* ***1966***, *31*, 1969.
[26] Chandler, W.D.; Lee, D.G. *Can. J. Chem.* ***1990***, *68*, 1757.
[27] For a discussion, see Campbell, M.L.; Waite, B.A. *J. Chem. Educ.* ***1990***, *67*, 386.

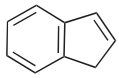
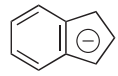
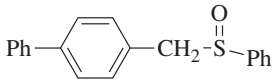
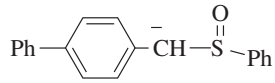
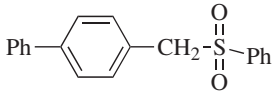
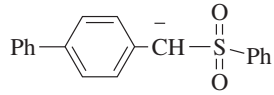
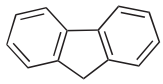
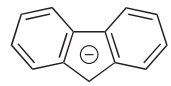
TABLE 8.1 (*Continued*)

Acid	Base	Approximate pK_a (relative to water)	References
$Ar-C(=O)-NH_2$ + OH [14]	$Ar-C(=O)-NH_2$	−1.5	28
HNO_3	NO_3^-	−1.4	11
$R-C(=O)-NH_2$ + OH [14]	$R-C(=O)-NH_2$	−0.5	28
$Ar_2NH_2^+$	Ar_2NH	1	21
HSO_4^-	SO_4^{2-}	1.99	29
HF	F^-	3.17	29
HONO	NO_2^-	3.29	29
$ArNH_3^+$	$ArNH_2$	3–5	30
$ArNR_2H^+$	$ArNR_2$	3–5	30
RCOOH	$RCOO^-$	4–5	30
$HCOCH_2CHO$	$HCOC^-HCHO$	5	31
H_2CO_3 [32]	HCO_3^-	6.35	29
H_2S	HS^-	7.00	29
ArSH	ArS^-	6–8	33
$CH_3COCH_2COCH_3$ [34]	$CH_3COC^-HCOCH_3$	9	31
HCN	CN^-	9.2	35
NH_4^+	NH_3	9.24	29
ArOH	ArO^-	8–11	36
RCH_2NO_2	RC^-HNO_2	10	37
R_3NH^+	R_3N	10–11	30
RNH_3^+	RNH_2	10–11	30
HCO_3^-	CO_3^{2-}	10.33	29
RSH	RS^-	10–11	33
$R_2NH_2^+$	R_2NH	11	30
$N{\equiv}CCH_2C{\equiv}N$	$N{\equiv}CC^-HC{\equiv}N$	11	31, 38
CH_3COCH_2COOR	CH_3COC^-HCOOR	11	31

(*continued*)

[28] Grant, H.M.; McTigue, P.; Ward, D.G. *Aust. J. Chem.* ***1983***, *36*, 2211.
[29] Bruckenstein, S.; Kolthoff, I.M. in Kolthoff, I.M.; Elving, P.J. *Treatise on Analytical Chemistry*, Vol. 1, pt. 1, Wiley, NY, ***1959***, pp. 432–433.
[30] Brown, H.C.; McDaniel, D.H.; Häflinger, O. in Braude, E.A.; Nachod, F.C. *Determination of Organic Structures by Physical Methods*, Vol. 1, Academic Press, NY, ***1955***, pp. 567–662.
[31] Pearson, R.G.; Dillon, R.L. *J. Am. Chem. Soc.* ***1953***, *75*, 2439.
[32] This value includes the CO_2 usually present. The value for H_2CO_3 alone is 3.9 in Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***.
[33] Crampton, M.R. in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, ***1974***, pp. 396–410.
[34] See Bunting, J.W.; Kanter, J.P. *J. Am. Chem. Soc.* ***1993***, *115*, 11705.
[35] Perrin, D.D. *Ionisation Constants of Inorganic Acids and Bases in Aqueous Solution*, 2nd ed., Pergamon, Elmsford, NY, ***1982***.
[36] Rochester, C.H. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, p. 374.
[37] Cram, D.J. *Chem. Eng. News* ***1963***, *41* (No. 33, Aug. 19), 94.
[38] Bowden, K.; Stewart, R. *Tetrahedron* ***1965***, *21*, 261.

TABLE 8.1 (*Continued*)

Acid	Base	Approximate pK_a (relative to water)	References
$CH_3SO_2CH_2SO_2CH_3$	$CH_3SO_2C^-HSO_2CH_3$	12.5	39
$EtOOCCH_2COOEt$	$EtOOCC^-HCOOEt$	13	31
CH_3OH	CH_3O^-	15.2	40, 41
H_2O	OH^-	14.0 (15.7)	42
		16	43
RCH_2OH	RCH_2O^-	16	40
RCH_2CHO	RC^-HCHO	16	44
R_2CHOH	R_2CHO^-	16.5	40
R_3COH	R_3CO^-	17	40
$RCONH_2$	$RCONH^-$	17	45
Imidazolium salts		18–20[b]	46
$RCOCH_2R$	$RCOC^-HR$	19–20[47]	48
		20	49, 50
		20.08[a]	51
		18.91[a]	51
		23	49, 50

[39] Hine, J.; Philips, J.C.; Maxwel, J.I. *J. Org. Chem.* ***1970***, *35*, 3943. See also, Ang, K.P.; Lee, T.W.S. *Aust. J. Chem.* ***1977***, *30*, 521.

[40] Reeve, W.; Erikson, C.M.; Aluotto, P.F. *Can. J. Chem.* ***1979***, *57*, 2747.

[41] See also, Olmstead, W.N.; Margolin, Z.; Bordwell, F.G. *J. Org. Chem.* ***1980***, *45*, 3295.

[42] Harned, H.S.; Robinson, R.A. *Trans. Faraday Soc.* ***1940***, *36*, 973. It has been suggested that the pK_a of water should be 14, not 15.7. See Neils, T.; Schaertel, S. https://chem.libretexts.org/Textbook_Maps/Organic_Chemistry/Supplemental_Modules_(Organic_Chemistry)/Fundamentals/What_is_the_pKa_of_water%3F.

[43] Streitwieser Jr., A.; Nebenzahl, L. *J. Am. Chem. Soc.* ***1976***, *98*, 2188.

[44] Guthrie, J.P.; Cossar, J. *Can. J. Chem.* ***1986***, *64*, 2470.

[45] Homer, R.B.; Johnson, C.D. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 238–240.

[46] Dunn, M.H.; Konstandaras, N.; Cole, M.L.; Harper, J.B. *J. Org. Chem.* ***2017***, *82*, 7324.

[47] The pK_a of acetone in DMSO is reported to be 26.5. See Bordwell, F.G.; Zhang, X.-M. *Accts. Chem. Res.* ***1997***, *26*, 510. Also see Yang, C.; Xue, X.-S.; Li, X.; Cheng, J.-P. *J. Org. Chem.* ***2014***, *79*, 4340. The pK_a of cyclobutanone in water has been determined to be 19.7–20.2: see Cope, S.M.; Tailor, D.; Nagorski, R.W. *J. Org. Chem.* ***2011***, *76*, 380.

[48] Guthrie, J.P.; Cossar, J.; Klym, A. *J. Am. Chem. Soc.* ***1984***, *106*, 1351; Chiang, Y.; Kresge, A.J.; Tang, Y.S.; Wirz, J. *J. Am. Chem. Soc.* ***1984***, *106*, 460.

[49] Streitwieser Jr., A.; Ciuffarin, E.; Hammons, J.H. *J. Am. Chem. Soc.* ***1967***, *89*, 63.

[50] Streitwieser Jr., A.; Hollyhead, W.B.; Pudjaatmaka, H.; Owens, P.H.; Kruger, T.L.; Rubenstein, P.A.; MacQuarrie, R.A.; Brokaw, M.L.; Chu, W.K.C.; Niemeyer, H.M. *J. Am. Chem. Soc.* ***1971***, *93*, 5088.

[51] Streitwieser, A.; Wang, G.P.; Bors, D.A. *Tetrahedron* ***1997***, *53*, 10103.

TABLE 8.1 (*Continued*)

Acid	Base	Approximate pK_a (relative to water)	References
$ROOCCH_2R$	$ROOCC^-HR$	24.5	31
$RCH_2C{\equiv}N$	$RC^-HC{\equiv}N$	25	31, 52
$HC{\equiv}CH$	$HC{\equiv}CC^-$	25	53
Ph_2NH	PH_2N^-	24.95[b]	62
$EtOCOCH_3$	$EtOCOCH_2^-$	25.6	54
$PhNH_2$	$PhNH^-$	30.6[b]	47
Ar_3CH	Ar_3C^-	31.5	49, 55
Ar_2CH_2	Ar_2CH^-	33.5	49, 50
H_2	H^-	35	56
NH_2	NH_2^-	38	57
$PhCH_3$	$PhCH_2^-$	40	58
$CH_2{=}CHCH_3$		43	59
PhH	Ph^-	43	60
$CH_2{=}CH_2$	$CH_2{=}CH^-$	44	61
cyclo-C_3H_6	*cyclo*-$C_3H_5^-$	46	62
CH_4[63]	CH_3^-	48	64
C_2H_6	$C_2H_5^-$	50	65
$(CH_3)_2CH_2$[63]	$(CH_3)_2CH^-$	51	65
$(CH_3)_3CH$[63]	$(CH_3)_3C^-$	–	66

[a] pK_a in THF; [b] pK_a in DMSO

[52] For a review of the acidity of cyano compounds, see Hibbert, F. in Patai, S.; Rappoport, Z. *The Chemistry of Triple-bonded Functional Groups*, pt. 1; Wiley, NY, ***1983***, pp. 699–736.

[53] Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, p. 19. See also, Dessy, R.E.; Kitching, W.; Psarras, T.; Salinger, R.; Chen, A.; Chivers, T. *J. Am. Chem. Soc.* ***1966***, *88*, 460.

[54] Amyes, T.L.; Richard, J.P. *J. Am. Chem. Soc.* ***1996***, *118*, 3129.

[55] Streitwieser Jr., A.; Hollyhead, W.B.; Sonnichsen, G.; Pudjaatmaka, H.; Chang, C.J.; Kruger, T.L. *J. Am. Chem. Soc.* ***1971***, *93*, 5096.

[56] Buncel, E.; Menon, B. *J. Am. Chem. Soc.* ***1977***, *99*, 4457.

[57] Buncel, E.; Menon, B. *J. Organomet. Chem.* ***1977***, *141*, 1.

[58] Albrech, H.; Schneider, G. *Tetrahedron* ***1986***, *42*, 4729.

[59] Boerth, D.W.; Streitwieser Jr., A. *J. Am. Chem. Soc.* ***1981***, *103*, 6443.

[60] Streitwieser Jr., A.; Scannon, P.J.; Niemeyer, H.M. *J. Am. Chem. Soc.* ***1972***, *94*, 7936.

[61] Streitwieser Jr., A.; Boerth, D.W. *J. Am. Chem. Soc.* ***1978***, *100*, 755.

[62] This value is calculated from results given in Streitwieser Jr., A.; Caldwell, R.A.; Young, W.R. *J. Am. Chem. Soc.* ***1969***, *91*, 529. For a review of acidity and basicity of cyclopropanes, see Battiste, M.A.; Coxon, J.M. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, ***1987***, pp. 255–305.

[63] See Daasbjerg, K. *Acta Chem. Scand. B* ***1995***, *49*, 878 for pK_a values of various hydrocarbons in DMF.

[64] This value is calculated from results given in Streitwieser Jr., A.; Taylor, D.R. *J. Chem. Soc. D* ***1970***, 1248.

[65] These values are based on those given in Cram, D.J. *Chem. Eng. News* ***1963***, *41* (No. 33, Aug. 19), 94, but are corrected to the newer scale of Streitwieser, A.; Streitwieser Jr., A.; Scannon, P.J.; Niemeyer, H.M. *J. Am. Chem. Soc.* ***1972***, *94*, 7936; Streitwieser Jr., A.; Boerth, D.W. *J. Am. Chem. Soc.* ***1978***, *100*, 755.

[66] Breslow, R. and co-workers report a value of 71 [Breslow, R.; Grant, J.L. *J. Am. Chem. Soc.* ***1977***, *99*, 7745], but this was obtained by a different method, and is not comparable to the other values in Table 8.1. A more comparable value is about 53. See also, Juan, B.; Schwarz, J.; Breslow, R. *J. Am. Chem. Soc.* ***1980***, *102*, 5741.

table. The pK_a values are much harder to measure[67] for very strong acids and very weak acids, and these values must be regarded as approximate. If one did not have the pK_a values available, it can be determined experimentally that $HClO_4$ is a stronger acid than H_2SO_4. A mixture of $HClO_4$ and H_2SO_4 in 4-methylpentan-2-one can be titrated to an $HClO_4$ end point without interference by H_2SO_4.[68] Similarly, $HClO_4$ can be shown to be stronger than HNO_3 or HCl. However, this is not quantitative, and the value of −10 in the table is not much more than an educated guess. The values for RNO_2H^+, $ArNO_2H^+$, HI, $RCNH^+$, and RSH_2^+ must also be regarded as highly speculative.[69] A wide variety of pK_a values have been reported for the conjugate acids of even such simple bases as acetone[70] (−0.24 to −7.2), diethyl ether (−0.30 to −6.2), ethanol (−0.33 to −4.8), methanol (−0.34 to −4.9), and propan-2-ol (−0.35 to −5.2), depending on the method used to measure them.[71] Very accurate values can be obtained only for acids weaker than hydronium ion and stronger than water.

A crystallographic scale of acidity has been developed, including the acidity of C—H compounds.[72] The effect of hydrogen bonds on pK_a values has been discussed.[73] Measuring the mean C—H••••O distances in crystal structures correlated well with conventional $pK_{a(DMSO)}$ values,[74] where DMSO is dimethyl sulfoxide. An *ab initio* study was able to correlate ring strain in strained hydrocarbons with hydrogen-bond acidity.[75] The kinetic acidity of aliphatic hydrocarbons has been determined.[76]

The bottom portion of Table 8.1 consists of very weak acids (pK_a above that of water ≈15.8; recent data corrects this to 14.0).[77] In most of these acids, the proton is lost from a carbon atom, and such acids are known as *carbon acids*. The pK_a values for such weak acids are often difficult to measure and are known only approximately. The methods used to determine the relative positions of these acids are discussed in Chapter 5.[78] The acidity of carbon acids is proportional to the stability of the carbanions that are their conjugate bases (Sec. 5.B.i).

[67] For a review of methods of determining pK_a values, see Cookson, R.F. *Chem. Rev.* ***1974***, *74*, 5.

[68] Kolthoff, I.M.; Bruckenstein, S. in Kolthoff, I.M.; Elving, P.J. *Treatise on Analytical Chemistry*, Vol. 1, pt. 1, Wiley, NY, ***1959***, pp. 475–542 (p. 479).

[69] For reviews of organic compounds protonated at O, N, or S, see Olah, G.A.; White, A.M.; O'Brien, D.H. *Chem. Rev.* ***1970***, *70*, 561; Olah, G.A.; White, A.M.; O'Brien, D.H. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1973***, pp. 1697–1781.

[70] For discussions of pK_a determinations for the conjugate acids of ketones, see Bagno, A.; Lucchini, V.; Scorrano, G. *Bull. Soc. Chim. Fr.* ***1987***, 563; Toullec, J. *Tetrahedron Lett.* ***1988***, *29*, 5541.

[71] Rochester, C.H. *Acidity Functions*, Academic Press, NY, ***1970***. For discussion of the basicity of such compounds, see Liler, M. *Reaction Mechanisms in Sulfuric Acid*, Academic Press, NY, ***1971***, pp. 118–139.

[72] See Samet, M.; Buhle, J.; Zhou, Y.; Kass, S.R. *J. Am. Chem. Soc.* ***2015***, *137*, 4678.

[73] Shokri, A.; Abedin, A.; Fattahi, A.; Kass, S.R. *J. Am. Chem. Soc.* ***2012***, *134*, 10646.

[74] Pedireddi, V.R.; Desiraju, G.R. *J. Chem. Soc., Chem. Commun.* ***1992***, 988.

[75] Alkorta, I.; Campillo, N.; Rozas, I.; Elguero, J. *J. Org. Chem.* ***1998***, *63*, 7759.

[76] Streitwieser, A.; Keevil, T.A.; Taylor, D.R.; Dart, E.C. *J. Am. Chem. Soc.* ***2005***, *127*, 9290.

[77] See Reutov, O.A.; Beletskaya, I.P.; Butin, K.P. *CH-Acids*, Pergamon, NY, ***1978***; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 1–45; Streitwieser Jr., A.; Hammons, J.H. *Prog. Phys. Org. Chem.* ***1965***, *3*, 41; Wiberg, K.B. *J. Org. Chem.* ***2002***, *67*, 1613. See, however, Silverstein, T.P.; Heller, S.T. *J. Chem. Ed.* ***2017***, *94*, 690.

[78] See Jones, J.R. *Q. Rev. Chem. Soc.* ***1971***, *25*, 365; Fischer, H.; Rewicki, D. *Prog. Org. Chem.* ***1968***, *7*, 116; Reutov, O.A.; Beletskaya, I.P.; Butin, K.P. *CH-Acids*, Chapter 1, Pergamon, NY, ***1978*** [an earlier version of this chapter appeared in *Russ. Chem. Rev.* ***1974***, *43*, 17]; Gau, G.; Assadourian, L.; Veracini, S. *Prog. Phys. Org. Chem.* ***1987***, *16*, 237; in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. A, Elsevier, NY, ***1980***, see the reviews by Pellerite, M.J.; Brauman, J.I. pp. 55–96 (gas phase acidities) and Streitwieser Jr., A.; Juaristi, E.; Nebenzahl, L. pp. 323–381.

The extremely strong acids at the top of the table are known as *superacids* (Sec. 5.A.ii).[79] The actual species present in the FSO_3H–SbF_5 mixture are probably $H[SbF_5(SO_3F)]$ and $H[SbF_2(SO_3F)_4$.[80] The addition of SO_3 causes formation of the still stronger $H[SbF_4(SO_3F)_2]$, $H[SbF_3(SO_3F)_3]$, and $H[(SbF_5)_2(SO_3F)]$.[80] There is a study of electrophilic intermediates that are generated in superacids[81] (also see Chapter 10).

By the use of tables such as Table 8.1,[82] it is possible to determine whether a given acid will react with a given base to give reasonable concentrations of the conjugate acid and conjugate base. For tables in which acids are listed in order of decreasing strength, the rule is that *any acid will react with any base in the table that is below it but not with any above it*.[83] The greater the separation in the table, the better the reaction. It must be emphasized that the order of acid strength in Table 8.1 applies when a given acid and base react without a solvent or, when possible, in water. In other solvents the order may be greatly different (Sec. 8.G). In the gas phase, where solvation effects are completely or almost completely absent, acidity orders may also differ greatly.[84] For example, in the gas phase, toluene is a stronger acid than water and *tert*-butoxide ion is a weaker base than methoxide ion[85] (see also Sec. 8.G). It is also possible for the acidity order to change with temperature. For example, >50 °C the order of base strength is $BuOH > H_2O > Bu_2O$; from 1 to 50 °C the order is $BuOH > Bu_2O > H_2O$; while <1 °C the order becomes $Bu_2O > BuOH > H_2O$.[86]

8.A.ii. Brønsted Bases

Basicity may be measured by a parameter known as proton affinity of an anion. The dissociation of a hydrogen ion for a molecule in the gas phase is called the *proton affinity* of the conjugate base.[87] A hydrogen-bond basicity scale has been developed that can be used to determine the relative basicity of molecules. Table 8.2 gives the pK_{HB} values for several common heteroatom-containing molecules.[88] This value is obtained from the protonated form (conjugated acid) of the base in question. The larger the number, the more basic is

[79] See Olah, G.A.; Prakash, G.K.S.; Sommer, J. *Superacids* Wiley, NY, ***1985***; Gillespie, R.J.; Peel, T.E. *Adv. Phys. Org. Chem.* ***1971***, *9*, 1; Arata, K. *Adv. Catal.* ***1990***, *37*, 165. For a review of methods of measuring superacidity, see Jost, R.; Sommer, J. *Rev. Chem. Intermed.* ***1988***, *9*, 171. The equilibrium acidities are presented, see Kütt, A.; Rodima, T.; Saame, J.; Raamat, E.; Mäemets, V.; Kaljurand, I.; Koppel, I.A.; Garlyauskayte, R.Yu.; Yagupol'ski, Y.L.; Yagupol'ski, L.M.; Bernhardt, E.; Helge Willner, H.; Leito, I. *J. Org. Chem.* ***2011***, *76*, 391.

[80] Gillespie, R.J. *Acc. Chem. Res.* ***1968***, *1*, 202.

[81] Prakash, G.K.S. *J. Org. Chem.* ***2006***, *71*, 3661.

[82] For a discussion of the ionization of carbon acids in liquid ammonia, see Ji, P.; Powles, N.T.; Atherton, J.H.; Page, M.I. *Org. Lett.* ***2011***, *13*, 6118.

[83] These reactions are equilibria. What the rule actually says is that the position of equilibrium will be such that the weaker acid predominates. However, this needs to be taken into account only when the acid and base are close to each other in the table (within about 2 p*K* units).

[84] See Gal, J.; Maria, P. *Prog. Phys. Org. Chem.* ***1990***, *17*, 159.

[85] Bohme, D.K.; Lee-Ruff, E.; Young, L.B. *J. Am. Chem. Soc.* ***1972***, *94*, 4608, 5153.

[86] Gerrard, W.; Macklen, E.D. *Chem. Rev.* ***1959***, *59*, 1105. For other examples, see Calder, G.V.; Barton, T.J. *J. Chem. Educ.* ***1971***, *48*, 338; Hambly, A.N. *Rev. Pure Appl. Chem.* ***1965***, *15*, 87 (88).

[87] DeKock, R.L. *J. Am. Chem. Soc.* ***1975***, *97*, 5592; McDaniel, D.H.; Coffman, N.B.; Strong, J.M. *J. Am. Chem. Soc.* ***1970***, *92*, 6697. For a computational study of the proton affinities of carbonyl compounds see Taskinen, A.; Nieminen, V.; Toukoniitty, E.; Murzin, D.Yu.; Hotokka, M. *Tetrahedron* ***2005***, *61*, 8109.

[88] For measurement of amine basicity via ion pair stability in ionic liquids (Sec. 9.D.iii), see D'Anna, F.; Noto, R. *Tetrahedron* ***2007***, *63*, 11681.

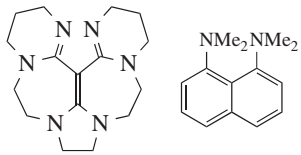
TABLE 8.2 pK_{HB} values for many types of bases

Base	Approximate pK_{HB}	Ref.
N-Methyl-2-piperidone	2.60	89
$Et_2NCONEt_2$	2.43	89
N-Methyl-2-pyrrolidinone	2.38	89
$PhCONMe_2$	2.23	89
$HCONMe_2$	2.10	89
PhCONHMe	2.03	89
18-Crown-6	1.98	90
HCONHMe	1.96	89
Aniline	4.60	91
N-Methylaniline	4.85	91
$PhNHNH_2$	5.27	91
$Ph(Me)NNH_2$	4.99	91
15-Crown-5	1.82	90
12-Crown-4	1.73	90
$PhOCONMe_2$	1.70	89
$Et_2N—CN$	1.63	92
$Me_2N—CN$	1.56	92
δ-Valerolactone	1.43	93
Oxetane	1.36	90
γ-Butyrolactone	1.32	93
Tetrahydrofuran (THF)	1.28	90
Cyclopentanone	1.27	94
t-BuOMe	1.19	90
Acetone	1.18	94
MeCOOEt	1.07	93
1,4-Dioxane	1.03	90
Et_2O	1.01	90
1,3-Dioxane	0.93	90
1-Methyloxirane	0.97	90
PhCOOMe	0.89	93
MeOCOOMe	0.82	93
PhCHO	0.78	94
Bu_2O	0.75	109
HCOOEt	0.66	89
MeCHO	0.65	90
Me_2NO_2	0.41	95
$MeNO_2$	0.27	91
$PhNO_2$	0.30	91
Furan	−0.40	109

[89] Le Questel, J.-Y.; Laurence, C.; Lachkar, A.; Helbert, M.; Berthelot, M. *J. Chem. Soc., Perkin Trans. 2* ***1992***, 2091.
[90] Berthelot, M.; Besseau, F.; Laurence, C. *Eur. J. Org. Chem.* ***1998***, 925.
[91] Korzhenevskaya, N.G.; Rybachenko, V.I.; Kovalenko, V.V.; Lyashchuk, S.N.; Red'ko, A.N. *Russ. J. Org. Chem.* ***2007***, *43*, 1475.
[92] Berthelot, M.; Helbert, M.; Laurence, C.; Le Questel, J.-Y.; Anvia, F.; Taft, R.W. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 625.
[93] Besseau, F.; Laurence, C.; Berthelot, M. *J. Chem. Soc., Perkin Trans. 2* ***1994***, 485.
[94] Besseau, F.; Luçon, M.; Laurence, C.; Berthelot, M. *J. Chem. Soc., Perkin Trans. 2* ***1998***, 101.
[95] Laurence, C.; Berthelot, M.; Luçon, M.; Morris, D.G. *J. Chem. Soc., Perkin Trans. 2* ***1994***, 491.

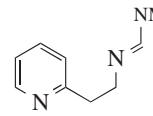
that compound. The basicity of aliphatic amines has been calculated,[96] the ion-pair basicity of amines in THF[97] and in water[98] has been determined, and the basicity of pyridine was examined.[99] There are secondary deuterium isotope effects for measuring the basicity of secondary amines, and deuteration was found to increase the basicity.[100] Weaker bases have also been examined, and the basicity of carbonyl compound in carbon tetrachloride has been determined.[101] Alkenes are weak bases[102] that react with strong acids such as HCl or HBr (**15-2**). It has been noted that extremely twisted amides (Sec. 4.Q.ii) exhibit high basicity.[103]

A class of organic compounds termed *superbases* has been developed.[104] Magnetic superbasic proton sponges have been developed.[105] Vinamidine-type or Schwesinger proton sponges (Sec. 8.F), **1**,[106] are dubbed superbases and are probably the most powerful organic neutral bases known. The pK_a, which is actually p$K_{BH}{}^+$, in MeCN was measured as 31.94. The pK_a values of strong neutral organic superbases in acetonitrile are well described by the density functional theory.[107] The fundamental type of proton sponge is 1,8-bis(dimethylamino)naphthalene, **2** (Sec. 8.F), with a p$K_{BH}{}^+$ of 18.18.[108] Other superbase-type compounds include amidinazines such as N^1,N^1-dimethyl-N^2-β-(2-pyridylethyl)-formamidine (**3**), p$K_{BH}{}^+$ in DMSO = 25.1,[109] 1,8-bis(tetramethylguanidino)naphthalene, **4**,[110] and quinolino[7,8-*h*]quinolines such as **5** with a p$K_{BH}{}^+$ = 12.8.[111]

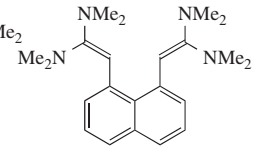


1

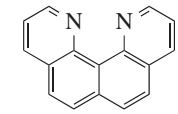
2



3



4



5

[96] Caskey, D.C.; Damrauer, R.; McGoff, D. *J. Org. Chem.* ***2002***, *67*, 5098. See Streitwieser Jr., A.; Facchetti, A.; Xie, L.; Zhang, X.; Wu, E.C. *J. Org. Chem.* ***2012***, *77*, 985.

[97] Streitwieser, A.; Kim, H.-J. *J. Am. Chem. Soc.* ***2000***, *122*, 11783; Garrido, G.; Koort, E.; Ràfols, C.; Bosch, E.; Rodima, T.; Leito, I.; Rosés, M. *J. Org. Chem.* ***2006***, *71*, 9062.

[98] Canle, L.M.; Demirtas, I.; Freire, A.; Maskill, H.; Mishima, M. *Eur. J. Org. Chem.* ***2004***, 5031.

[99] Chmurzynski, L. *J. Heterocyclic Chem.* ***2000***, *37*, 71.

[100] Perrin, C.L.; Ohta, B.K.; Kuperman, J.; Liberman, J.; Erdélyi, M. *J. Am. Chem. Soc.* ***2005***, *127*, 9641.

[101] Carrasco, N.; González-Nilo, F.; Rezende, M.C. *Tetrahedron* ***2002***, *58*, 5141.

[102] A new scale of π basicity is proposed. See Stoyanov, E.S.; Stoyanova, I.V.; Reed, C.A. *Chem. Eur. J.* ***2008***, *14*, 7880.

[103] Ly, T.; Krout, M.; Pham, D.K.; Tani, K.; Stoltz, B.M.; Julian, R.R. *J. Am. Chem. Soc.* ***2007***, *129*, 1864.

[104] For calculated basicities of superbases see Glasovac, Z.; Eckert-Maksić, M.; Maksić, Z.B. *New J. Chem.* ***2009***, *33*, 588. See Chatelet, B.; Gornitzka, H.; Dufaud, V.; Jeanneau, E.; Dutasta, J.-P.; Martinez, A. *J. Am. Chem. Soc.* ***2013***, *135*, 18659.

[105] Schneider, E.M.; Raso, R.A.; Hofer, C.J.; Zeltner, M.; Stettler, R.D.; Hess, S.C.; Grass, R.N.; Stark, W.J. *J. Org. Chem.* ***2014***, *79*, 10908.

[106] Schwesinger, R.; Mißfeldt, M.; Peters, K.; von Schnering, H.G. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1165.

[107] Kovačević, B.; Maksić, Z.B. *Org. Lett.* ***2001***, *3*, 1523.

[108] Alder, R.W.; Bowman, P.S.; Steele, W.R.S.; Winterman, D.R. *Chem. Commun.* ***1968***, 723; Alder, R.W. *Chem. Rev.* ***1989***, *89*, 1215.

[109] Raczynska, E.D.; Darowska, M.; Dabkowska, I.; Decouzon, M.; Gal, J.-F.; Maria, P.-C.; Poliart, C.D. *J. Org. Chem.* ***2004***, *69*, 4023.

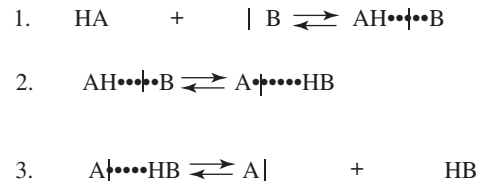
[110] Raab, V.; Kipke, J.; Gschwind, R.M.; Sundermeyer, J. *Chem. Eur. J.* ***2002***, *8*, 1682.

[111] Krieger, C.; Newsom, I.; Zirnstein, M.A.; Staab, H.A. *Angew. Chem. Int. Ed.* ***1989***, *28*, 84.

It is important to note that organometallic compounds such as *Grignard reagents* (RMgX) and organolithium reagents (RLi)[112] are powerful bases. The conjugate bases of both of these bases are alkanes, R—H, which are very weak acids indeed (see Table 8.1).

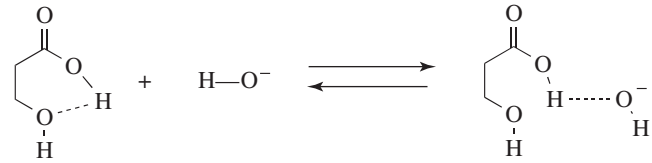
8.B. THE MECHANISM OF PROTON TRANSFER REACTIONS

Proton transfers between a base and an oxygen or nitrogen acid are usually extremely fast.[113] Such reactions are generally diffusion controlled in the thermodynamically favored direction.[114] In fact, a *normal acid* is defined[115] as one whose proton transfer reactions are completely diffusion controlled, except when the conjugate acid of the base to which the proton is transferred has a pK value very close (differs by <~2 pK units) to that of the acid. The normal acid–base reaction mechanism consists of three steps:



The actual proton transfer takes place in the second step. But the first step is formation of a hydrogen-bonded complex.[116] The product of the second step is another hydrogen-bonded complex, which dissociates in the third step.

However, not all such proton transfers are diffusion controlled. For example, if an internal hydrogen bond exists in a molecule, reaction with an external acid or base is often much slower.[117] In a case such as 3-hydroxypropanoic acid, the $^-$OH ion can form a hydrogen bond with the acidic hydrogen only if the internal hydrogen bond breaks. Therefore only some of the collisions between $^-$OH ions and 3-hydroxypropanoic acid molecules result in proton transfer. In many collisions the $^-$OH ions will come away "empty-handed," resulting in a lower reaction rate. Note that this affects only the rate, not the equilibrium.



3-Hydroxypropanoic acid

[112] Gorecka-Kobylinska, J.; Schlosser, M. *J. Org. Chem.* ***2009***, *74*, 222.

[113] For reviews of such proton transfers, see Hibbert, F. *Adv. Phys. Org. Chem.* ***1986***, *22*, 113; Crooks, J.E. in Bamford, C.H.; Tipper, C.F.H. *Chemical Kinetics*, Vol. 8; Elsevier, NY, ***1977***, pp. 197–250. See Bernasconi, C.F.; Fairchild, D.E.; Montañez, R.L.; Aleshi, P.; Zheng, H.; Lorance, E. *J. Org. Chem.* ***2005***, *70*, 7721.

[114] See Eigen, M. *Angew. Chem. Int. Ed.* ***1964***, *3*, 1.

[115] See, for example, Hojatti, M.; Kresge, A.J.; Wang, W. *J. Am. Chem. Soc.* ***1987***, *109*, 4023.

[116] For the use of ^{19}F DOSY to characterize Brønsted acid–base complexes, see Subramanian, H.; Jasperse, C.P.; Sibi, M.P. *Org. Lett.* ***2015***, *17*, 1429–1432.

[117] See Ritchie, C.D.; Lu, S. *J. Am. Chem. Soc.* ***1989***, *111*, 8542.

Other systems are capable of hydrogen bonding, such as 1,2-diols. In the case of cyclohexane-1,2-diols, hydrogen bonding, ion–dipole interactions, polarizability, and stereochemistry all play a role in determining the acidity.[118] The presence of halogen atoms such as chlorine can lead to hydrogen-bonding effects.[119] Another factor that can create lower rates is a molecular structure in which the acidic proton is protected within a molecular cavity (e.g., the in–in and out–in isomers shown in Sec. 4.L). See also the proton sponges mentioned in Sec. 8.F. Proton transfers between an acidic group and a basic group within the same molecule can also be slow, if the two groups are too far apart for hydrogen bonding. In such cases, participation of solvent molecules may be necessary.

Proton transfers to or from a carbon atom[120] in most cases are much slower than those strictly between oxygen or nitrogen atoms. At least three factors can be responsible for this,[121] not all of them applying in every case.

1. Hydrogen bonding is very weak or altogether absent for carbon (Chapter 3).
2. Loss of a proton from many carbon acids leads to carbanions that are stabilized by resonance. Calculations show that carbon acidity is influenced by coordination based on electrophile coordination geometry.[122] Structural reorganization (movement of atoms to different positions within the molecule) may accompany this process. Chloroform, HCN, and 1-alkynes do not form resonance-stabilized carbanions, and these[123] behave kinetically as normal acids.[124] It has been reported that carborane acids such as $H(CHB_{11}H_5Cl_6)$ are the strongest isolable (Lewis-free) Brønsted acids known.[125]
3. There may be considerable reorganization of solvent molecules around the ion as compared to the neutral molecule.[126]

In connection with factors 2 and 3, it has been proposed[121] that any factor that stabilizes the product (e.g., by resonance or solvation) lowers the rate constant if it develops late on the reaction coordinate, but increases the rate constant if it develops early. This is called the *principle of imperfect synchronization*.

Mechanisms of proton transfer have been studied for many compounds, including the reactions of acids with lactams,[127] amides with various bases,[128] and amines with alkoxide bases.[129]

[118] Chen, X.; Walthall, D.A.; Brauman, J.I. *J. Am. Chem. Soc.* ***2004***, *126*, 12614.
[119] Abraham, M. H.; Enomoto, K.; Clarke, E.D.; Sexton, G. *J. Org. Chem.* ***2002***, *67*, 4782.
[120] See Hibbert, F. in Bamford, C.H.; Tipper, C.F.H. *Chemical Kinetics*, Vol. 8, Elsevier, NY, ***1977***, pp. 97–196; Kreevoy, M.M. *Isot. Org. Chem.* ***1976***, *2*, 1; Leffek, K.T. *Isot. Org. Chem.* ***1976***, *2*, 89.
[121] See Bernasconi, C.F. *Tetrahedron* ***1985***, *41*, 3219.
[122] Houk, R.J.T.; Anslyn, E.V.; Stanton, J.F. *Org. Lett.* ***2006***, *8*, 3461. See Ho, J.; Zwicker, V.E.; Yuen, K.K.Y.; Jolliffe, K.A. *J. Org. Chem.* ***2017***, *82*, 10732.
[123] Kresge, A.J.; Powell, M.F. *J. Org. Chem.* ***1986***, *51*, 822; Formosinho, S.J.; Gal, V.M.S. *J. Chem. Soc., Perkin Trans. 2* ***1987***, 1655.
[124] Not all 1-alkynes behave as normal acids; see Aroella, T.; Arrowsmith, C.H.; Hojatti, M.; Kresge, A.J.; Powell, M.F.; Tang, Y.S.; Wang, W. *J. Am. Chem. Soc.* ***1987***, *109*, 7198.
[125] Juhasz, M.; Hoffmann, S.; Stoyanov, E.; Kim, K.-C.; Reed, C.A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 5352.
[126] See Kurz, J.L. *J. Am. Chem. Soc.* ***1989***, *111*, 8631.
[127] Wang, W.; Cheng, P.; Huang, C.; Jong, Y. *Bull. Chem. Soc. Jpn.* ***1992***, *65*, 562.
[128] Wang, W.-h.; Cheng, C.-c. *Bull. Chem. Soc. Jpn.* ***1994***, *67*, 1054.
[129] Lambert, C.; Hampel, F.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.* ***1992***, *31*, 1209.

8.C. MEASUREMENTS OF SOLVENT ACIDITY[130]

When a solute is added to an acidic solvent it may become protonated by the solvent. This effect can lead to an enhancement of acidity, as in the effect of using formic acid rather than methanol.[131] An acidity scale has been reported for ionic liquids[132] (Sec. 9.D.iii), and the Lewis acidity of ionic liquids has been established using IR.[133] If the solvent is water and the concentration of solute is not very great, then the pH of the solution is a good measure of the proton-donating ability of the solvent. Unfortunately, this is no longer true in concentrated solutions because activity coefficients are no longer unity. A measurement of solvent acidity is needed which works in concentrated solutions and applies to mixed solvents as well. The *Hammett acidity function*[134] is a measurement that is used for acidic solvents of high dielectric constant.[135] For any solvent, including mixtures of solvents (but the proportions of the mixture must be specified), a value H_0 is defined as

$$H_0 = \mathrm{p}K_{\mathrm{BH}^+_w} - \log \frac{[\mathrm{BH}^+]}{[\mathrm{B}]}$$

H_0 is measured by using "indicators" that are weak bases (B)[136] and so are partly converted, in these acidic solvents, to the conjugate acids BH^+. Typical indicators are *o*-nitroanilinium ion, with a pK in water of −0.29, and 2,4-dinitroanilinium ion, with a pK in water of −4.53. For a given solvent, $[\mathrm{BH}^+]/[\mathrm{B}]$ is measured for one indicator, usually by spectrophotometric means and with the known pK in water ($\mathrm{p}K_{\mathrm{BH}^+_w}$) for that indicator, H_0 can be calculated for that solvent system. In practice, several indicators are used, so that an average H_0 is taken. Once H_0 is known for a given solvent system, $\mathrm{p}K_\mathrm{a}$ values in it can be calculated for any other acid–base pair.

The symbol H_0 is defined as

$$h_0 = \frac{a_{\mathrm{H}^+} f_\mathrm{I}}{f_{HI^+}}$$

where a_{H^+} is the activity of the proton and f_I and f_{HI^+} are the activity coefficients of the indicator and conjugate acid of the indicator,[137] respectively. H_0 is related to H_0 by

$$H_0 = -\log\ h_0$$

so that H_0 is analogous to pH and h_0 to $[\mathrm{H}^+]$, and indeed in dilute aqueous solution $H_0 = \mathrm{pH}$.

[130] For fuller treatments, see Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, ***1970***, pp. 263–313; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 83–93; Arnett, E.M.; Scorrano, G. *Adv. Phys. Org. Chem.* ***1976***, *13*, 83.

[131] Holt, J.; Karty, J.M. *J. Am. Chem. Soc.* ***2003***, *125*, 2797.

[132] Thomazeau, C.; Olivier-Bourbigou, H.; Magna, L.; Luts, S.; Gilbert, B. *J. Am. Chem. Soc.* ***2003***, *125*, 5264; Deng, H.; Li, X.; Chu, Y.; He, J.; Cheng, J.-P. *J. Org. Chem.* ***2012***, *77*, 7291. For the $\mathrm{p}K_\mathrm{a}$ of sulfonamides in ionic liquids see Wang, Z.; Li, X.; Ji, P.; Cheng, J.-P. *J. Org. Chem.* ***2016***, *81*, 11195.

[133] Yang, Y.-l.; Kou, Y. *Chem. Commun.* ***2004***, 226.

[134] Hammett, L.P.; Deyrup, A.J. *J. Am. Chem. Soc.* ***1932***, *54*, 2721.

[135] See Rochester, C.H. *Acidity Functions*, Academic Press, NY, ***1970***; Cox, R.A.; Yates, K. *Can. J. Chem.* ***1983***, *61*, 2225; Boyd, R.H. in Coetzee, J.F.; Ritchie, C.D. *Solute–Solvent Interactions*, Marcel Dekker, NY, ***1969***, pp. 97–218.

[136] The basicity of very weak bases has been discussed, see Kaupmees, K.; Järviste, R.; Leito, I. *Chem. Eur. J.* ***2016***, *22*, 17445.

[137] See Yates, K.; McClelland, R.A. *Prog. Phys. Org. Chem.* ***1974***, *11*, 323.

The parameter H_0 reflects the ability of the solvent system to donate protons, but it can be applied only to acidic solutions of high dielectric constant, mostly mixtures of water with acids such as nitric, sulfuric, perchloric, and so on. It is apparent that the H_0 treatment is valid only when f_I/f_{HI^+} is independent of the nature of the base (the indicator). Since this is so only when the bases are structurally similar, the treatment is limited. Even when similar bases are compared, many deviations are found.[138] Other acidity scales[139] have been set up, including a scale for C—H acids,[140] among them H_- for bases with a charge of -1, H_R for aryl carbinols,[141] H_C for bases that protonate on carbon,[142] and H_A for unsubstituted amides.[143] It is now clear that there is no single acidity scale that can be applied to a series of solvent mixtures, irrespective of the bases employed.[144]

Although most acidity functions have been applied only to acidic solutions, some work has also been done with strongly basic solutions.[145] The H_- function, which is used for highly acidic solutions when the base has a charge of -1, can also be used for strongly basic solvents, in which case it measures the ability of these solvents to abstract a proton from a neutral acid BH.[146] When a solvent becomes protonated, its conjugate acid is known as a *lyonium ion*.

Another approach to the acidity function problem was proposed by Bunnett et. al.,[147] who derived the equation

$$\log \frac{[SH^+]}{[S]} + H_0 = \phi \left(H_0 + \log[H^+]\right) + pK_{SH^+}$$

where S is a base that is protonated by an acidic solvent. Thus the slope of a plot of log $([SH^+]/[S]) + H_0$ against $H_0 + \log [H^+]$ is the parameter ϕ, while the intercept is the pK_a of the lyonium ion SH^+ (referred to infinite dilution in water). The value of ϕ expresses the response of the equilibrium

$$S + H^+ \rightleftarrows SH^+$$

to changing acid concentration. A negative ϕ indicates that the log of the ionization ratio $[SH^+]/[S]$ increases, as the acid concentration increases, more rapidly than $-H_0$. A positive ϕ value indicates the reverse. The Bunnett-Olsen equation given above is a linear

[138] See Kreevoy, M.M.; Baughman, E.H. *J. Am. Chem. Soc.* ***1973***, *95*, 8178; García, B.; Leal, J.M.; Herrero, L.A.; Palacios, J.C. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 1759; Arnett, E.M.; Quirk, R.P.; Burke, J.J. *J. Am. Chem. Soc.* ***1970***, *92*, 1260.

[139] For lengthy tables of many acidity scales, with references, see Cox, R.A.; Yates, K. *Can. J. Chem.* ***1983***, *61*, 2225. For an equation that is said to combine the vast majority of acidity functions, see Zalewski, R.I.; Sarkice, A.Y.; Geltz, Z. *J. Chem. Soc., Perkin Trans. 2* ***1983***, 1059.

[140] See Vianello, R.; Maksić, Z.B. *Eur. J. Org. Chem.* ***2004***, 5003.

[141] Deno, N.C.; Berkheimer, H.E.; Evans, W.L.; Peterson, H.J. *J. Am. Chem. Soc.* ***1959***, *81*, 2344.

[142] Reagan, M.T. *J. Am. Chem. Soc.* ***1969***, *91*, 5506.

[143] Liler, M.; Marković, D. *J. Chem. Soc., Perkin Trans. 2* ***1982***, 551.

[144] Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, ***1970***, p. 278; Rochester, C.H. *Acidity Functions*, Academic Press, NY, ***1970***, p. 21.

[145] For another approach to solvent basicity scales, see Catalán, J.; Gómez, J.; Couto, A.; Laynez, J. *J. Am. Chem. Soc.* ***1990***, *112*, 1678.

[146] See Rochester, C.H. *Q. Rev. Chem. Soc.* ***1966***, *20*, 511; Rochester, C.H. *Acidity Functions*, Academic Press, NY, ***1970***, pp. 234–264; Bowden, K. *Chem. Rev.* ***1966***, *66*, 119.

[147] Bunnett, J.F.; McDonald, R.L.; Olsen, F.P. *J. Am. Chem. Soc.* ***1974***, *96*, 2855.

free-energy relationship (Sec. 9.C) that pertains to acid–base equilibria. A corresponding equation that applies to kinetic data is

$$\log k_\psi + H_o = \Phi(H_o + \log[H^+]) + \log k_2^\circ$$

where k_ψ is the pseudo-first-order rate constant for a reaction of a weakly basic substrate taking place in an acidic solution and k_2° is the second-order rate constant at infinite dilution in water. In this case ϕ characterizes the response of the reaction rate to changing acid concentration of the solvent. The *Bunnett-Olsen treatment* has also been applied to basic media, where, in a group of nine reactions in concentrated NaOMe solutions, no correlation was found between reaction rates and either H_- or stoichiometric base concentration but where the rates were successfully correlated by a linear free-energy equation similar to those given above.[148]

A treatment partially based on the Bunnett-Olsen one is that of Bagno, Scorrano, and More O'Ferrall,[149] which formulates medium effects (changes in acidity of solvent) on acid–base equilibria.[150] An appropriate equilibrium is chosen as reference, and the acidity dependence of other reactions compared with it, by use of the linear free-energy equation:

$$\log \frac{K'}{K'_0} = m^* \log \frac{K}{K_0}$$

where the K values are the equilibrium constants for the following: K for the reaction under study in any particular medium; K' for the reference reaction in the same medium; K_0 for the reaction under study in a reference solvent; K'_0 for the reference reaction in the same reference solvent; and m^* is the slope of the relationship [corresponding to $(1 - \phi)$ of the Bunnett-Olsen treatment]. This equation has been shown to apply to many acid–base reactions.[151]

Another type of classification system was devised by Bunnett[152] for reactions occurring in moderately concentrated acid solutions. Log $k_\psi + H_0$ is plotted against log a_{H_2O}, where k_ψ is the pseudo-first-order rate constant for the protonated species and a_{H_2O} is the activity of water. Most such plots are linear or nearly so. According to Bunnett, the slope of this plot w tells something about the mechanism. Where w is between -2.5 and 0, water is not involved in the rate-determining step; where w is between 1.2 and 3.3, water is a nucleophile in the rate-determining step; where w is between 3.3 and 7, water is a proton-transfer agent. These rules hold for acids in which the proton is attached to oxygen or nitrogen.

A new acidity scale has been developed based on calorimetric measurement of *N*-methylimidazole and *N*-methylpyrrole in bulk solvents.[153] A revised version of this method was shown to give better results in some cases.[154] Another scale of solvent acidities was

[148] More O'Ferrall, R.A. *J. Chem. Soc., Perkin Trans. 2* ***1972***, 976.
[149] Bagno, A.; Scorrano, G.; More O'Ferrall, R.A. *Rev. Chem. Intermed.* ***1987***, *7*, 313. See also, Cox, R.A. *Acc. Chem. Res.* ***1987***, *20*, 27.
[150] Meister, E.C.; Willeke, M.; Angst, W.; Togni, A.l.; Walde. P. *Helv. Chim. Acta* ***2014***, *97*, 1.
[151] For a discussion of philicities, fugalities, and equilibrium constants, see Mayr, H.; Ofial, A.R. *Acc. Chem. Res.* ***2016***, *49*, 952.
[152] Bunnett, J.F. *J. Am. Chem. Soc.* ***1961***, *83*, 4956, 4968, 4973, 4978.
[153] Catalán, J.; Couto, A.; Gomez, J.; Saiz, J.L.; Laynez, J. *J. Chem. Soc., Perkin Trans. 2* ***1992***, 1181.
[154] Abraham, M.H.; Taft, R.W. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 305.

developed based on the hydrogen-bond donor acidities in aqueous DMSO.[155] It is noted that bond energies, acidities, and electron affinities are related in a thermodynamic cycle, and Kass and Fattahi have shown that by measuring two of these quantities the third can be found.[156]

8.D. ACID AND BASE CATALYSIS[157]

Many reactions are catalyzed by acids or bases. Some reactions are catalyzed by both acids and bases. In such cases, the catalyst is involved in a fundamental way in the mechanism. The first step of such a reaction is nearly always a proton transfer between the catalyst and the substrate.

Reactions can be catalyzed by acid or base in two different ways, called *general catalysis* and *specific catalysis*. If the rate of an acid-catalyzed (HA) reaction run in a solvent S is proportional to its conjugate acid [SH^+], the reaction is said to be subject to *specific acid catalysis*, the acid being the lyonium ion SH^+. The acid that is put into the solvent may be stronger or weaker than SH^+, but the rate is proportional only to the [SH^+] that is actually present in the solution derived from the equilibrium:

$$S + HA \rightleftarrows SH^+ + A^-$$

The identity of HA is important only to the extent that it determines the position of equilibrium and hence the [SH^+]. Most measurements have been made in water, where SH^+ is H_3O^+.

In *general acid catalysis*, the rate is increased not only by an increase in [SH^+] but also by an increase in the concentration of other acids (e.g., in water by phenols or carboxylic acids). These other acids increase the rate even when [SH^+] is held constant. In this type of catalysis the strongest acids catalyze best, so that, in the example given, an increase in the phenol concentration catalyzes the reaction much less than a similar increase in [H_3O^+]. This relationship between acid strength of the catalyst and its catalytic ability can be expressed by the *Brønsted catalysis equation*[158]

$$\log k = \alpha \log K_\alpha + C$$

where k is the rate constant for a reaction catalyzed by an acid of ionization constant K_α. According to this equation, when log k is plotted against log K_α for catalysis of a given reaction by a series of acids, a straight line should be obtained with slope and intercept

[155] Liu, P.C.; Hoz, S.; Buncel, E. *Gazz. Chim. Ital.* ***1996***, *126*, 31. See also, Abraham, M.H.; Zhao, Y.J. *J. Org. Chem.* ***2004***, *69*, 4677.

[156] Fattahi, A.; Kass, S.R. *J. Org. Chem.* ***2004***, *69*, 9176.

[157] See Stewart, R. *The Proton: Applications to Organic Chemistry*, Academic Press, NY, ***1985***, pp. 251–305; Willi, A.V. in Bamford, C.H.; Tipper, C.F.H. *Chemical Kinetics*, Vol. 8, Elsevier, NY, ***1977***, pp. 1–95; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry,* 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 72–82; Bender, M.L. *Mechanisms of Homogeneous Catalysis from Protons to Proteins,* Wiley, NY, ***1971***, pp. 19–144.

[158] See Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 167–179; Bell, R.P. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum Press, ***1978***, pp. 55–84; Kresge, A.J. *Chem. Soc. Rev.* ***1973***, *2*, 475.

C. Straight lines are obtained in many cases, but not always. The relationship usually fails when acids of different types are compared. For example, it is much more likely to hold for a group of substituted phenols than for a collection of acids that contains both phenols[159] and carboxylic acids. The Brønsted equation is another linear free-energy relationship (Sec. 9.C).

Analogously, there are *general* and *specific* (S^- from an acidic solvent SH) *base-catalyzed reactions*. The Brønsted law for bases is

$$\log k = \beta \ \log K_\beta + C$$

The Brønsted equations relate a rate constant k to an equilibrium constant K_a. In Chapter 6, the *Marcus equation* (Sec. 6.I) was seen to relate a rate term (in that case $\Delta G^\ddagger$) to an equilibrium term ΔG°. When the Marcus treatment is applied to proton transfers[160] between a carbon and an oxygen (or a nitrogen), the simplified[161] equation (Sec. 6.I)

$$\Delta G^\ddagger = \Delta G^\ddagger + \frac{1}{2}\Delta G^\circ + \frac{(\Delta G^\circ)^2}{16\ \Delta G^\ddagger_{\text{int}}}$$

where

$$\Delta G^\ddagger_{\text{int}} = \frac{1}{2}\left(\Delta G^\ddagger_{(O,O)} + \Delta G^\ddagger_{(C,C)}\right)$$

can be further simplified: Because proton transfers between oxygen and oxygen (or nitrogen and nitrogen) are much faster than those between carbon and carbon, $\Delta G^\ddagger_{(O,O)}$ is much smaller than $\Delta G^\ddagger_{(C,C)}$ and one can write[162]

$$\Delta G^\ddagger = \frac{1}{2}\Delta G^\ddagger_{(C,C)} + \frac{1}{2}\Delta G^\circ + \frac{(\Delta G^\circ)^2}{8\ \Delta G^\ddagger_{(C,C)}}$$

Thus, if the carbon part of the reaction is kept constant and only the A of HA is changed (where A is an oxygen or nitrogen moiety), then $\Delta G^\ddagger$ is dependent only on ΔG°. Differentiation of this equation yields the Brønsted α:

$$\frac{\Delta G^\ddagger}{\Delta G^\circ} = \alpha = \frac{1}{2}\left(1 + \frac{\Delta G^\circ}{2\ \Delta G^\ddagger_{(C,C)}}\right)$$

The Brønsted law is therefore a special case of the Marcus equation.

[159] See Silva, P.J. *J. Org. Chem.* ***2009***, *74*, 914.
[160] See Marcus, R.A. *J. Phys. Chem.* ***1968***, *72*, 891; Kresge, A.J. *Chem. Soc. Rev.* ***1973***, *2*, 475.
[161] Omitting the work terms.
[162] Albery, W.J. *Annu. Rev. Phys. Chem.* ***1980***, *31*, 227, p. 244.

A knowledge of whether a reaction is subject to general or specific acid catalysis supplies information about the mechanism. For any acid-catalyzed reaction we can write

$$\begin{array}{lrcl} \text{Step 1} & A + SH^+ & \rightleftharpoons & AH^+ \\ \text{Step 2} & AH^+ & \longrightarrow & \text{products} \end{array}$$

If the reaction is catalyzed only by the specific acid SH^+, it means that step 1 is rapid and step 2 is rate controlling. This means that an equilibrium has been rapidly established between A and the strongest acid present in the solution, namely SH^+ (since this is the strongest acid that can be present in S). On the other hand, if step 2 is faster, there is no time to establish equilibrium and the rate-determining step must be step 1. This step is affected by all the acids that may be present, and the rate reflects the sum of the effects of each acid (general acid catalysis). General acid catalysis is also observed if the slow step is the reaction of a hydrogen-bond complex A•••HB, since each complex reacts with a base at a different rate. A comparable discussion can be used for general and specific base catalysis.[163] Further information can be obtained from the values α and β in the Brønsted catalysis equations, since these are approximate measures of the extent of proton transfer in the transition state. In most cases values of α and β are between 1 and 0. A value of α or β near 0 is generally taken to mean that the transition state resembles the reactants; that is, the proton has been transferred very little when the transition state has been reached. A value of α or β near 1 is taken to mean the opposite; that is, in the transition state the proton has been almost completely transferred. However, cases are known in which these generalizations are not followed,[164] and their theoretical basis has been challenged.[165] In general, the proton in the transition state lies closer to the weaker base.

8.E. LEWIS ACIDS AND BASES

At about the same time that Brønsted proposed his acid–base theory, Lewis put forth a broader theory. A base in the Lewis theory is the same as in the Brønsted one, namely, a compound with an available pair of electrons, either unshared or in a π orbital. However, a *Lewis base* donates electrons to an atom other than H or C.[166] A *Lewis acid* is any species with a vacant orbital.[167] In a Lewis acid–base reaction the unshared pair of the base forms a covalent bond with the vacant orbital of the acid, as represented by the general equation

$$A + :B \longrightarrow A—B$$

in which charges are not shown, since they may differ. A specific example is

$$BF_3 + :NH_3 \longrightarrow F_3\overset{-}{B} \rightarrow \overset{+}{N}H_3$$

[163] See Jencks, W.P. *Acc. Chem. Res.* ***1976***, *9*, 425; Stewart, R.; Srinivasan, R. *Acc. Chem. Res.* ***1978***, *11*, 271; Guthrie, J.P. *J. Am. Chem. Soc.* ***1980***, *102*, 5286.

[164] See Agmon, N. *J. Am. Chem. Soc.* ***1980***, *102*, 2164; Murray, C.J.; Jencks, W.P. *J. Am. Chem. Soc.* ***1988***, *110*, 7561.

[165] Pross, A.; Shaik, S.S. *New J. Chem.* ***1989***, *13*, 427; Lewis, E.S. *J. Phys. Org. Chem.* ***1990***, *3*, 1.

[166] Lewis bases are useful catalysts in organic synthesis. See Denmark, S.E.; Beutner, G.L. *Angew. Chem. Int. Ed.* ***2008***, *47*, 1560.

[167] For a monograph on Lewis acid–base theory, see Jensen, W.B. *The Lewis Acid–Base Concept*, Wiley, NY, ***1980***. For a discussion of the definitions of Lewis acid and base, see Jensen, W.B. *Chem. Rev.* ***1978***, *78*, 1.

In the Brønsted picture, the acid is a proton donor, but in the Lewis picture the proton itself is the acid since it has a vacant orbital. P-Chiral phosphines have been developed as functional chiral Lewis bases.[168]

A Brønsted acid becomes, in the Lewis picture, the compound that gives up the actual acid. The advantage of the Lewis theory is that it correlates the behavior of many more processes. For example, $AlCl_3$ and BF_3 are Lewis acids because they have only six electrons in the outer shell and have room for eight. Lewis acids $SnCl_4$ and SO_3 have eight, but their central elements, not being in the first row of the periodic table, have room for ten or twelve. Other Lewis acids are simple cations, like Ag^+. The simple reaction $A + B \rightarrow A—B$ is not very common in organic chemistry, but the scope of the Lewis picture is much larger because reactions of the types shown here, which are very common in organic chemistry, are also Lewis acid–base reactions. In fact, all reactions in which a covalent bond is formed through one species contributing a filled orbital and the other a vacant orbital may be regarded as Lewis acid–base reactions. An *ab initio* analysis of the factors that determine Lewis versus Lowry-Brønsted acidity/basicity is available.[169] The Lewis acidity of iodine(II) species has been examined.[170]

$$\begin{aligned} A^1 + A^2—B &\longrightarrow A^1—B + A^2 \\ B^1 + A—B^2 &\longrightarrow A—B^1 + B^2 \\ A^1 - B^1 + A^2—B^2 &\longrightarrow A^1—B^2 + A^2—B^1 \end{aligned}$$

When a Lewis acid combines with a base to give a negative ion in which the central atom has a higher-than-normal valence, the resulting salt is called an *ate complex*.[171] Examples are:

$$\begin{aligned} Me_3B + LiMe &\longrightarrow Me_4B^- Li^+ \\ Ph_5Sb + LiPh &\longrightarrow Ph_6Sb^- Li^+ \end{aligned}$$

Ate complexes

Ate complexes are analogous to the onium salts formed when a Lewis base expands its valence, for example,

$$Me_3N + MeI \longrightarrow Me_4N^+ I^-$$

Onium saalt

Far fewer quantitative measurements have been made of Lewis acid strength compared to that of Brønsted acids.[172] A simple table of Lewis acidities based on some quantitative measurement (e.g., that given for Brønsted acids in Table 8.1) is not feasible because Lewis acidity depends on the nature of the base and any solvent that can function as a base. For example, lithium perchlorate functions as a weak Lewis acid in

[168] Rémond, E.; Bayardon, J.; Takizawa, S.; Rousselin, Y.; Sasai, H.; Jugé, S. *Org. Lett.* ***2013***, *15*, 1870.

[169] Rauk, A.; Hunt, I.R.; Keay, B.A. *J. Org. Chem.* ***1994***, *59*, 6808. For review of Lewis basicity and affinity scales, see Laurence, C.; Gal, J.-F., *Lewis Basicity and Affinity Scales: Data and Measurement*, Wiley, Chichester, ***2010***. A Lewis basicity scale in dichloromethane for amines has been determined. See Oliveri, I.P.; Maccarrone, G.; Di Bella, S. *J. Org. Chem.* ***2011***, *76*, 8879.

[170] Labattut, A.; Tremblay, P.-L.; Moutounet, O.; Legault, C.Y. *J. Org. Chem.* ***2017***, *82*, 11891.

[171] For a review of ate complexes, see Wittig, G. *Q. Rev. Chem. Soc.* ***1966***, *20*, 191.

[172] See Satchell, D.P.N.; Satchell, R.S. *Q. Rev. Chem. Soc.* ***1971***, *25*, 171. See also, Sandström, M.; Persson, I.; Persson, P. *Acta Chem. Scand.* ***1990***, *44*, 653; Laszlo, P.; Teston-Henry, M. *Tetrahedron Lett.* ***1991***, *32*, 3837.

ether.[173] Qualitatively, the following approximate sequence of acidity of Lewis acids of the type MX_n has been suggested, where X is a halogen atom or an inorganic radical: $BX_3 > AlX_3 > FeX_3 > GaX_3 > SbX_5 > SnX_4 > AsX_5 > ZnX_2 > HgX_2$.

8.E.i. Hard–Soft Acids–Bases

The ease with which an acid–base reaction takes place depends of course on the strengths of the acid and the base. But it also depends on quite another quality, called the *hardness*[174] or *softness* of the acid or base.[175] Hard and soft acids and bases have these characteristics:

- *Soft bases*. The donor atoms are of low electronegativity and high polarizability, and are easy to oxidize. They hold their valence electrons loosely.
- *Hard bases*. The donor atoms are of high electronegativity and low polarizability, and are hard to oxidize. They hold their valence electrons tightly.
- *Soft acids*. The acceptor atoms are large, have low positive charge, and contain unshared pairs of electrons (*p* or *d*) in their valence shells. They have high polarizability and low electronegativity.
- *Hard acids*. The acceptor atoms are small, have high positive charge, and do not contain unshared pairs in their valence shells. They have low polarizability and high electronegativity.

A qualitative listing of the hardness of some acids and bases is given in Table 8.3.[176]

The treatment has also been made quantitative,[177] with the following operational definition:

$$\eta = \frac{I - A}{2}$$

In this equation, η, the *absolute hardness*, is half the difference between I, the ionization potential, and A, the electron affinity.[178] The softness, σ, is the reciprocal of η. Values of η for some molecules and ions are given in Table 8.4.[179] Note that the proton, which is involved in all Brønsted acid–base reactions, is the hardest acid listed, with $\eta = \infty$ (it has no ionization potential). The above equation cannot be applied to anions, because electron affinities cannot be measured for them. Instead, the assumption is made that η for an anion

[173] Springer, G.; Elam, C.; Edwards, A.; Bowe, C.; Boyles, D.; Bartmess, J.; Chandler, M.; West, K.; Williams, J.; Green, J.; Pagni, R.M.; Kabalka, G.W. *J. Org. Chem.* ***1999***, *64*, 2202.

[174] See Ayers, P.W.; Parr, R.G. *J. Am. Chem. Soc.* ***2000***, *122*, 2010.

[175] Pearson, R.G.; Songstad, J. *J. Am. Chem. Soc.* ***1967***, *89*, 1827. For a monograph on the concept, see Ho, T. *Hard and Soft Acids and Bases Principle in Organic Chemistry*, Academic Press, NY, ***1977***; Pearson, R.G. *J. Chem. Educ.* ***1987***, *64*, 561; Ho, T. *Tetrahedron* ***1985***, *41*, 1; Pearson, R.G. in Chapman, N.B.; Shorter, J. *Advances in Linear Free-Energy Relationships*, Plenum Press, NY, ***1972***, pp. 281–319. For a collection of papers, see Pearson, R.G. *Hard and Soft Acids and Bases*, Dowden, Hutchinson, and Ross, Stroudsberg, PA, ***1973***.

[176] Taken from Pearson, R.G. *J. Chem. Educ.* ***1968***, *45*, 581, 643.

[177] Pearson, R.G. *J. Org. Chem.* ***1989***, *54*, 1423; Orsky, A.R.; Whitehead M.A. *Can. J. Chem.* ***1987***, *65*, 1970.

[178] See Sauers, R.R. *Tetrahedron* ***1999***, *55*, 10013.

[179] Parr, R.G.; Pearson, R.G. *J. Am. Chem. Soc.* ***1983***, *105*, 7512. Note that there is not always a strict correlation between the values in Table 8.4 and the categories of Table 8.3.

TABLE 8.3 Hard and soft acids and bases[176]

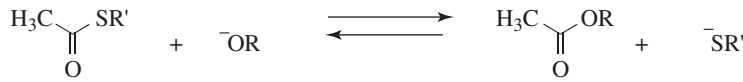
Hard bases	Soft bases	Borderline cases
H_2O, OH^-, F^-	R_2S, RSH, RS^-	$ArNH_2$, C_5H_5N
AcO^-, SO_4^{2-}, Cl^-	I^-, R_3P, $(RO)_3P$	N_3^-, Br
CO_3^{2-}, NO_3^-, ROH	CN^-, RCN, CO	NO_2^-
RO^-, R_2O, NH_3	C_2H_4, C_6H_6	
RNH_2	H^-, R^-	
Hard acids	**Soft acids**	**Borderline cases**
H^+, Li^+, Na^+	Cu^+, Ag^+, Pd^{2+}	Fe^{2+}, Co^{2+}, Cu^{2+}
K^+, Mg^{2+}, Ca^{2+}	Pt^{2+}, Hg^{2+}, BH_3	Zn^{2+}, Sn^{2+}, Sb^{3+}
Al^{3+}, Cr^{2+}, Fe^{3+}	$GaCl_3$, I_2, Br_2	Bi^{3+}, BMe_3, SO_2
BF_3, $B(OR)_3$, $AlMe_3$	CH_2, carbenes	R_3C^+, NO^+, GaH_3
$AlCl_3$, AlH_3, SO_3		$C_6H_5^+$
RCO^+	CO_2	
HX (hydrogen-bonding molecules)		

Reprinted with permission Pearson, R.G. *J. Chem. Educ.* ***1968***, *45*, 581, 643. Copyright 1968 American Chemical Society.

X^- is the same as that for the radical X•.[180] Other methods are also needed to apply the treatment to polyatomic cations.[180]

Once acids and bases have been classified as hard or soft, a simple rule can be given: *hard acids prefer to bond to hard bases*, *and soft acids prefer to bond to soft bases – the HSAB (hard–soft acid–base) principle*.[181] The rule has nothing to do with acid or base *strength* but merely says that the product A—B will have extra stability if both A and B are hard or if both are soft. Another rule is that a soft Lewis acid and a soft Lewis base tend to form a covalent bond, while a hard acid and a hard base tend to form ionic bonds.

One application of the first rule given above is found in complexes between alkenes or aromatic compounds and metal ions (see above). Alkenes and aromatic rings are soft bases and should prefer to complex with soft acids. Thus, Ag^+, Pt^{2+}, and Hg^{2+} complexes are common, but complexes of Na^+, Mg^{2+}, or Al^{3+} are rare. Chromium complexes are also common, but in such complexes the chromium is in a low or zero oxidation state (which softens it) or attached to other soft ligands. Another application is the reaction:



The HSAB principle predicts that the equilibrium should lie to the right, because the hard acid CH_3CO^+ should have a greater affinity for the hard base RO^- than for the soft base RS^-. Indeed, thiol esters are easily cleaved by RO^- or hydrolyzed by dilute base (^-OH is also a hard base).[182] Another application of the rule is discussed in Sec. 10.G.ii.[183] The

[180] Pearson, R.G. *J. Am. Chem. Soc.* ***1988***, *110*, 7684.
[181] For proofs of this principle, see Chattaraj, P.K.; Lee, H.; Parr, R.G. *J. Am. Chem. Soc.* ***1991***, *113*, 1855.
[182] Wolman, Y. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, p. 677; Maskill, H. *The Physical Basis of Organic Chemistry*, Oxford University Press, Oxford, ***1985***, p. 159.
[183] See also, Bochkov, A.F. *J. Org. Chem. USSR* ***1986***, *22*, 1830, 1837.

TABLE 8.4 Some absolute hardness values in electron volts[179]

Cations		Molecules		Anions[b]	
Ion	η	Compound	η	Ion	η
H^+	∞	HF	11.0	F^-	7.0
Al^{3+}	45.8	CH_4	10.3	H^-	6.4
Li^+	35.1	BF_3	9.7	OH^-	5.7
Mg^{2+}	32.6	H_2O	9.5	NH_2^-	5.3
Na^+	21.1	NH_3	8.2	CN^-	5.1
Ca^{2+}	19.5	HCN	8.0	CH_3^-	4.9
K^+	13.6	$(CH_3)_2O$	8.0	Cl^-	4.7
Zn^{2+}	10.9	CO	7.9	$CH_3CH_2^-$	4.4
Cr^{3+}	9.1	C_2H_2	7.0	Br^-	4.2
Cu^{2+}	8.3	$(CH_3)_3N$	6.3	$C_6H_5^-$	4.1
Pt^{2+}	8.0	H_2S	6.2	SH^-	4.1
Sn^{2+}	7.9	C_2H_4	6.2	$(CH_3)_2CH^-$	4.0
Hg^{2+}	7.7	$(CH_3)_2S$	6.0	I^-	3.7
Fe^{2+}	7.2	$(CH_3)_3P$	5.9	$(CH_3)_3C^-$	3.6
Pd^{2+}	6.8	CH_3COCH_3	5.6		
Cu^+	6.3	C_6H_6	5.3		
		HI	5.3		
		C_5H_5N	5.0		
		C_6H_5OH	4.8		
		CH_2[a]	4.7		
		C_6H_5SH	4.6		
		Cl_2	4.6		
		$C_6H_5NH_2$	4.4		
		Br_2	4.0		
		I_2	3.4		

[a]For singlet state. [b]The same as for the corresponding radical.
Reprinted with permission from Parr, R.G.; Pearson, R.G. *J. Am. Chem. Soc.* ***1983****, 105*, 7512. Copyright 1983 American Chemical Society.

HSAB principles have been applied to analyze the reactivity of ketone and ester enolate anions,[184] and in analyzing catalyst selectivity in synthesis.[185]

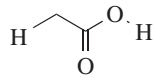
8.F. THE EFFECTS OF STRUCTURE ON THE STRENGTHS OF ACIDS AND BASES[186]

The structure of a molecule can affect its acidity or basicity in a number of ways. Unfortunately, in most molecules two or more of these effects (as well as solvent effects) are

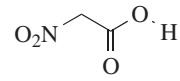
[184] Méndez, F.; Gázguez, J.L. *J. Am. Chem. Soc.* ***1994***, *116*, 9298.
[185] Woodward, S. *Tetrahedron* ***2002***, *58*, 1017.
[186] See Hine, J. *Structural Effects on Equilibria in Organic Chemistry*, Wiley, NY, ***1975***; Taft, R.W. *Prog. Phys. Org. Chem.* ***1983***, *14*, 247; Petrov, E.S. *Russ. Chem. Rev.* ***1983***, *52*, 1144 (NH acids); Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***, pp. 86–110. For a monograph on methods of estimating p*K* values by analogy, extrapolation, etc., see Perrin, D.D.; Dempsey, B.; Serjeant, E.P. pK_a *Prediction for Organic Acids and Bases*, Chapman and Hall, NY, ***1981***.

operating, and it is usually very difficult or impossible to say how much each effect contributes to the acid or base strength.[187] Small differences in acidity or basicity between similar molecules are particularly difficult to interpret. It is well to be cautious when attributing them to any particular effect.

1. *Field effects*. These effects were discussed in Sec. 1.I. In general, changes in substituents can have an effect on acidity. As an example of the influence of field effects on acidity, compare the acidity of acetic acid and 2-nitroacetic acid:



$pK_a = 4.76$



$pK_a = 1.68$

The only difference in the structure of these molecules is the substitution of NO_2 for H. Since NO_2 is a strongly electron-withdrawing group, it withdraws electron density from the negatively charged COO^- group in the anion of 2-nitroacetic acid (compared with the anion of acetic acid). As the pK_a values indicate, 2-nitroacetic acid is ~1000 times stronger than acetic acid.[188] Any effect that results in electron withdrawal from a negatively charged center ($-I$ effect) is a stabilizing effect because it spreads the charge. Thus, $-I$ groups increase the acidity of uncharged acids such as acetic acid because they spread the negative charge of the anion. However, $-I$ groups also increase the acidity of any acid, no matter what the charge. For example, if the acid has a charge of +1 (and its conjugate base is therefore uncharged), a $-I$ group destabilizes the positive center (by increasing and concentrating the positive charge) of the acid, a destabilization that will be relieved when the proton is lost. In general, *groups that withdraw electrons by the field effect increase acidity and decrease basicity*, *while electron-donating groups act in the opposite direction*. Another example is the molecule $(C_6F_5)_3CH$, which has three strongly electron-withdrawing C_6F_5 groups and a pK_a of 16,[189] compared with Ph_3CH, with a pK_a of 31.5 (Table 8.1), an acidity enhancement of ~10^{15}. Table 8.5 shows pK_a values for some acids. An approximate idea of field effects can be obtained from this table. In the case of the chlorobutyric acids, the effect decreases with distance. It must be remembered, however, that field effects are not the sole cause of the acidity differences noted and that in fact solvation effects may be more important in many cases (Sec. 8.G).[190]

The influence of various substituents on the acidity of acetic acid has been calculated.[191] Substituent effects for weak acids such as phenols[192] and benzyl alcohols, have been discussed.[193]

[187] The varying degrees by which the different factors that affect gas-phase acidities of 25 acids has been calculated: Taft, R.W.; Koppel, I.A.; Topsom, R.D.; Anvia, F. *J. Am. Chem. Soc.* ***1990***, *112*, 2047.

[188] For a review of the enhancement of acidity by NO_2, see Lewis, E.S. in Patai, S. *The Chemistry of Functional Groups*, *Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 715–729.

[189] Filler, R.; Wang, C. *Chem. Commun.* ***1968***, 287.

[190] See Edward, J.T. *J. Chem. Educ.* ***1982***, *59*, 354; Schwartz, L.M. *J. Chem. Educ.* ***1981***, *58*, 778.

[191] Headley, A.D.; McMurry, M.E.; Starnes, S.D. *J. Org. Chem.* ***1994***, *59*, 1863.

[192] For the use of ^1H NMR to predict the pK_a of substituted phenols, see Penhoat, M. *Tetrahedron Lett.* ***2013***, *54*, 2571.

[193] Wiberg, K.B. *J. Org. Chem.* ***2003***, *68*, 875.

TABLE 8.5 The p*K* values for some acids[49]

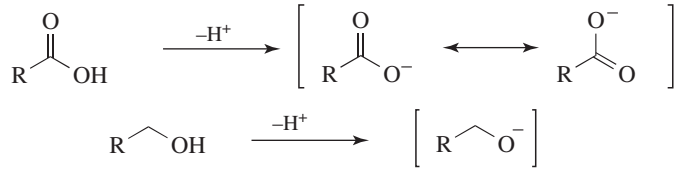
Acid	p*K*	Acid	p*K*
HCOOH	3.77	$ClCH_2COOH$	2.86
CH_3COOH	4.76	$Cl_2CHCOOH$	1.29
CH_3CH_2COOH	4.88	Cl_3COOH	0.65
$CH_3(CH_2)_nCOOH$ ($n = 2$–7)	4.82–4.95	O_2NCH_2COOH	1.68
$(CH_3)_2CHCOOH$	4.86	$(CH_3)_3N^+CH_2COOH$	1.83
$(CH_3)_3CCOOH$	5.05	$HOOCCH_2COOH$	2.83
FCH_2COOH	2.66	$PhCH_2COOH$	4.31
$ClCH_2COOH$	2.86	$^-OOCCH_2COOH$	5.69
$BrCH_2COOH$	2.86	$^-O_3SCH_2COOH$	4.05
ICH_2COOH	3.12	$HOCH_2COOH$	3.83
$ClCH_2CH_2CH_2COOH$	4.52	$H_2C{=}CHCH_2COOH$	4.35
$CH_3CHClCH_2COOH$	4.06		
$CH_3CH_2CHClCOOH$	2.84		

Reprinted with permission from Brown, H.C.; McDaniel, D.H.; Häflinger, O. in Braude, E.A.; Nachod, F.C. *Determination of Organic Structures by Physical Methods*, Vol. 1, Academic Press, NY, ***1955***, pp. 567–662, Copyright 1955, with permission from Elsevier Science.

Field effects are important in benzoic acid derivatives, and the pK_a of the acid will vary with the nature and placement of the "X" group in **6**.[194] The pK_a of 3-OMe **6** is 5.55, but 4-OMe **6** is 6.02 in 50% aq. methanol,[195] compared with a pK_a of 5.67 when X = H. When X = 4-NO_2, the pK_a is 4.76 and 4-Br is 5.36.[183] The pK_a of 2,6-diphenylbenzoic acid is 6.39.[196]

6

2. *Resonance effects*. Resonance that stabilizes a base but not its conjugate acid results in the acid having a higher acidity than otherwise expected and vice versa. An example is found in the higher acidity of carboxylic acids[197] compared with primary alcohols.



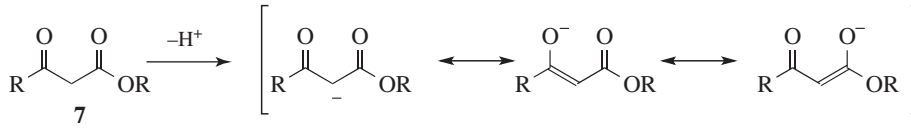
[194] For calculated gas-phase acidities of substituted benzoic acids see Wiberg, K.B. *J. Org. Chem.* ***2002***, *67*, 4787. Also see Gupta, K.; Giri, S.; Chattaraj, P.K. *New J. Chem.* ***2008***, *32*, 1945.

[195] DeMaria, P.; Fontana, A.; Spinelli, D.; Dell'Erba, C.; Novi, M.; Petrillo, G.; Sancassan, F. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 649.

[196] Chen, C.-T.; Siegel, J.S. *J. Am. Chem. Soc.* ***1994***, *116*, 5959. See also, Sotomatsu, T.; Shigemura, M.; Murata, Y.; Fujita, T. *Bull. Chem. Soc. Jpn.* ***1992***, *65*, 3157.

[197] See Exner, O.; Čársky, P. *J. Am. Chem. Soc.* ***2001***, *123*, 9564. See also, Liptak, M.D.; Shields, G.C. *J. Am. Chem. Soc.* ***2001***, *123*, 7314.

The $RCOO^-$ ion is stabilized by resonance not available to the RCH_2O^- ion (or to RCOOH).[198] Note that the $RCOO^-$ is stabilized not only by the fact that there are two equivalent canonical forms but also by the fact that the negative charge is spread over both oxygen atoms, and is therefore less concentrated than in RCH_2O^-. The same effect is found in other compounds containing a C═O or C≡N group. Thus amides $RCONH_2$ are more acidic than amines RCH_2NH_2; esters RCH_2COOR' than ethers RCH_2CH_2OR'; and ketones RCH_2COR' than alkanes RCH_2CH_2R' (Table 8.1). The effect is enhanced when two carbonyl groups are attached to the same carbon (because of additional resonance and spreading of charge); for example, β-keto esters (see **7**) are more acidic than simple ketones or carboxylic esters (Table 8.1). Compounds such as **7** are generically referred to as *active methylene compounds*, $X{-}CH_2{-}X$, where X is an electron-withdrawing group such as a carbonyl, cyano, sulfonyl, etc.[199]



7

The influence of substituents in the α position of substituted ethyl acetate derivatives has been studied.[200] Extreme examples of this effect are found in the molecules tricyanomethane $(NC)_3CH$, with a pK_a of −5 (Table 8.1, Sec. 8.A), and 2-(dicyanomethylene)-1,1,3,3-tetracyanopropene $(NC)_2C{=}C[CH(CN)_2]_2$, whose first pK_a is below −8.5 and whose second pK_a is −2.5.

Resonance effects are also important in aromatic amines. *m*-Nitroaniline is a weaker base than aniline, a fact that can be accounted for by the $-I$ effect of the nitro group. But *p*-nitroaniline is weaker still, though the $-I$ effect should be less because of the greater distance. This result is obtained by taking the canonical form **A** into account. Because **A** contributes to the resonance hybrid,[201] the electron density of the unshared pair is lower in *p*-nitroaniline than in *m*-nitroaniline, where a canonical form such as **A** is impossible. It is noted that the pK_a values reported are those of the conjugate acid, the ammonium ion.[202] The basicity is lower in the *para* compound for two reasons, both caused by the same effect: (i) the unshared pair is less available for attack by a proton, and (ii) when the conjugate acid is formed, the resonance stabilization afforded by **A** is no longer available because the previously unshared pair is now being shared by the proton.

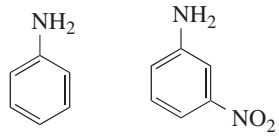
[198] It has been contended that resonance delocalization plays only a minor role in the increased strength of carboxylic acids compared to alcohols, and the "… higher acidity of acids arises principally because the electrostatic potential of the acidic hydrogens is more positive in the neutral acid molecule …": Siggel, M.R.; Streitwieser Jr., A.; Thomas, T.D. *J. Am. Chem. Soc.* ***1988***, *110*, 8022; Thomas, T.D.; Carroll, T.X.; Siggel, M.R. *J. Org. Chem.* ***1988***, *53*, 1812. For contrary views, see Exner, O. *J. Org. Chem.* ***1988***, *53*, 1810; Perrin, D.D. *J. Am. Chem. Soc.* ***1991***, *113*, 2865. See also, Godfrey, M. *Tetrahedron Lett.* ***1990***, *31*, 5181.

[199] Copper complexes of active methylene compounds show large pK_a shifts. See Zhong, Z.; Postnikova, B.J.; Hanes, R.E.; Lynch, V.M.; Anslyn, E.V. *Chem.: Eur. J.* ***2005***, *11*, 2385.

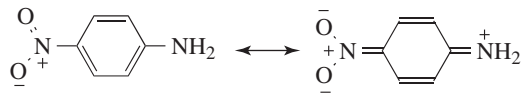
[200] Goumont, R.; Magnier, E.; Kizilian, E.; Terrier, F. *J. Org. Chem.* ***2003***, *68*, 6566.

[201] See, however, Krygowski, T.M.; Maurin, J. *J. Chem. Soc., Perkin Trans. 2* ***1989***, 695.

[202] Smith, J.W. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 161–204.



4.60 2.47



1.11 A

The acidity of phenols is affected by substituents in a similar manner.[203]

In general, resonance effects lead to the same result as field effects. That is, here too, electron-withdrawing groups increase acidity and decrease basicity,[204] and electron-donating groups act in the opposite manner. As a result of both resonance and field effects, charge dispersal leads to greater stability.

3. *Periodic table correlations*. When comparing Brønsted acids and bases that differ in the position of an element in the periodic table:
   a. Acidity increases and basicity decreases in going from left to right across a row of the periodic table. Thus acidity increases in the order $CH_4 < NH_3 < H_2O < HF$, and basicity decreases in the order $^-CH_3 > ^-NH_2 > ^-OH > F^-$. This behavior can be explained by the increase in electronegativity upon going from left to right across the periodic table. It is this effect that is responsible for the great differences in acidity between carboxylic acids, amides, and ketones: $RCOOH \gg RCONH_2 \gg RCOCH_3$.
   b. Acidity increases and basicity decreases in going down a column of the periodic table, despite the decrease in electronegativity. Thus acidity increases in the order $HF < HCl < HBr < HI$ and $H_2O < H_2S$, and basicity decreases in the order $NH_3 > PH_3 > AsH_3$. This behavior is related to the size of the species involved. Thus, for example, F^-, which is much smaller than I^-, attracts a proton much more readily because its negative charge occupies a smaller volume, and is therefore more concentrated (note that F^- is also much harder than I^- and is thus more attracted to the hard proton; Sec. 8.E). This rule does not always hold for positively charged acids. Thus, although the order of acidity for the group 16 hydrides is $H_2O < H_2S < H_2Se$, the acidity order for the positively charged ions is $H_3O^+ > H_3S^+ > H_3Se^+$.[205]

      Lewis acidity is also affected by periodic table considerations. In comparing acid strengths of Lewis acids of the form MX_n:[172]
   c. Acids that require only one electron pair to complete an outer shell are stronger than those that require two, so $GaCl_3$ is stronger than $ZnCl_2$. This results from the relatively smaller energy gain in adding an electron pair that does not complete an outer shell and from the buildup of negative charge if two pairs come in.
   d. Other things being equal, the acidity of MX_n decreases in going down the periodic table because as the size of the molecule increases, the attraction between the

[203] Liptak, M.D.; Gross, K.C.; Seybold, P.G.; Feldus, S.; Shields, G.C. *J. Am. Chem. Soc.* ***2002***, *124*, 6421.
[204] For a discussion of trifluoromethanesulfonic acid in organic synthesis, see Kazakova, A.N.; Vasilyev, A.V. *Russ. J. Org. Chem.* ***2017***, *53*, 485.
[205] Taft, R.W. *Prog. Phys. Org. Chem.* ***1983***, *14*, 247, see also Sec. 5.B.i.

positive nucleus and the incoming electron pair is weaker. Thus BCl_3 is a stronger acid than $AlCl_3$.[206]

4. *Statistical effects*. In a symmetrical diprotic acid, the first dissociation constant is twice as large as expected since there are two equivalent ionizable hydrogens, while the second constant is only half as large as expected because the conjugate base can accept a proton at two equivalent sites. So K_1/K_2 should be 4, and approximately this value is found for dicarboxylic acids where the two groups are sufficiently far apart in the molecule that they do not influence each other. A similar argument holds for molecules with two equivalent basic groups.[207]
5. *Hydrogen bonding*. Internal hydrogen bonding can greatly influence acid or base strength.[208] For example, the pK for *o*-hydroxybenzoic acid is 2.98, while the value for the *para* isomer is 4.58. Internal hydrogen bonding between the OH and COO^- groups of the conjugate base of the *ortho* isomer stabilizes it and results in an increased acidity.
6. *Steric effects*. The proton itself is so small that direct steric hindrance is seldom encountered in proton transfers. Steric effects are much more common in Lewis acid–base reactions in which larger acids are used. Spectacular changes in the order of base strength have been demonstrated when the size of the acid was changed. The order of base strength of simple amines changes in comparison against different acids of various size.[209] It can be seen that the usual order of basicity of amines (when the proton is the reference acid) can be completely inverted by using a large enough acid. The strain caused by formation of a covalent bond when the two atoms involved each have three large groups is called *face strain* or *F strain*.

   Steric effects can indirectly affect acidity or basicity by affecting the resonance (Sec. 2.F). For example, *o-tert*-butylbenzoic acid is ~10 times as strong as the *para* isomer, because the carboxyl group is forced out of the plane by the *tert*-butyl group. Indeed, virtually all *ortho* benzoic acids are stronger than the corresponding *para* isomers, regardless of whether the group on the ring is electron donating or electron withdrawing.

   Steric effects can also be caused by other types of strain. 1,8-Bis(diethylamino)-2,7-dimethoxynaphthalene (**8**) is an extremely strong base for a tertiary amine (pK_a of the conjugate acid = 16.3; compare *N,N*-dimethylaniline, pK_a = 5.1), but proton transfers to and from the nitrogen are exceptionally slow; slow enough to be followed by a UV spectrophotometer.[210] Compound **8** is severely strained because the two nitrogen lone pairs are forced to be near each other.[211] Protonation relieves

[206] Note that Lewis acidity *decreases*, whereas Brønsted acidity *increases*, going down the periodic table. There is no contradiction here when we remember that in the Lewis picture the actual acid in all Brønsted acids is the same, namely, the proton. In comparing, say, HI and HF, we are not comparing different Lewis acids but only how easily F^- and I^- give up the proton.

[207] The effect discussed here is an example of a symmetry factor. For an extended discussion, see Eberson, L. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 211–293.

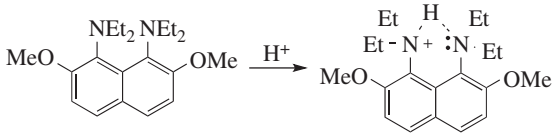
[208] For the effect of pK_a values, see Shokri, A.; Abedin, A.; Fattahi, A.; Kass, S.R. *J. Am. Chem. Soc.* ***2012***, *134*, 10646.

[209] Brown, H.C. *J. Am. Chem. Soc.* ***1945***, *67*, 378, 1452; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 53–64. See also, Brown, H.C.; Krishnamurthy, S.; Hubbard, J.L. *J. Am. Chem. Soc.* ***1978***, *100*, 3343.

[210] Hibbert, F.; Simpson, G.R. *J. Chem. Soc., Perkin Trans. 2* ***1987***, 243, 613.

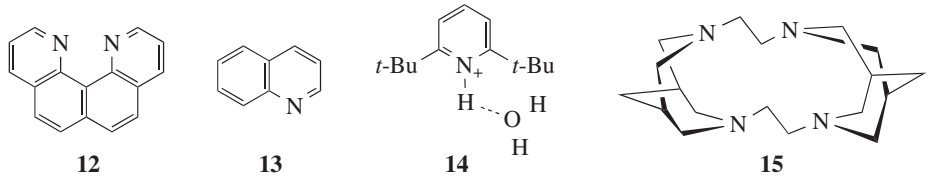
[211] For a review of the effect of strain on amine basicities, see Alder, R.W. *Chem. Rev.* ***1989***, *89*, 1215.

the strain: one lone pair is now connected to a hydrogen, which forms a hydrogen bond to the other lone pair (shown in **9**). The same effects are found in 4,5-bis(dimethylamino)fluorene (**10**)[212] and 4,5-bis(dimethylamino)phenanthrene (**11**).[213]



8 **9** **10** **11**

Compounds such as **8**, **10**, and **11** are known as *proton sponges*.[214] The basicity of proton sponges has been calculated as the sum of the proton affinity[161] of an appropriate reference monoamine, the strain released on protonation, and the energy of the intramolecular hydrogen bond formed on protonation.[215] Another type of proton sponge is quino[7,8-*h*]quinoline (**12**).[216] Protonation of this compound also gives a stable mono-protonated ion similar to **9**, but the steric hindrance found in **8**, **10**, and **11** is absent. Therefore, **12** is a much stronger base than quinoline (**13**) (pK_a values of the conjugate acids are 12.8 for **12** and 4.9 for **13**), but proton transfers are not abnormally slow. A cyclam-like macrocyclic tetramine (**15**) was prepared by a coupling reaction of bispidine, and was shown to be a new class of proton sponge.[217]



12 **13** **14** **15**

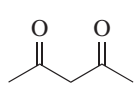
Chiral Lewis acids are known. Indeed, an air stable and storable chiral Lewis acid catalyst has been prepared, a chiral zirconium catalyst combined with molecular sieves powder.[218] Association of a bulky silicon group with the bis(trifluoromethanesulfonyl)imide (known as triflimide) anion leads to enhancement of the electrophilic character of R_3SiNTf_2. The presence of a chiral substituent derived from (−)-myrtenal on the silicon atom led to a chiral silicon Lewis acid.[219]

Another type of steric effect is the result of an entropy effect. The compound 2,6-di-*tert*-butylpyridine is a weaker base than either pyridine or 2,6-dimethylpyridine.[220] The reason is that the conjugate acid (**14**) is less stable than

[212] Staab, H.A.; Saupe, T.; Krieger, C. *Angew. Chem. Int. Ed.* ***1983***, *22*, 731.
[213] Saupe, T.; Krieger, C.; Staab, H.A. *Angew. Chem. Int. Ed.* ***1986***, *25*, 451.
[214] For a review, see Staab, H.A.; Saupe, T. *Angew. Chem. Int. Ed.* ***1988***, *27*, 865.
[215] Howard, S.T. *J. Am. Chem. Soc.* ***2000***, *122*, 8238.
[216] Krieger, C.; Newsom, I.; Zirnstein, M.A.; Staab, H.A. *Angew. Chem. Int. Ed.* ***1989***, *28*, 84. See also, Staab, H.A.; Zirnstein, M.A.; Krieger, C. *Angew. Chem. Int. Ed.* ***1989***, *28*, 86.
[217] Miyahara, Y.; Goto, K.; Inazu, T. *Tetrahedron Lett.* ***2001***, *42*, 3097.
[218] Ueno, M.; Ishitani, H.; Kobayashi, S. *Org. Lett.* ***2002***, *4*, 3395.
[219] Mathieu, B.; de Fays, L.; Ghosez, L. *Tetrahedron Lett* ***2000***, *41*, 9651.
[220] Brown, H.C.; Kanner, B. *J. Am. Chem. Soc.* ***1953***, *75*, 3865; ***1966***, *88*, 986.

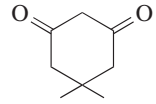
the conjugate acids of nonsterically hindered pyridines. In all cases, the conjugate acids are hydrogen bonded to a water molecule, but in the case of **14** the bulky *tert*-butyl groups restrict rotations in the water molecule, lowering the entropy.[221]

The conformation of a molecule can also affect its acidity. The following pK_a values were determined for compounds **16** to **19**.[222]



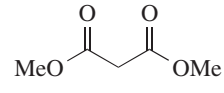
16

pK_a 13.3



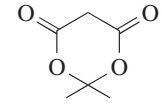
17

11.2



18

15.9

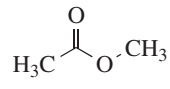


19

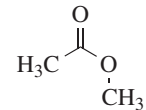
7.3

Since ketones are stronger acids than carboxylic esters (Table 8.1), it is not surprising that **16** is a stronger acid than **18**.[223] A comparison of **16** with cyclic diketone **17** shows an increase in acidity of only 2.1 p*K* units, while a comparison of **18** with cyclic diester **19** shows an increase of 8.6 units. Indeed, **19** (called *Meldrum's acid*) is an unusually strong acid for a 1,3-diester.

In order to account for this very large effect of a ring, molecular orbital calculations were carried out for two conformations of methyl acetate and of its enolate ion.[224] Loss of a proton is easier by ~5 kcal mol^{-1} (21 kJ mol^{-1}) for the *syn* than for the *anti* conformer of the ester. In an acyclic molecule like **18**, the preferred conformations are *anti*, but in Meldrum's acid (**19**) the conformation on both sides is constrained to be *syn*.



Syn



Anti

Facial differences in proton reactivity can lead to enantioselective deprotonation. Enantioselective deprotonation is also achieved by using a chiral base and/or a chiral complexing agent. Enantioselective deprotonation in cyclic ketones[225] and with heterodimer bases has been studied.[226] When a Lewis acid coordinates to a base, the resulting complex can have conformational properties that influence reactivity. Coordination of $SnCl_4$ with aldehydes and esters, for example, leads to a complex where the conformation is determined by interactions of the C═O••••$SnCl_4$ unit with substituents attached to the carbonyl.[227]

7. *Hybridization*. An *s* orbital has a lower energy than a *p* orbital. Therefore, the more *s* character a hybrid orbital contains, the lower the energy of that orbital. It follows

[221] Meot-Ner, M.; Smith, S.C. *J. Am. Chem. Soc.* ***1991***, *113*, 862, and references cited therein. See also, Benoit, R.L.; Fréchette, M.; Lefebvre, D. *Can. J. Chem.* ***1988***, *66*, 1159.

[222] Arnett, E.M.; Harrelson Jr., J.A. *J. Am. Chem. Soc.* ***1987***, *109*, 809.

[223] For a discussion of why esters and amides are weaker acids than ketones, see Fersner, A.; Karty, J.M.; Mo, Y. *J. Org. Chem.* ***2009***, *74*, 7245.

[224] Wang, X.; Houk, K.N. *J. Am. Chem. Soc.* ***1988***, *110*, 1870; Wiberg, K.B.; Laidig, K.E. *J. Am. Chem. Soc.* ***1988***, *110*, 1872.

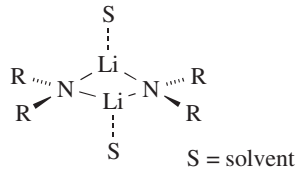
[225] Majewski, M.; Wang, F. *Tetrahedron* ***2002***, *58*, 4567.

[226] Amedjkouh, M. *Tetrahedron Asymm.* ***2004***, *15*, 577.

[227] Gung, B.W.; Yanik, M.M. *J. Org. Chem.* ***1996***, *61*, 947.

that a carbanion at an *sp* carbon is more stable than a corresponding carbanion at an sp^2 carbon. Thus $HC{\equiv}C^-$, which has more *s* character in its unshared pair than $CH_2{=}CH^-$ or $CH_3CH_2^-$ (*sp* versus sp^2 versus sp^3, respectively), is a much weaker base. This explains the relatively high acidity of acetylenes and HCN. Another example is that alcohol and ether oxygen atoms, where the unshared pair is sp^3, are more strongly basic than carbonyl oxygen atoms, where the unshared pair is sp^2 (Table 8.1).

An understanding of the reactivity of bases arises from the study of their structures in solution and in the crystalline state. Due to the importance of dialkylamide bases, there is a significant body of work, led by independent work by Williard and by Collum, that has attempted to understand the structures of these reactive molecules. It is clear that the dialkylamide bases are aggregates. Note that the simplest member of the amide base family, lithium amide ($LiNH_2$) was shown to be monomeric and unsolvated, as determined using a combination of gas-phase synthesis and millimeter/submillimeter-wave spectroscopy.[228] Both monomeric $LiNH_2$ and $LiNMe_2$ are planar.[229] Lithium diisopropylamide ($LiNiPr_2$, LDA) was isolated from a THF solution and X-ray crystallography revealed a dimeric structure (**20**; R = iPr, S = THF) in the solid state.[230] Lithium diisopropylamide was also shown to be a dimer in solutions of THF[231] and/or HMPA (see **20**, R = iPr and S = THF, HMPA).[232] In the presence of HMPA, many derivatives of **20** tend to be mixed aggregates.[233]



20

Extremely hindered $LiNR_2$ (R = 2-adamantyl) are monomeric under all conditions.[234] In hydrocarbon solvents, lithium tetramethylpiperidide [LTMP, RR′NLi where RR′ = —$CMe_2(CH_2)_3C(Me_2)$—] forms cyclic trimers and tetramers, with the tetrameric species predominating.[235] In THF, lithium hexamethyldisilazide [LHMDS, $(Me_3Si)_2NLi$] forms a five-coordinate tetrasolvate [$(Me_3Si)_2NLi(THF)_4$],[236] but in ether there is an equilibrium mixture of monomer and dimer.[237] A review is available that discusses the solution

[228] Grotjahn, D.B.; Sheridan, P.M.; Al Jihad, I.; Ziurys, L.M. *J. Am. Chem. Soc.* ***2001***, *123*, 5489.
[229] Fressigné, C.; Maddaluno, J.; Giessner-Prettre, C.; Silvi, B. *J. Org. Chem.* ***2001***, *66*, 6476.
[230] Williard, P.G.; Salvino, J.M. *J. Org. Chem.* ***1993***, *58*, 1. For a study of the oligomer structure of LDA at low ligand concentrations, see Rutherford, J.L.; Collum, D.B. *J. Am. Chem. Soc.* ***2001***, *123*, 199.
[231] Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* ***1992***, *33*, 3769.
[232] Aubrecht, K.B.; Collum, D.B. *J. Org. Chem.* ***1996***, *61*, 8674.
[233] Romesberg, F.E.; Collum, D.B. *J. Am. Chem. Soc.* ***1994***, *116*, 9187, 9198. For a study of other mixed aggregates, see Thomas, R.D.; Huang, J. *J. Am. Chem. Soc.* ***1999***, *121*, 11239.
[234] Sakuma, K.; Gilchrist, J.H.; Romesberg, F.E.; Cajthami, C.E.; Collum, D.B. *Tetrahedron Lett.* ***1993***, *34*, 5213.
[235] Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1994***, *116*, 7949.
[236] Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1995***, *117*, 9863. See also, Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1996***, *118*, 2217, 3529. See Romesberg, F.E.; Bernstein, M.P.; Gilchrist, J.H.; Harrison, A.T.; Fuller, D.J.; Collum, D.B. *J. Am. Chem. Soc.* ***1993***, *115*, 3475 for the structure in HMPA. For the ligand-binding constants, see Tai, O.; Hopson, R.; Williard, P.G. *J. Org. Chem.* ***2017***, *82*, 6223.
[237] Lucht, B.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1994***, *116*, 6009.

structures of amide bases $LiNR_2$.[238] Chiral lithium amide bases are known and they show similar behavior in solution.[239] Chelation effects are common in enantioenriched amide bases, which also form aggregates.[240] The aggregation state of lithium phenylacetonitrile has been studied.[241] Dianion aggregates can be generated, and in the case of the lithiation reaction of *N*-silyl allylamine, X-ray structure determination showed the presence of three uniquely different aggregates.[242] A mixed aggregate is formed when the lithium enolate of a ketone is mixed with a lithium amide.[243]

Similar information is available for other bases. Lithium phenoxide (LiOPh) is a tetramer in THF.[244] Lithium 3,5-dimethylphenoxide is a tetramer in ether, but addition of HMPA leads to dissociation to a monomer.[245]

Enolate anions are nucleophiles in reactions with alkyl halides (reaction **10-68**), with aldehydes and ketones (reactions **16-34** and **16-36**) and with acid derivatives (reaction **16-81**). Enolate anions are also bases, reacting with water, alcohols and other protic solvents, and even the carbonyl precursor to the enolate anion. Enolate anions exist as aggregates, and the effect of solvent on aggregation and reactivity of lithium enolate anions has been studied.[246] Alkyl substitution has a significant influence on the energetics of enolate anions.[247]

8.G. THE EFFECTS OF THE MEDIUM ON ACID AND BASE STRENGTH

Structural features are not the only factors that affect acidity or basicity. The same compound can have its acidity or basicity changed when the reaction conditions are changed. The effect of temperature (Sec. 8.A) has already been mentioned. More important is the effect of the solvent,[248] which can exert considerable influence on acid and base strengths by differential solvation.[249] If a base is more solvated than its conjugate acid, its stability is increased relative to the conjugate acid. For example, in reactions with a proton,[250] where steric effects are absent, methylamine is a stronger base than ammonia and dimethylamine is stronger still.[251] These results are easily explainable if one assumes that methyl groups are electron donating. However, trimethylamine, which should be even stronger,

[238] Collum, D.B. *Acc. Chem. Res.* ***1993***, *26*, 227. For NMR studies of $LiNEt_2$ and ring laddering, see Rutherford, J.L.; Collum, D.B. *J. Am. Chem. Soc.* ***1999***, *121*, 10198.

[239] Hilmersson, G.; Davidsson, Ö. *J. Org. Chem.* ***1995***, *60*, 7660. See O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* ***1998***, 1439; Sott, R.; Grandander, J.; Dinér, P.; Hilmersson, G. *Tetrahedron Asymm.* ***2004***, *15*, 267.

[240] Arvidsson, P.I.; Hilmersson, G.; Ahlberg, P. *J. Am. Chem. Soc.* ***1999***, *121*, 183.

[241] Carlier, P.R.; Madura, J.D. *J. Org. Chem.* ***2002***, *67*, 3832.

[242] Williard, P.G.; Jacobson, M.A. *Org. Lett.* ***2000***, *2*, 2753. For the structure and bonding of dilithiodiamines, see Pratt, L.M.; Mu, R. *J. Org. Chem.* ***2004***, *69*, 7519.

[243] Sun, C.; Williard, P.G. *J. Am. Chem. Soc.* ***2000***, *122*, 7829. See also, Pratt, L.M.; Streitwieser, A. *J. Org. Chem.* ***2003***, *68*, 2830.

[244] Jackman, L.M.; Çizmeciyan, D.; Williard, P.G.; Nichols, M.A. *J. Am. Chem. Soc.* ***1993***, *115*, 6262.

[245] Jackman, L.M.; Chen, X. *J. Am. Chem. Soc.* ***1992***, *114*, 403.

[246] Streitwieser, A.; Juaristi, E.; Kim, Y.-J.; Pugh, J.K. *Org. Lett.* ***2000***, *2*, 3839.

[247] Alconcel, L.S.; Deyerl, H.-J.; Continetti, R.E. *J. Am. Chem. Soc.* ***2001***, *123*, 12675.

[248] Cox, B.G., *Acids and Bases: Solvent Effects on Acid–Base Strength*, Oxford University Press, Oxford, ***2013***.

[249] See Epshtein, L.M.; Iogansen, A.V. *Russ. Chem. Rev.* ***1990***, *59*, 134; Dyumaev, K.M.; Korolev, B.A. *Russ. Chem. Rev.* ***1980***, *49*, 1021; Taft, R.W.; Bordwell, F.G. *Acc. Chem. Res.* ***1988***, *21*, 463; Heemstra, J.M.; Moore, J.S. *Tetrahedron* ***2004***, *60*, 7287.

[250] See Reed, C.A. *Acc. Chem. Res.* ***2013***, *46*, 2567.

[251] See Smith, J.W. in Patai, S., *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 161–204.

is a weaker base than dimethylamine or methylamine. This apparently anomalous behavior can be explained by differential hydration.[252] Thus, NH_4^+ is much better hydrated (by hydrogen bonding to the water solvent) than NH_3 because of its positive charge.[253] It has been estimated that this effect contributes ~11 pK units to the base strength of ammonia.[254] When methyl groups replace hydrogen, this difference in hydration decreases[255] until, for trimethylamine, it contributes only ~6 pK units to the base strength.[209] Thus two effects act in opposite directions, with the field effect increasing the basicity as the number of methyl groups increases and the hydration effect decreasing it. Taken together, the strongest base is dimethylamine and the weakest is ammonia in solution. If alkyl groups are electron donating, one would expect that in the gas phase,[256] where the solvation effect does not exist, the basicity order of amines toward the proton should be $R_3N > R_2NH > RNH_2 > NH_3$, and this has indeed been confirmed, for R = Me as well as R = Et and Pr.[257] Aniline too, in the gas phase, is a stronger base than NH_3,[258] so its much lower basicity in aqueous solution (pK_a of $PhNH_3^+$ 4.60 compared with 9.24 for aqueous NH_4^+) is caused by similar solvation effects and not by resonance and field electron-withdrawing effects of a phenyl group. Similarly, pyridine[259] and pyrrole[260] are both much less basic than NH_3 in aqueous solution (pyrrole[261] is neutral in aqueous solution) but *more* basic in the gas phase. Care must be taken in attributing relative acidities or basicities to any particular effect. Solvent has a significant influence on the *Hammett reaction constant* (Sec. 11.D), which influences the acidity of substituted benzoic acids.[262]

In the case of Lewis acids, protic solvents such as water or alcohol can strongly influence their reactivity, cause it to react via an alternative path to the one desired, or even cause decomposition. Rare earth metal triflates have been used to develop water-tolerant Lewis acids that can be used in many organic reactions.[263]

For simple alcohols, the order of gas-phase *acidity* is completely reversed from that in aqueous solution. In aqueous solution the acidity is in the order $H_2O > MeCH_2OH > Me_2CHOH > Me_3COH$, but in the gas phase the order is precisely

[252] Mucci, A.; Domain, R.; Benoit, R.L. *Can. J. Chem.* ***1980***, *58*, 953. See also, Drago, R.S.; Cundari, T.R.; Ferris, D.C. *J. Org. Chem.* ***1989***, *54*, 1042.

[253] For discussions of the solvation of ammonia and amines, see Jones III, F.M.; Arnett, E.M. *Prog. Phys. Org. Chem.* ***1974***, *11*, 263; Grunwald, E.; Ralph, E.K. *Acc. Chem. Res.* ***1971***, *4*, 107.

[254] Condon, F.E. *J. Am. Chem. Soc.* ***1965***, *87*, 4481, 4485.

[255] For two reasons: (i) the alkyl groups are poorly solvated by the water molecules, and (ii) the strength of the hydrogen bonds of the BH^+ ions decreases as the basicity of B increases: Lau, Y.K.; Kebarle, P. *Can. J. Chem.* ***1981***, *59*, 151. See also Glasovac, Z.; Eckert-Maksić, M. *Aust. J. Chem.* ***2014***, *67*, 1056.

[256] See Liebman, J.F. *Mol. Struct. Energ.* ***1987***, *4*, 49; Dixon, D.A.; Lias, S.G. *Mol. Struct. Energ.* ***1987***, *2*, 269; Bohme, D.K. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 731–762; Arnett, E.M. *Acc. Chem. Res.* ***1973***, *6*, 404. See Lias, S.G.; Liebman, J.F.; Levin, R.D. *J. Phys. Chem. Ref. Data*, ***1984***, *13*, 695. See also, the tables of gas-phase acidities and basicities in the following articles, and their cited references: Meot-Ner, M.; Kafafi, S.A. *J. Am. Chem. Soc.* ***1988***, *110*, 6297; Headley, A.D. *J. Am. Chem. Soc.* ***1987***, *109*, 2347.

[257] Briggs, J.P.; Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* ***1972***, *94*, 5128; Aue, D.H.; Webb, H.M.; Bowers, M.T. *J. Am. Chem. Soc.* ***1972***, *94*, 4726; ***1976***, *98*, 311, 318.

[258] Ikuta, S.; Kebarle, P. *Can. J. Chem.* ***1983***, *61*, 97.

[259] Taft, R.W.; Taagepera, M.; Summerhays, K.D.; Mitsky, J. *J. Am. Chem. Soc.* ***1973***, *95*, 3811.

[260] Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* ***1973***, *95*, 3504.

[261] See Catalan, J.; Abboud, J.L.M.; Elguero, J. *Adv. Heterocycl. Chem.* ***1987***, *41*, 187.

[262] Bartnicka, H.; Bojanowska, I.; Kalinowski, M.K. *Aust. J. Chem.* ***1993***, *46*, 31. For the absolute pK_a scale of substituted benzoic acids, see Wang, Z.; Deng, H.; Li, X.; Ji, P.; Cheng, J.-P. *J. Org. Chem.* ***2013***, *78*, 12487.

[263] Kobayashi, S. *Synlett*, ***1994***, 689.

the opposite.[264] Once again solvation effects can be invoked to explain the differences. Comparing the two extremes, H_2O and Me_3COH, we see that the OH^- ion is very well solvated by water while the bulky Me_3CO^- is much more poorly solvated because the water molecules cannot get as close to the oxygen. Thus in aqueous solution H_2O gives up its proton more readily. When solvent effects are absent, however, the intrinsic acidity is revealed and Me_3COH is a stronger acid than H_2O. This result demonstrates that simple alkyl groups cannot be simply regarded as electron donating. If methyl is an electron-donating group, then Me_3COH should be an intrinsically weaker acid than H_2O, yet it is stronger. A similar pattern is found with carboxylic acids, where simple aliphatic acids, such as propanoic acid, are stronger than acetic acid in the gas phase,[265] although weaker in aqueous solution (Table 8.5). The evidence in these and other cases[266] is that alkyl groups can be electron donating when connected to unsaturated systems but may have either no effect or may actually be electron withdrawing in other systems. It appears that the intrinsic gas-phase acidity order of alcohols as well as the basicity order of amines is due to the effect of alkyl groups, because of their polarizability, which can spread both positive and negative charges.[267] It has been calculated that even in the case of alcohols the field effects of the alkyl groups are still operating normally, but are swamped by the greater polarizability effects.[268] Polarizability effects on anionic centers are a major factor in gas-phase acid–base reactions.[269] It has been shown (by running reactions on ions that are solvated in the gas phase) that solvation by even one molecule of solvent can substantially affect the order of basicities.[270]

The effect on the orientation of solvent molecules when an acid or base is converted to its conjugate is an important aspect of solvent effects. For example, consider an acid RCOOH converted to $RCOO^-$ in aqueous solution. The solvent molecules, by hydrogen bonding, arrange themselves around the COO^- group in a much more orderly fashion than they had been arranged around the COOH group (because they are more strongly attracted to the negative charge). This leads to a considerable loss of freedom and a decrease in entropy. Thermodynamic measurements show that for simple aliphatic and halogenated aliphatic acids in aqueous solution at room temperature, the entropy ($T\Delta S$) usually contributes much more to the total free-energy change ΔG than does the enthalpy ΔH.[271] Two examples are shown in Table 8.6.[272] Resonance and field effects of functional groups therefore affect the acidity of RCOOH in two distinct ways. They affect the enthalpy (electron-withdrawing groups will increase acidity by stabilizing $RCOO^-$ by charge dispersal), but they also affect the entropy (by lowering the charge on the COO^- group and by changing the electron-density

[264] Arnett, E.M.; Small, L.E.; McIver Jr., R.T.; Miller, J.S. *J. Am. Chem. Soc.* ***1974***, *96*, 5638. Also see Bartmess, J.E.; McIver Jr., R.T. *J. Am. Chem. Soc.* ***1977***, *99*, 4163.

[265] See Caldwell, G.; Renneboog, R.; Kebarle, P. *Can. J. Chem.* ***1989***, *67*, 611.

[266] Brauman, J.I.; Blair, L.K. *J. Am. Chem. Soc.* ***1971***, *93*, 4315; Laurie, V.W.; Muenter, J.S. *J. Am. Chem. Soc.* ***1966***, *88*, 2883.

[267] Huheey, J.E. *J. Org. Chem.* ***1971***, *36*, 204; Radom, L. *Aust. J. Chem.* ***1975***, *28*, 1; Aitken, E.J.; Bahl, M.K.; Bomben, K.D.; Gimzewski, J.K.; Nolan, G.S.; Thomas, T.D. *J. Am. Chem. Soc.* ***1980***, *102*, 4873.

[268] Taft, R.W.; Taagepera, M.; Abboud, J.M.; Wolf, J.F.; DeFrees, D.J.; Hehre, W.J.; Bartmess, J.E.; McIver Jr., R.T. *J. Am. Chem. Soc.* ***1978***, *100*, 7765. For a scale of polarizability parameters, see Hehre, W.J.; Pau, C.; Headley, A.D.; Taft, R.W.; Topsom, R.D. *J. Am. Chem. Soc.* ***1986***, *108*, 1711.

[269] Bartmess, J.E.; Scott, J.A.; McIver Jr., R.T. *J. Am. Chem. Soc.* ***1979***, *101*, 6056.

[270] Bohme, D.K.; Rakshit, A.B.; Mackay, G.I. *J. Am. Chem. Soc.* ***1982***, *104*, 1100.

[271] Bolton, P.D.; Hepler, L.G. *Q. Rev. Chem. Soc.* ***1971***, *25*, 521; Gerrard, W.; Macklen, E.D. *Chem. Rev.* ***1959***, *59*, 1105. See also, Wilson, B.; Georgiadis, R.; Bartmess, J.E. *J. Am. Chem. Soc.* ***1991***, *113*, 1762.

[272] Bolton, P.D.; Hepler, L.G. *Q. Rev. Chem. Soc.* ***1971***, *25*, 521 (p. 529).

TABLE 8.6 Thermodynamic values for the ionizations of acetic acid and chloroacetic acid in H_2O at 25 °C[272]

		ΔG		ΔH		$T\Delta S$	
Acid	pK_a	kcal mol^{-1}	kJ mol^{-1}	kcal mol^{-1}	kJ mol^{-1}	kcal mol^{-1}	kJ mol^{-1}
CH_3COOH	4.76	+6.5	+27	−0.1	−0.4	−6.6	−28
$ClCH_2COOH$	2.86	+3.9	+16	−1.1	−4.6	−5.0	−21
Cl_3CCOOH	0.65	+0.9	+3.8	+1.5	+6.3	+0.6	+2.5

Reproduced from Bolton, P.D.; Hepler, L.G. *Q. Rev. Chem. Soc.* ***1971****, 25*, 521 with permission from the Royal Society of Chemistry. These values are calculated from the results, and differ significantly from those of Kurz, J.L.; Farrar, J.M. *J. Am. Chem. Soc.* ***1969****, 91*, 6057. Reprinted with permission Kurz, J.L.; Farrar, J.M. *J. Am. Chem. Soc.* ***1969****, 91*, 6057. Copyright 1969 American Chemical Society.

distribution in the COOH group, electron-withdrawing groups alter the solvent orientation patterns around both the acid and the ion, and consequently change ΔS).

A change from a protic solvent to an aprotic solvent can also affect the acidity or basicity, since there is a difference in solvation of anions by a protic solvent (which can form hydrogen bonds) and an aprotic one.[273] The effect can be extreme: in DMF, picric acid is a stronger acid than HBr,[274] though in water HBr is far stronger. This particular result can be attributed to size. That is, the large ion $(O_2N)_3C_6H_2O^-$ is better solvated by DMF than the smaller ion Br^-.[275] The ionic strength of the solvent also influences acidity or basicity, since it has an influence on activity coefficients.

In summary, solvation can have powerful effects on acidity and basicity. In the gas phase, the effects discussed in the previous section, especially resonance and field effects, operate unhindered by solvent molecules. Electron-withdrawing groups generally increase acidity (and decrease basicity); electron-donating groups act in the opposite way. In solution, especially aqueous solution, these effects still largely persist (which is why pK values in Table 8.5 do largely correlate with resonance and field effects), but in general are much weakened, and are occasionally reversed.[190]

[273] For a review, see Parker, A.J. *Q. Rev. Chem. Soc.* ***1962***, *16*, 163.
[274] Sears, P.G.; Wolford, R.K.; Dawson, L.R. *J. Electrochem. Soc.* ***1956***, *103*, 633.
[275] Miller, J.; Parker, A.J. *J. Am. Chem. Soc.* ***1961***, *83*, 117.

CHAPTER 9

Effects of Structure and Medium on Reactivity

When the equation for a reaction of, say, carboxylic acids, is written, it is customary to use the formula RCOOH, where R is a generic alkyl group, which implies that all carboxylic acids undergo the reaction. Since most compounds with a given functional group usually give more or less the same reactions, the custom is useful, and the practice is used in this book. It allows a large number of individual reactions to be classified together and serves as an aid both for memory and understanding. Nevertheless, it must be borne in mind that a given functional group does not always react the same way, regardless of what molecule it is a part of. In other words, a reaction at the functional group is influenced by the rest of the molecule. This influence may be great enough to stop the reaction completely or to make it take an entirely different course. Even when two compounds with the same functional group undergo the same reaction, the rates and/or the positions of equilibrium are usually different, sometimes slightly, sometimes greatly, depending on the structures of the compounds. The greatest variations may be expected when additional functional groups are present.

The effects of structure on reactivity can be divided into three major types: field, resonance (or mesomeric), and steric.[1] In most cases two or all three of these are operating, and it is usually not easy to tell how much of the rate enhancement (or decrease) is caused by each of the three effects.

9.A. RESONANCE AND FIELD EFFECTS

It is often particularly difficult to separate resonance and field effects; they are frequently grouped together under the heading of *electrical effects*.[2] Field effects were discussed in Section 1.I. Table 1.3 contains a list of some $+I$ and $-I$ groups. As for resonance effects, in Section 2.F it was shown how the electron density distribution in aniline is not the same as it would be if there were no resonance interaction between the ring and the NH_2 group. Most groups that contain an unshared pair on an atom connected to an unsaturated system display a similar effect; that is, the electron density on the group is less than expected, and

[1] See Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***. For a general theoretical approach to organic reactivity, see Pross, A. *Adv. Phys. Org. Chem.* ***1985***, *21*, 99.

[2] See Topsom, R.D. *Prog. Phys. Org. Chem.* ***1987***, *16*, 125; *Mol. Struct. Energ.* ***1987***, *4*, 235.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

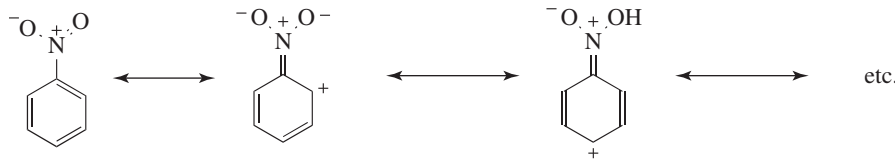
TABLE 9.1 Some groups with +*M* and −*M* effects, not listed in order of strength of effect[a]

+*M*		−*M*	
O^-	SR	NO_2	CHO
S^-	SH	CN	COR
NR_2	Br	COOH	SO_2R
NHR	I	COOR	SO_2OR
NH_2	Cl	$CONH_2$	NO
NHCOR	F	CONHR	Ar
OR	R	$CONR_2$	
OH	Ar		
OCOR			

[a] Ar (aryl) appears in both lists because it is capable of both kinds of effect. Reproduced from Hughes, E.D. *Q. Rev. Chem. Soc.* ***1948***, *2*, 107 with permission from the Royal Society of Chemistry.

the density on the unsaturated system is greater. Such groups are said to be electron donating by the resonance effect (+*M* groups). Alkyl groups, which do not have an unshared pair, are also +*M* groups, presumably because of hyperconjugation (Sec. 2.M).

On the other hand, groups that have a multiple-bonded electronegative atom directly connected to an unsaturated system are −*M* groups. In such cases canonical forms can be drawn in which electrons are delocalized from the unsaturated system into the group, as in nitrobenzene, **1**.

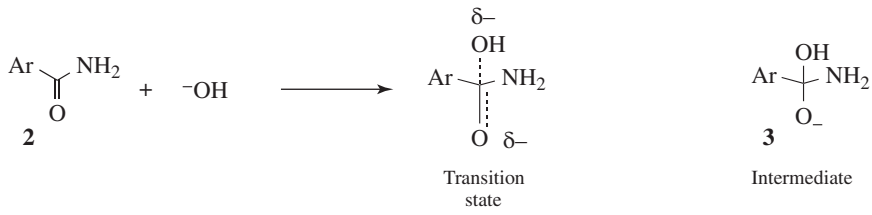


1

Table 9.1 contains a list of some +*M* and −*M* groups.

The resonance effect of a group, whether +*M* or −*M*, operates only when the group is directly connected to an unsaturated system, so that, for example, in explaining the effect of the CH_3O group on the reactivity of the COOH group in $CH_3OCH_2CH_2COOH$, only the field effect of the CH_3O need be considered. This is one way of separating the two effects. In *p*-methoxybenzoic acid both effects must be considered. The field effect operates through space, solvent molecules, or the σ bonds of a system, while the resonance effect operates through π electrons.

It must be emphasized once again that neither by the resonance effect nor by the field effect are any electrons actually being donated or withdrawn, though these terms are convenient (and we will use them). As a result of both effects, the electron-density distribution is not the same as it would be without the effect (Sec. 1.I, 2.F). Complicating the study of these effects on the reactivity of compounds is the fact that a given group may have an effect in the transition state that is considerably more or less than it has in the molecule that does not react.



In the alkaline hydrolysis of aromatic amides (reaction **16-59**), the rate-determining step is the attack of hydroxide ion at the carbonyl carbon. The conversion of **2** to **3** illustrates the nature of electrical effects (resonance and field) on reactivity. In the transition state, which has a structure somewhere between that of the starting amide (**2**) and the intermediate (**3**), the electron density on the carbonyl carbon is increased. Therefore, electron-withdrawing groups ($-I$ or $-M$) on the aromatic ring will lower the free energy of the transition state (by spreading the negative charge). These groups have much less effect on the free energy of **2**. Since G is lowered for the transition state, but not substantially for **2**, $\Delta G^{\ddagger}$ is lowered and the reaction rate is increased (Chapter 6). Conversely, electron-donating groups ($+I$ or $+M$) should decrease the rate of this reaction. Of course, many groups are $-I$ and $+M$, and for these it is not always possible to predict which effect will predominate.

9.B. STERIC EFFECTS

It occasionally happens that a reaction proceeds much faster or much slower than expected on the basis of electrical effects alone. In these cases it can often be shown that steric effects have a significant influence on the rate. For example, Table 9.2 lists relative rates for the S_N2 ethanolysis of certain alkyl halides (Sec. 10.A.i).[3] All these compounds are primary bromides; the branching is on the second carbon, so that field-effect differences should be small. As Table 9.2 shows, the rate decreases with increasing β branching and reaches a very low value for neopentyl bromide. This reaction is known to involve an attack by the nucleophile from a position opposite to that of the bromine (Sec. 10.A.i). The great decrease in rate can be attributed to *steric hindrance* in the transition state of the reaction, which makes attack of the nucleophile more difficult.

Another example of steric hindrance is found in 2,6-disubstituted benzoic acids, which are difficult to esterify no matter what the resonance or field effects of the groups in the 2

TABLE 9.2 Relative rates of reaction of RBr with ethanol[3]

R	Relative rate
CH_3	17.6
CH_3CH_2	1
$CH_3CH_2CH_2$	0.28
$(CH_3)_2CHCH_2$	0.030
$(CH_3)_3CCH_2$	4.2×10^{-6}

Reproduced from Hughes, E.D. *Q. Rev. Chem. Soc.* ***1948***, *2*, 107 with permission from the Royal Society of Chemistry

[3] Hughes, E.D. *Q. Rev. Chem. Soc.* ***1948***, *2*, 107.

TABLE 9.3 Rates of hydrolysis of tertiary alkyl chlorides at 25 °C in 80% aqueous ethanol[6]

Halide	Rate
Me_3Cl	0.033
Me_2EtCCl	0.055
$MeEt_2CCl$	0.086
Et_3CCl	0.099
$Me_3(i\text{-Pr})CCl$	0.029
$Me(i\text{-Pr})_2CCl$	0.45

Reprinted with permission from Brown, H.C.; Fletcher, R.S. *J. Am. Chem. Soc.* ***1949***, *71*, 1845. Copyright 1949 American Chemical Society.

or the 6 positions. Similarly, once 2,6-disubstituted benzoic acids *are* esterified, the esters are difficult to hydrolyze.

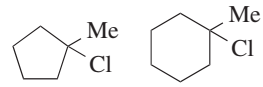
Not all steric effects decrease reaction rates. In the hydrolysis of RCl by an S_N1 mechanism (Sec. 10.A.ii), the first step, which is rate determining, involves ionization of the alkyl chloride to a carbocation:

The central carbon in the alkyl chloride is sp^3 hybridized, with angles of ~109.5°, but when it is converted to the carbocation, the hybridization becomes sp^2 and the preferred angle is 120°. If the halide is tertiary and the three alkyl groups are large enough, they will be pushed together by the enforced tetrahedral angle, resulting in strain (Sec. 4.Q.iv). This type of strain is called *B strain*[4] (for back strain), and it can be relieved by ionization to the carbocation.[5]

The rate of ionization (and hence the solvolysis rate) of a molecule in which there is B strain is expected to be larger than in cases where B strain is not present. Table 9.3 shows that this is so.[6] Substitution of ethyl groups for the methyl groups of *tert*-butyl chloride does not cause B strain; the increase in rate is relatively small, and the rate smoothly rises with the increasing number of ethyl groups. The increase is caused by normal field and resonance (hyperconjugation) effects. Substitution by one isopropyl group is not greatly different. But with the second isopropyl group the crowding is now great enough to cause B strain, and the rate is increased 10-fold. Substitution of a third isopropyl group increases the rate still more. Another example where B strain increases the rate of solvolysis is found with the highly crowded molecules tri-*tert*-butylcarbinol, di-*tert*-butylneopentylcarbinol, *tert*-butyldineopentylcarbinol, and trineopentylcarbinol, where rates of solvolysis of the *p*-nitrobenzoate esters are faster than that of *tert*-butyl nitrobenzoate by factors of 13 000, 19 000, 68 000, and 560, respectively.[7]

[4] Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 114–121.
[5] See Stirling, C.J.M. *Tetrahedron* ***1985***, *41*, 1613; *Pure Appl. Chem.* ***1984***, *56*, 1781.
[6] Brown, H.C.; Fletcher, R.S. *J. Am. Chem. Soc.* ***1949***, *71*, 1845.
[7] Bartlett, P.D.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1968***, *90*, 4421.

Another type of strain that can affect rates of cyclic compounds is called *I strain* (internal strain).[8] This type of strain results from changes in ring strain in going from a tetrahedral to a trigonal carbon or vice versa. For example, as mentioned above, S_N1 solvolysis of an alkyl halide involves a change in the bond angle of the central carbon from ~109.5° to ~120°. This change is highly favored in 1-chloro-1-methylcyclopentane because it relieves eclipsing strain (Sec. 4.Q.iv); thus this compound undergoes solvolysis in 80% ethanol at 25 °C, 43.7 times faster than the reference compound *tert*-butyl chloride.[9] In the corresponding cyclohexyl compound this factor is absent because the substrate does not have eclipsing strain (Sec. 4.Q.iv), and this compound undergoes the reaction at about one-third the rate of *tert*-butyl chloride.



	t-BuCl		
Relative solvolysis rates	1.0	43.7	0.35

The reasons for this small decrease in rate are not clear. Corresponding behavior is found in the other direction, in changes from a trigonal to a tetrahedral carbon. Thus cyclohexanone undergoes addition reactions faster than cyclopentanone. Similar considerations apply to larger rings. Rings of 7–11 members exhibit eclipsing and transannular strain; and in these systems reactions in which a tetrahedral carbon becomes trigonal generally proceed faster than in open-chain systems.[10] I-strain has been shown to be a factor in other reactions as well.[11]

Conformational effects on reactivity can be considered under the heading of steric effects,[12] but in these cases the effect of a group X and that of another group X′ upon reactivity at a site Y are not considered, but the effect of the conformation of the molecule must be considered. Many reactions fail entirely unless the molecules are able to assume the proper conformation. An example is the rearrangement of *N*-benzoylnorephedrine. The two diastereomers of this compound (**4** and **5**) behave very differently when treated with alcoholic HCl. In one of the isomers nitrogen-to-oxygen migration takes place, while the other does not react at all.[13] In order for the migration to take place, the nitrogen must be near the oxygen (*gauche* to it). When **4** assumes this conformation, the methyl and phenyl groups are *anti* to each other, which is a favorable position, but when **5** has the nitrogen *gauche* to the oxygen, the methyl must be *gauche* to the phenyl, which is so unfavorable that the reaction does not occur. Other examples are electrophilic additions to C═C double bonds (Sec. 15.A.i) and E2 elimination reactions (Sec. 17.A.i). Also, many examples are known where axial and equatorial groups behave differently.[14]

[8] See Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 105–107, pp. 126–128.

[9] Brown, H.C.; Borkowski, M. *J. Am. Chem. Soc.* ***1952***, *74*, 1894. See also, Brown, H.C.; Ravindranathan, M.; Peters, E.N.; Rao, C.G.; Rho, M.M. *J. Am. Chem. Soc.* ***1977***, *99*, 5373.

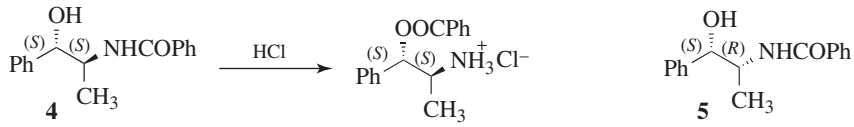
[10] See Schneider, H.; Thomas, F. *J. Am. Chem. Soc.* ***1980***, *102*, 1424.

[11] Sands, R.D. *J. Org. Chem.* ***1994***, *59*, 468.

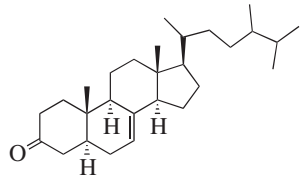
[12] See Green, B.S.; Arad-Yellin, R.; Cohen, M.D. *Top. Stereochem.* ***1986***, *16*, 131; Öki, M. *Acc. Chem. Res.* ***1984***, *17*, 154; Seeman, J.I. *Chem. Rev.* ***1983***, *83*, 83. See also, Öki, M.; Tsukahara, J.; Moriyama, K.; Nakamura, N. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 223, and other papers in this series.

[13] Fodor, G.; Bruckner, V.; Kiss, J.; Óhegyi, G. *J. Org. Chem.* ***1949***, *14*, 337.

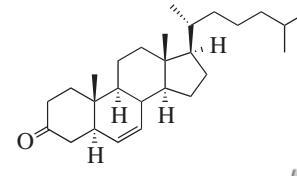
[14] See Eliel, E.L. *Stereochemistry of Carbon Compounds*, McGraw-Hill, NY, ***1962***, pp. 219–234.



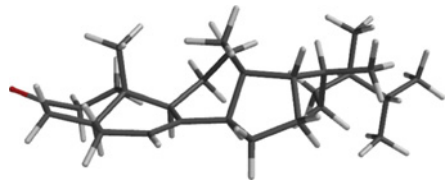
In steroids and other rigid systems, a functional group in one part of the molecule can strongly affect the rate of a reaction taking place at a remote part of the same molecule by altering the conformation of the whole skeleton. An example of this effect, called *conformational transmission*, is found in ergost-7-en-3-one (**6**) and cholest-6-en-3-one (**7**), where **7** condenses with benzaldehyde 15 times faster than **6**.[15] The reaction site in both cases is the carbonyl group, and the rate increases because moving the double bond from the 7 to the 6 position causes a change in conformation at the carbonyl group. (The difference in the side chain at C-17 does not affect the rate.) Molecular models of **6** and **7** are provided for illustration.

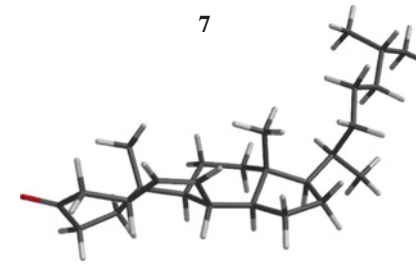


6



7





9.C. QUANTITATIVE TREATMENTS OF THE EFFECT OF STRUCTURE ON REACTIVITY[16]

Suppose a reaction is performed on a substrate molecule that can be represented as XGY, where Y is the site of the reaction, X a variable substituent, and G is a skeleton group to which X and Y are attached. In such a molecule, changing X from H to CH_3 results in a rate increase by a factor, say, 10. What part of the increase is due to each of the effects previously mentioned? The obvious way to approach such a problem is to try to find compounds in

[15] Barton, D.H.R.; McCapra, F.; May, P.J.; Thudium, F. *J. Chem. Soc.* ***1960***, 1297.

[16] See Exner, O. *Correlation Analysis of Chemical Data*, Plenum, NY, ***1988***; Johnson, C.D. *The Hammett Equation*, Cambridge University Press, Cambridge, ***1973***; Shorter, J. *Correlation Analysis of Organic Reactivity*, Wiley, NY, ***1982***; Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***. Also see Connors, K.A. *Chemical Kinetics*, VCH, NY, ***1990***, pp. 311–383; Lewis, E.S. in Bernasconi, C.F. *Investigation of Rates and Mechanisms of Reactions* (Vol. 6 of Weissberger, A. *Techniques of Chemistry*), 4th ed., Wiley, NY, ***1986***, pp. 871–901; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 38–68; Hine, J. *Structural Effects in Organic Chemistry*, Wiley, NY, ***1975***, pp. 55–102. For a historical perspective, see Grunwald, E. *CHEMTECH* ***1984***, 698.

which one or two of the factors are absent or at least negligible. This is difficult because factors that seem negligible to one investigator do not always appear so to another. The first attempt to give numerical values was that of Hammett.[17] For the cases of *m*- and *p*-XC_6H_4Y, Hammett set up the equation

$$\log \frac{k}{k_0} = \sigma \rho$$

where k_0 is the rate constant or equilibrium constant for X = H, k is the constant for the group X, ρ is a constant for a given reaction under a given set of conditions, and σ is a constant characteristic of the group X. The equation is called the *Hammett equation*.

The value of ρ was set at 1.00 for ionization of XC_6H_4COOH in water at 25 °C. The values of σ_m and σ_p were then calculated for each group (for a group X, σ is different for the *meta* and *para* positions). Once a set of σ values was obtained, ρ values could be obtained for other reactions from the rates of just two X-substituted compounds, if the σ values of the X groups were known (in practice, at least four well-spaced values are used to calculate ρ because of experimental error and because the treatment is not exact). With the ρ value calculated and the known σ values for other groups, rates can be predicted for reactions that have not yet been run.

The σ values are numbers that sum up the total electrical effects (resonance plus field) of a group X when attached to a benzene ring. The treatment usually fails for the *ortho* position. The Hammett treatment has been applied to many reactions and to many functional groups and correlates an enormous amount of data quite well. Jaffé's review article[17] listed ρ values for 204 reactions,[18] many of which have different ρ values for different conditions.

Rate constants are available for the following reactions:

$$ArCOOMe + OH^- \longrightarrow ArCOO^-$$
$$ArCH_2Cl + I^- \longrightarrow ArCH_2I$$
$$ArNH_2 + PhCOCl \longrightarrow ArNHCOPh$$
$$ArH + NO_2^+ \longrightarrow ArNO_2$$
$$ArCO_2OCMe_3 \longrightarrow \text{Decomposition (a free radical process)}$$

Equilibrium constants are available for:

$$ArCOOH + H_2O \rightleftharpoons ArCOO^- + H_3O^+$$
$$ArCHO + HCN \rightleftharpoons ArCH(CN)OH$$

The Hammett equation has also been shown to apply to many physical measurements, including IR frequencies and NMR chemical shifts.[19] The treatment is reasonably successful whether the substrates are attacked by electrophilic, nucleophilic, or free-radical reagents, the important thing being that the mechanism be the same *within* a given reaction series.

[17] For a review, see Jaffé, H.H. *Chem. Rev.* ***1953***, *53*, 191.

[18] Additional ρ values are given in Wells, P.R. *Chem. Rev.* ***1963***, *63*, 171 and in van Bekkum, H.; Verkade, P.E.; Wepster, B.M. *Recl. Trav. Chim. Pays-Bas* ***1959***, *78*, 821.

[19] For a review of Hammett treatment of NMR chemical shifts, see Ewing, D.F. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 357–396.

However, there are many reactions that do not fit the treatment. These are mostly reactions where the attack is directly on the ring and where the X group can enter into direct resonance interaction with the reaction site in the transition state (i.e., the substrate is XY rather than XGY). For these cases, two new sets of σ values have been devised: σ^+ values (proposed by H.C. Brown) for cases in which an electron-donating group interacts with a developing positive charge in the transition state (this includes the important case of electrophilic aromatic substitutions; see Chapter 11), and σ values, where electron-withdrawing groups interact with a developing negative charge. The σ, σ^+, and σ^- values are given for some common X groups,[20] and σ is not very different from σ^+ for most electron-withdrawing groups. The values of σ_m^- are essentially the same as the σ_m values.

A positive value of σ indicates an electron-withdrawing group and a negative value an electron-donating group.[21] The constant ρ measures the susceptibility of the reaction to electrical effects.[22] Reactions with a positive ρ are helped by electron-withdrawing groups and vice versa. The following ρ values for the ionization of some carboxylic acids illustrate this:[23]

XC_6H_4—COOH	1.00	XC_6H_4—CH=CH—COOH	0.47
XC_6H_4—CH_2—COOH	0.49	XC_6H_4—CH_2CH_2—COOH	0.21

As noted, the σ_p, σ_m, σ_p^+, σ_m^+, and σ_p^- values indicate the electron-withdrawing or electron-donating characteristics of *ortho*, *meta*, and *para* substituents. The σ_p for alkoxide ($-O^-$) is -0.81[24] and σ_p^+ is -4.27.[25] The σ_p for —OH is -0.38[26] and σ_p^+ is —0.92.[27] The σ_m^+ for phenyl is -0.10[28] and σ_p is 0.05.[29] Values for the —N=NPh[30] group, the —COOH[31] group, and the —CN[32] group have been reported. Finally, σ_p for the $-NMe_3^+$ group is 0.82[33] and σ_p^- for the N_2 group is 3.[34]

[20] Unless otherwise noted, σ values are from Exner, O. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 439–540, and σ^+ values from Okamoto, Y.; Inukai, T.; Brown, H.C. *J. Am. Chem. Soc.* ***1958***, *80*, 4969; Brown, H.C.; Okamoto, Y. *J. Am. Chem. Soc.* ***1958***, *80*, 4979. σ^- values, except as noted, are from Jaffé, H.H. *Chem. Rev.* ***1953***, *53*, 191. Also see Hansch, C.; Leo, A.; Taft, R.W. *Chem. Rev.* ***1991***, *91*, 165; Egorochkin, A.N.; Razuvaev, G.A. *Russ. Chem. Rev.* ***1987***, *56*, 846. For values for heteroaromatic groups, see Mamaev, V.P.; Shkurko, O.P.; Baram, S.G. *Adv. Heterocycl. Chem.* ***1987***, *42*, 1.

[21] See Dubois, J.E.; Ruasse, M.; Argile, A. *J. Am. Chem. Soc.* ***1984***, *106*, 4840; Ruasse, M.; Argile, A.; Dubois, J.E. *J. Am. Chem. Soc.* ***1984***, *106*, 4846; Lee, I.; Shim, C.S.; Chung, S.Y.; Kim, H.Y.; Lee, H.W. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 1919.

[22] Hine, J. *J. Am. Chem. Soc.* ***1960***, *82*, 4877.

[23] Binev, I.G.; Kuzmanova, R.B.; Kaneti, J.; Juchnovski, I.N. *J. Chem. Soc., Perkin Trans. 2* ***1982***, 1533.

[24] Hine, J. *J. Am. Chem. Soc.* ***1960***, *82*, 4877; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1984***, p. 42.

[25] See Hine, J. *J. Am. Chem. Soc.* ***1960***, *82*, 4877.

[26] Matsui, T.; Ko, H.C.; Hepler, L.G. *Can. J. Chem.* ***1974***, *52*, 2906.

[27] de la Mare, P.B.D.; Newman, P.A. *Tetrahedron Lett.* ***1982***, *23*, 1305 give this value as −1.6.

[28] Amin, H.B.; Taylor, R. *Tetrahedron Lett.* ***1978***, 267.

[29] Sjöström, M.; Wold, S. *Chem. Scr.* ***1976***, *9*, 200.

[30] Byrne, C.J.; Happer, D.A.R.; Hartshorn, M.P.; Powell, H.K.J. *J. Chem. Soc., Perkin Trans. 2* ***1987***, 1649.

[31] For a review of directing and activating effects of C=O, C=C, C=N, and C=S groups, see Charton, M. in Patai, S. *The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 239–298.

[32] For a review of directing and activating effects of C≡N and C≡C groups, see Charton, M. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement C*, pt. 1, Wiley, NY, ***1983***, pp. 269–323.

[33] McDaniel, D.H.; Brown, H.C. *J. Org. Chem.* ***1958***, *23*, 420.

[34] Lewis, E.S.; Johnson, M.D. *J. Am. Chem. Soc.* ***1959***, *81*, 2070.

This example shows that the insertion of a CH_2 or a CH═CH group diminishes electrical effects to about the same extent, while a CH_2CH_2 group diminishes them much more. A $\rho > 1$ would mean that the reaction is more sensitive to electrical effects than is the ionization of XC_6H_4COOH ($\rho = 1.00$).

Similar calculations have been made for compounds with two groups X and X′ on one ring, where the σ values are sometimes additive and sometimes not,[35] for other ring systems, such as naphthalene[36] and heterocyclic rings,[37] and for ethylenic and acetylenic systems.[38]

The *Hammett equation* is a *linear free-energy relationship* (LFER). This can be demonstrated as follows for the case of equilibrium constants (for rate constants a similar demonstration can be made with $\Delta G^{\ddagger}$ instead of ΔG). For each reaction, where X is any group,

$$\Delta G = -RT \ln K$$

For the unsubstituted case,

$$\Delta G_0 = -RT \ln K_0$$

The Hammett equation can be rewritten

$$\log K - \log K_0 = \sigma \rho$$

so that

$$\frac{-\Delta G}{2.3RT} = \frac{\Delta G_0}{2.3RT} = \sigma \rho$$

and

$$-\Delta G = \sigma \rho \, 2.3RT - \Delta G_0$$

For a given reaction under a given set of conditions, σ, R, T, and ΔG_0 are all constant, so that σ is linear with ΔG.

The Hammett equation is not the only LFER.[39] Some, like the Hammett equation, correlate structural changes in reactants, but the *Grunwald-Winstein relationship* (Sec. 10.G.iv) correlates changes in solvent and the *Brønsted relation* (Sec. 8.D) relates acidity to catalysis. The *Taft equation* is a structure–reactivity equation that correlates only field effects.[40]

[35] Stone, R.M.; Pearson, D.E. *J. Org. Chem.* ***1961***, *26*, 257.

[36] Berliner, E.; Winikov, E.H. *J. Am. Chem. Soc.* ***1959***, *81*, 1630; See also, Wells, P.R.; Ehrenson, S.; Taft, R.W. *Prog. Phys.Org. Chem.* ***1968***, *6*, 147.

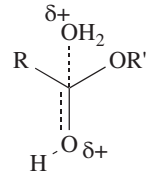
[37] See Charton, M. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 175–268; Tomasik, P.; Johnson, C.D. *Adv. Heterocycl. Chem.* ***1976***, *20*, 1.

[38] See Ford, G.P.; Katritzky, A.R.; Topsom, R.D. in *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 269–311; Charton, M. *Prog. Phys. Org. Chem.* ***1973***, *10*, 81.

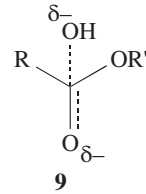
[39] See Exner, O. *Prog. Phys. Org. Chem.* ***1990***, *18*, 129.

[40] For reviews of the separation of resonance and field effects, see Charton, M. *Prog. Phys. Org. Chem.* ***1981***, *13*, 119; Shorter, J. *Q. Rev. Chem. Soc.* ***1970***, *24*, 433; *Chem. Ber.* ***1969***, *5*, 269. For a review of field and inductive effects, see Reynolds, W.F. *Prog. Phys. Org. Chem.* ***1983***, *14*, 165. For a review of field effects on reactivity, see Grob, C.A. *Angew. Chem. Int. Ed.* ***1976***, *15*, 569.

Taft, following Ingold,[41] assumed that for the hydrolysis of carboxylic esters, steric and resonance effects will be the same whether the hydrolysis is catalyzed by acid or base (see the discussion of ester-hydrolysis mechanisms, reaction **16-58**). Rate differences would therefore be caused only by the field effects of R and R′ in RCOOR′.



8



9

This is presumably a good system to use for this purpose because the transition state for acid-catalyzed hydrolysis (**8**) has a greater positive charge than the starting ester (and is hence destabilized by $-I$ and stabilized by $+I$ substituents), while the transition state for base-catalyzed hydrolysis (**9**) has a greater negative charge than the starting ester. Field effects of substituents X could therefore be determined by measuring the rates of acid- and base-catalyzed hydrolysis of a series XCH_2COOR',[42] where R′ is held constant.[38] From these rate constants, a value σ_I could be determined by the equation[43]

$$\sigma_I + 0.181\left[\log\left(\frac{k}{k_0}\right)_B - \log\left(\frac{k}{k_0}\right)_A\right]$$

In this equation $(k/k_0)_B$ is the rate constant for basic hydrolysis of XCH_2COOR' divided by the rate constant for basic hydrolysis of CH_3COOR', $(k/k_0)_A$ is the similar rate-constant ratio for acid catalysis, and 0.181 is an arbitrary constant. σ_I is a substituent constant for a group X, substituted at a saturated carbon, which reflects only field effects.[44] Once a set of σ_I values was obtained, it was found that the equation

$$\sigma_I + 0.181\left[\log\left(\frac{k}{k_0}\right)_B - \log\left(\frac{k}{k_0}\right)_A\right]$$

holds for a number of reactions, among them:[45]

$$RCH_2OH \longrightarrow RCH_2O^-$$

$$RCH_2Br + PhS^- \longrightarrow RCH_2SPh + Br^-$$

$$o\text{-Substituted-ArNH}_2 + PhCOCl \longrightarrow ArNHCOPh$$

As with the Hammett equation, σ_I is constant for a given reaction under a given set of conditions. For very large groups the relationship may fail because of the presence of steric

[41] Ingold, C.K. *J. Chem. Soc.* ***1930***, 1032.
[42] Also see Draffehn, J.; Ponsold, K. *J. Prakt. Chem.* ***1978***, *320*, 249.
[43] The symbol σ_F is also used in the literature; sometimes in place of σ_I, and sometimes to indicate only the field (not the inductive) portion of the total effect (See Sec. 1.G).
[44] There is another set of values (called σ* values) that are also used to correlate field effects. These are related to σ_I values by $\sigma_{I(X)} = 0.45\sigma$. Only σ_I, and not σ*, values are discussed.
[45] Wells, P.R. *Chem. Rev.* ***1963***, *63*, 171 (p. 196).

TABLE 9.4 The σ_I and σ_R^o values for some groups[46]

Group (R)	σ_I	σ_R^o
CMe_3	−0.07	−0.17
Me	−0.05	−0.13
H	0	0
$PhCH_2$	0.04	
NMe_3[46]	0.06	−0.55
Ph	0.10	−0.10
CH_3COCH_2	0.10	
NH_2	0.12	−0.50
CH_3CO	0.20	0.16
COOEt	0.20	0.16
NHAc	0.26	−0.22
OMe	0.27	−0.42
OH	0.27	−0.44
I	0.39	−0.12
CF_3	0.42	0.08
Br	0.44	−0.16
Cl	0.46	−0.18
F	0.50	−0.31
CN	0.56	0.08
SO_2Me	0.60	0.12
NO_2	0.65	0.15
NMe_3[47]	0.86	

Reprinted with permission from Bromilow, J.; Brownlee, R.T.C.; Lopez, V.O.; Taft, R.W. *J. Org. Chem.* ***1979****, 44*, 4766. Copyright 1979 American Chemical Society.

effects, which are not constant.[48] The equation also fails when X enters into resonance with the reaction center to different extents in the initial and transition states. A list of some σ_I values is given in Table 9.4.[49]

The σ_I values are about what is expected for pure field-effect values (Sec. 1.I) and are additive, as field effects (but not resonance or steric effects) would be expected to be. Thus, in moving a group one carbon down the chain, there is a decrease by a factor of 2.8 ± 0.5 (cf. the values of R in Table 9.4 for R = Ph and CH_3CO). An inspection of Table 9.4 shows that σ_I values for most groups are fairly close to the σ_m values for the same groups. This is

[46] For σ_R^o values for some other NR_2 groups, see Korzhenevskaya, N.G.; Titov, E.V.; Chotii, K.Yu.; Chekhuta, V.G. *J. Org. Chem. USSR* ***1987***, *28*, 1109.

[47] It has been shown that charged groups (called polar substituents) cannot be included with uncharged groups (dipolar substituents) in one general scale of electrical substituent effects: Marriott, S.; Reynolds, J.D.; Topsom, R.D. *J. Org. Chem.* ***1985***, *50*, 741.

[48] For an approach that accounts for steric effects in Hammett-type correlations, see Santiago, C.B.; Milo, A.; Sigman, M.S. *J. Am. Chem. Soc.* ***2016***, *138*, 13424.

[49] These values are from Bromilow, J.; Brownlee, R.T.C.; Lopez, V.O.; Taft, R.W. *J. Org. Chem.* ***1979***, *44*, 4766, but the values for NHAc, OH, and I are from Wells, P.R.; Ehrenson, S.; Taft, R.W. *Prog. Phys. Org. Chem.* ***1968***, *6*, 147, the values for Ph and NMe_3^+ are from Taft, R.W.; Ehrenson, S.; Lewis, I.C.; Glick, R. *J. Am. Chem. Soc.* ***1959***, *81*, 5352, and the value for CMe_3 is from Seth-Paul, W.A.; de Meyer-van Duyse, A.; Tollenaere, J.P. *J. Mol. Struct.* ***1973***, *19*, 811. The values for the CH_2Ph and CH_2COCH_3 groups were calculated from σ^* values by the formula given in reference 44. Also see Taylor, P.J.; Wait, A.R. *J. Chem. Soc., Perkin Trans. 2* ***1986***, 1765.

not surprising, since σ_m values would be expected to arise almost entirely from field effects, with little contribution from resonance.

Since σ_p values represent the sum of resonance and field effects, these values can be divided into resonance and field contributions if σ_I is taken to represent the field-effect portion.[50] The resonance contribution σ_R[51] is defined as

$$\sigma_R = \sigma_p - \sigma_I$$

As it stands, however, this equation is not very useful because the σ_R value for a given group, which should be constant if the equation is to have any meaning, is actually not constant but depends on the nature of the reaction.[52] In this respect, the σ_I values are much better. Although they vary with solvent in some cases, σ_I values are essentially invariant throughout a wide variety of reaction series. However, it is possible to overcome[53] the problem of varying σ_R values by using a special set of σ_R values, called $\sigma_R{}^o$,[54] that measure the ability to delocalize π electrons into or out of an unperturbed or "neutral" benzene ring. Several $\sigma_R{}^o$ scales have been reported; the most satisfactory values are obtained from ^{13}C chemical shifts of substituted benzenes.[55] Table 9.4 lists some values of $\sigma_R{}^o$, most of which were obtained in this way.[56]

An equation such as

$$\log \frac{k}{k_0} = \rho_I \sigma_I + \rho_R \sigma_R{}^o$$

which treats resonance and field effects separately, is known as a *dual substituent parameter equation*.[57]

The only groups in Table 9.4 with negative values of σ_I are the alkyl groups methyl and *tert*-butyl. There has been some controversy on this point.[58] One opinion is that σ_I values decrease in the series methyl, ethyl, isopropyl, *tert*-butyl (respectively, −0.046, −0.057, −0.065, −0.074).[59] Other evidence, however, has led to the belief that all alkyl groups have approximately the same field effect and that the σ_I values are invalid as a measure of the intrinsic field effects of alkyl groups.[60]

Another attempt to divide σ values into resonance and field contributions[61] is that of Swain and Lupton, who have shown that the large number of sets of σ values (σ_m, σ_p, σ_{p-},

[50] Taft, R.W. *J. Phys. Chem.* ***1960***, *64*, 1805; Taft, R.W.; Lewis, I.C. *J. Am. Chem. Soc.* ***1958***, *80*, 2436; Taft, R.W.; Deno, N.C.; Skell, P.S. *Annu. Rev. Phys. Chem.* ***1958***, *9*, 287 (see pp. 290–293).

[51] Ehrenson, S.; Brownlee, R.T.C.; Taft, R.W. *Prog. Phys. Org. Chem.* ***1973***, *10*, 1. See also, Taft, R.W.; Topsom, R.D. *Prog. Phys. Org. Chem.* ***1987***, *16*, 1; Charton, M. *Prog. Phys. Org. Chem.* ***1987***, *16*, 287.

[52] Taft, R.W.; Lewis, I.C. *J. Am. Chem. Soc.* ***1959***, *81*, 5343; Reynolds, W.F.; Dais, P.; MacIntyre, D.W.; Topsom, R.D.; Marriott, S.; von Nagy-Felsobuki, E.; Taft, R.W. *J. Am. Chem. Soc.* ***1983***, *105*, 378.

[53] Also see Happer, D.A.R.; Wright, G.J. *J. Chem. Soc., Perkin Trans. 2* ***1979***, 694.

[54] Taft, R.W.; Ehrenson, S.; Lewis, I.C.; Glick, R.E. *J. Am. Chem. Soc.* ***1959***, *81*, 5352.

[55] Bromilow, J.; Brownlee, R.T.C.; Lopez, V.O.; Taft, R.W. *J. Org. Chem.* ***1979***, *44*, 4766. See also, Marriott, S.; Topsom, R.D. *J. Chem. Soc., Perkin Trans. 2* ***1985***, 1045.

[56] For a set of σ_R values for use in XY^+ systems, see Charton, M. *Mol. Struct. Energ.* ***1987***, *4*, 271.

[57] See de Ligny, C.L.; van Houwelingen, H.C. *J. Chem. Soc., Perkin Trans. 2* ***1987***, 559.

[58] See Shorter, J. in Chapman, N.B.; Shorter, J. *Advances in Linear Free Energy Relationships*, Plenum, NY, ***1972***, pp. 98–103.

[59] See Screttas, C.G. *J. Org. Chem.* ***1979***, *44*, 3332; Hanson, P. *J. Chem. Soc., Perkin Trans. 2* ***1984***, 101.

[60] See DeTar, D.F. *J. Org. Chem.* ***1980***, *45*, 5166; *J. Am. Chem. Soc.* ***1980***, *102*, 7988.

[61] See Shorter, J. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 119–173 (pp. 126–144); Afanas'ev, I.B. *J. Chem. Soc., Perkin Trans. 2* ***1984***, 1589; Ponec, R. *Coll. Czech. Chem. Commun.* ***1983***, *48*, 1564.

TABLE 9.5 The *F* and *R* values for some groups[63]

Group	*F*	*R*
COO^-	−0.27	0.40
Me_3C	−0.11	−0.29
Et	−0.02	−0.44
Me	−0.01	−0.41
H	0	0
Ph	0.25	−0.37
NH_2	0.38	−2.52
COOH	0.44	0.66
OH	0.46	−1.89
COOEt	0.47	0.67
COMe	0.50	0.90
OMe	0.54	−1.68
CF_3	0.64	0.76
I	0.65	−0.12
Br	0.72	−0.18
Cl	0.72	−0.24
F	0.74	−0.60
NHCOMe	0.77	−1.43
CN	0.90	0.71
NMe_3^+	1.54	
N_2^+	2.36	2.81

Reprinted with permission from Swain, C.G.; Unger, S.H.; Rosenquist, N.R.; Swain, M.S. *J. Am. Chem. Soc.* ***1983***, *105*, 492. Copyright 1983 American Chemical Society.

σ_{p+}, σ_I, $\sigma_R{}^o$, etc., as well as others we have not mentioned) are not entirely independent and that linear combinations of two sets of new values *F* (which expresses the field-effect contribution) and *R* (the resonance contribution) satisfactorily express 43 sets of values.[62] Each set is expressed as

$$\sigma = f_F + r_R$$

where *f* and *r* are weighting factors. Some *F* and *R* values for common groups are given in Table 9.5.[63] From the calculated values of *f* and *r*, Swain and Lupton[63] calculated that the importance of resonance, *%R*, is 20% for σ_m, 38% for σ_p, and 62% for $\sigma_p{}^+$.[64] This is another dual substituent parameter approach.

Taft and co-workers[65] were also able to isolate steric effects.[65] For the acid-catalyzed hydrolysis of esters in aqueous acetone, log (k/k_0) was shown to be insensitive to polar

[62] Swain, C.G.; Unger, S.H.; Rosenquist, N.R.; Swain, M.S. *J. Am. Chem. Soc.* ***1983***, *105*, 492 and references cited therein.

[63] From Swain, C.G.; Unger, S.H.; Rosenquist, N.R.; Swain, M.S. *J. Am. Chem. Soc.* ***1983***, *105*, 492. Also see Hansch, C.; Leo, A.; Taft, R.W. *Chem. Rev.* ***1991***, *91*, 165.

[64] The Swain-Lupton treatment has been criticized by Reynolds, W.F.; Topsom, R.D. *J. Org. Chem.* ***1984***, *49*, 1989; Hoefnagel, A.J.; Oosterbeek, W.; Wepster, B.M. *J. Org. Chem.* ***1984***, *49*, 1993; Charton, M. *J. Org. Chem.* ***1984***, *49*, 1997. For a reply, see Swain, C.G. *J. Org. Chem.* ***1984***, *49*, 2005. See Charton, M. *Prog. Phys. Org. Chem.* ***1981***, *13*, 119; Nakazumi, H.; Kitao, T.; Zollinger, H. *J. Org. Chem.* ***1987***, *52*, 2825.

[65] See Gallo, R.; Roussel, C.; Berg, U. *Adv. Heterocycl. Chem.* ***1988***, *43*, 173; Gallo, R. *Prog. Phys. Org. Chem.* ***1983***, *14*, 115; Unger, S.H.; Hansch, C. *Prog. Phys. Org. Chem.* ***1976***, *12*, 91.

TABLE 9.6 The E_s, υ, and V^a values for some groups[82]

Group	E_s	υ	$V^a \times 10^2$
H	0	0	
F	−0.46	0.27	1.22
CN	−0.51		
OH	−0.55		
OMe	−0.55		3.39
NH_2	−0.61		
Cl	−0.97	0.55	2.54
Me	−1.24	0.52	2.84
Et	−1.31	0.56	4.31
I	−1.4	0.78	4.08
Pr	−1.6	0.68	4.78
i-Pr	−1.71	0.76	5.74
Cyclohexyl	−2.03	0.87	6.25
i-Bu	−2.17	0.98	5.26
sec-Bu	−2.37	1.02	6.21
CF_3	−2.4	0.91	3.54
t-Bu	−2.78	1.24	7.16
NMe_3^+	−2.84		
Neopentyl	−2.98	1.34	5.75
CCl_3	−3.3	1.38	6.43
CBr_3	−3.67	1.56	7.29
$(Me_3CCH_2)_2CH$	−4.42	2.03	
Et_3C	−5.04	2.38	
Ph_3C	−5.92	2.92	

Reprinted with permission from Charton, M. *Can. J. Chem.* ***1960***, *38*, 2493.

effects.[66] In cases where resonance interaction was absent, this value was proportional only to steric effects (and any others[67] that are not field or resonance). The equation is

$$\log \frac{k}{k_0} = E_S$$

Some E_s values are given in Table 9.6,[68] where hydrogen is taken as standard, with a value of 0.[69] This treatment is more restricted than those previously discussed, since it requires more assumptions, but the E_s values are approximately in order of the size of the groups. Charton has shown that E_s values for substituents of types CH_2X, CHX_2, and CX_3 are linear functions of the *van der Waals radii* for these groups.[70]

[66] Also see De Tar, D.F.; Delahunty, C. *J. Am. Chem. Soc.* ***1983***, *105*, 2734.
[67] See McClelland, R.A.; Steenken, S. *J. Am. Chem. Soc.* ***1988***, *110*, 5860.
[68] Taken from Gallo, R.; Roussel, C.; Berg, U. *Adv. Heterocycl. Chem.* ***1988***, *43*, 173; Gallo, R. *Prog. Phys. Org. Chem.* ***1983***, *14*, 115; Unger, S.H.; Hansch, C. *Prog. Phys. Org. Chem.* ***1976***, *12*, 91; Charton, M. *J. Org. Chem.* ***1976***, *41*, 2217; and Meyer, A.Y. *J. Chem. Soc., Perkin Trans. 2* ***1986***, 1567.
[69] In Taft's original work, Me was given the value 0. The E_s values in Table 9.6 can be converted to the original values by adding 1.24.
[70] Charton, M. *J. Am. Chem. Soc.* ***1969***, *91*, 615.

Two other steric parameters are independent of any kinetic data. Charton's υ values are derived from van der Waals radii,[71] and Meyer's V^a values from the volume of the portion of the substituent that is within 0.3 nm of the reaction center.[72] The V^a values are obtained by molecular mechanics calculations based on the structure of the molecule. Table 9.6 gives υ and V^a values for some groups.[73] As can be seen in Table 9.6, there is a fair, but not perfect, correlation among the E_s, υ, and V^a values. Other sets of steric values, for example, E_S^1,[74] E_S^*,[75] Ω_s,[76] and δ_f,[77] have also been proposed.[74]

Since the Hammett equation has been so successful in the treatment of the effects of groups in the *meta* and *para* positions, it is not surprising that attempts have been made to apply it to *ortho* positions also.[78] The effect on a reaction rate or equilibrium constant of a group in the *ortho* position is called the *ortho effect*.[79] Despite the many attempts made to quantify *ortho* effects, no set of values has so far commanded general agreement. However, the Hammett treatment is successful for *ortho* compounds when the group Y in *o*-XC_6H_4Y is separated from the ring; for example, ionization constants[80] of *o*-$XC_6H_4OCH_2CO_2H$ can be successfully correlated.[81]

Linear free-energy relationships can have mechanistic implications. If log (k/k_0) is linear with the appropriate σ, it is likely that the same mechanism operates throughout the series. If not, a smooth curve usually indicates a gradual change in mechanism, while a pair of intersecting straight lines indicates an abrupt change,[82] although nonlinear plots can also be due to other causes, such as complications arising from side reactions. If a reaction series follows σ^+ or σ^- better than σ it generally means that there is extensive resonance interaction in the transition state.[83]

Information can also be obtained from the magnitude and sign of ρ. For example, a strongly negative ρ value indicates a large electron demand at the reaction center, from which it may be concluded that a highly electron-deficient center, perhaps an incipient carbocation, is involved. Conversely, a positive ρ value is associated with a developing negative charge in the transition state.[84] The σ ρ relationship even applies to free-radical reactions, because free radicals can have some polar character (Sec. 14.A.ii), though ρ values here are usually small (less than ∼1.5) whether positive or negative. Reactions involving cyclic transition states (Sec. 6.B) also exhibit very small ρ values.

[71] Charton, M. *J. Am. Chem. Soc.* ***1975***, *97*, 1552; *J. Org. Chem.* ***1976***, *41*, 2217. See also, Charton, M. *J. Org. Chem.* ***1978***, *43*, 3995; Idoux, J.P.; Schreck, J.O. *J. Org. Chem.* ***1978***, *43*, 4002.
[72] Meyer, A.Y. *J. Chem. Soc., Perkin Trans. 2* ***1986***, 1567.
[73] See DeTar, D.F. *J. Org. Chem.* ***1980***, *45*, 5166; *J. Am. Chem. Soc.* ***1980***, *102*, 7988.
[74] MacPhee, J.A.; Panaye, A.; Dubois, J.E. *J. Org. Chem.* ***1980***, *45*, 1164; Dubois, J.E.; MacPhee, J.A.; Panaye, A. *Tetrahedron* ***1980***, *36*, 919. See also, Datta, D.; Sharma, G.T. *J. Chem. Res. (S)* ***1987***, 422.
[75] Fellous, R.; Luft, R. *J. Am. Chem. Soc.* ***1973***, *95*, 5593.
[76] Komatsuzaki, T.; Sakakibara, K.; Hirota, M. *Tetrahedron Lett.* ***1989***, *30*, 3309; *Chem. Lett.* ***1990***, 1913.
[77] Beckhaus, H. *Angew. Chem. Int. Ed.* ***1978***, *17*, 593.
[78] See Fujita, T.; Nishioka, T. *Prog. Phys. Org. Chem.* ***1976***, *12*, 49; Charton, M. *Prog. Phys. Org. Chem.* ***1971***, *8*, 235. See also, Robinson, C.N.; Horton, J.L.; Fosheé, D.O.; Jones, J.W.; Hanissian, S.H.; Slater, C.D. *J. Org. Chem.* ***1986***, *51*, 3535.
[79] This is not the same as the *ortho* effect discussed in Sec. 11.B.iv.
[80] For methods that estimate ionization constants of organic compounds in solution, see Zevatskii, Yu.E.; Samoilov, D.V. *Russ. J. Org. Chem.* ***2011***, *47*, 1445.
[81] Charton, M. *Can. J. Chem.* ***1960***, *38*, 2493.
[82] See Schreck, J.O. *J. Chem. Educ.* ***1971***, *48*, 103.
[83] See, however, Gawley, R.E. *J. Org. Chem.* ***1981***, *46*, 4595.
[84] Also see Williams, A. *Acc. Chem. Res.* ***1984***, *17*, 425.

9.D. EFFECT OF MEDIUM ON REACTIVITY AND RATE

There is no question that the solvent chosen for a given reaction has a profound influence on the course of that reaction. Protic versus aprotic solvents[85] as well as polar versus nonpolar solvents can have effects ranging from solubility to solvent-assisted ionization or stabilization of transition states. Simple hydrocarbons such as alkanes are used as organic solvents,[86] but hydrocarbon oligomers are alternatives.[87] Metastable liquid crystals have been used for "aging-induced dual enantioselective control."[88] Reactions can also be done neat in one of the reactants, in the gas phase, on solid support, or in the solid phase. Environmentally friendly chemistry (green chemistry) is becoming increasingly important,[89] and chemical reactions in nonpolluting (often nonorganic) solvents are of particular interest.[90]

9.E. HIGH PRESSURE

Acceleration of some chemical reactions is possible when high-pressure techniques are employed.[91,92] The effects on a given reaction can be predicted to a certain extent because the thermodynamic properties of solutions are well known. The rate of a reaction can be expressed in terms of the activation volume, $\Delta V^{\ddagger}$

$$\frac{\delta \ln k}{\delta p} = \frac{\Delta \mathrm{V}^{\ddagger}}{RT}$$

so rate constants vary with pressure.[93] "The activation volume is the difference in partial molal volume between the transition state and the initial state. From a synthetic point of view this could be approximated by the molar volume."[93] If the volume of activation is negative, the rate of the reaction will be accelerated by increasing pressure. As the pressure increases, the value of $\Delta V^{\ddagger}$ decreases and the system does not strictly obey the equation shown above at pressures >10 kbar ($1\ \mathrm{bar} = 0.986\ 924\ \mathrm{atm} = 1.101\ 9716\ \mathrm{kg\,cm^{-2}}$). If the transition state of a reaction involves bond formation, concentration of charge, or ionization, a negative volume of activation often results. There is a correlation between pressure and steric interactions in organic reactions.[94] Cleavage of a bond, dispersal of charge, or neutralization of the transition state and diffusion control lead to a positive

[85] Streidl, N.; Mayr, H. *Eur. J. Org. Chem.* ***2011***, 2498.
[86] Sen Gupta, S.K. *J. Phys. Org. Chem.* ***2016***, *29*, 251.
[87] Harrell, M.L.; Malinski, T.; Torres-López, C.; Gonzalez, K.; Suriboot, J.; Bergbreiter, D.E. *J. Am. Chem. Soc.* ***2016***, *138*, 14650.
[88] Ishida, Y.; Matsuoka, Y.; Kai, Y.; Yamada, K.; Nakagawa, K.; Asahi, T.; Saigo, K. *J. Am. Chem. Soc.* ***2013***, *135*, 6407.
[89] Andrade, C.K.Z.; Dar, A.R. *Tetrahedron* ***2016***, *72*, 7375.
[90] Kerton, F.M. *Alternative Solvents for Green Chemistry*, RSC Publishing, Cambridge, ***2009***.
[91] Jenner, G. *Tetrahedron* ***2002***, *58*, 5185; Matsumoto, K.; Morris, A.R. *Organic Synthesis at High Pressure*, Wiley, New York, ***1991***.
[92] Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* ***1985***, 1; Matsumoto, K.; Sera, A. *Synthesis.* ***1985***, 999. Also see Benito-López, F.; Egberink, R.J.M.; Reinhoudt, D.N.; Verboom, W. *Tetrahedron* ***2008***, *64*, 10023.
[93] See le Noble, W.J. *Progr. Phys. Org. Chem.* ***1967***, *5*, 207; Isaacs, N.S. *Liquid Phase High Pressure Chemistry*, Wiley, Chichester, ***1981***; Asano, T.; le Noble, W.J. *Chem. Rev.* ***1978,*** *78*, 407.
[94] Jenner, G. *Tetrahedron* ***2005***, *61*, 3621.

volume of activation. Matsumoto summarized the reactions for which rate enhancement is expected at high pressure:[93]

1. reactions in which the molecularity number (number of molecules) decreases when starting materials are converted to products: cycloadditions, condensations;
2. reactions that proceed via cyclic transition states;
3. reactions that take place through dipolar transition states;
4. reactions with steric hindrance.

Many high-pressure reactions are done neat, but if a solvent is used, the influence of pressure on that solvent is important. The melting point generally increases at elevated pressures, and this influences the viscosity of the medium (the viscosity of liquids increases approximately two times per kilobar increase in pressure). Controlling the rate of diffusion of reactants in the medium is also important, leading to another influence of high pressure on reactivity.[93,95] In most reactions, pressure is applied (5–20 kbar) at room temperature and then the temperature is increased until reaction takes place. The temperature is lowered and the pressure is reduced to isolate the products.

9.F. WATER AND OTHER NONORGANIC SOLVENTS

Although some reactions may be done in water,[96] chemical reactions of organic substrates usually employ an organic solvent, such as a hydrocarbon, ether, dichloromethane, small molecular weight alcohols, and so on, but other more exotic solvents are available. For example, poly(ethylene glycol), or PEG, has been used as a solvent medium for catalytic hydrogenation (**19-34**).[97] For some reactions in organic solvents, the presence of water may cause unwanted side reactions, and methods have been developed to detect the presence of water in those solvents.[98]

With the exception of small molecular weight molecules with polar functional groups and polyfunctional molecules or salts, organic chemicals have poor solubility in water. Nonetheless, some reactions show a faster rate of reaction in water or in aqueous media.[99] For some reactions, solubility of the organic reactant in water does influence the reaction.[100] The first indication that water accelerated a reaction was in a patent by Hopff and Rautenstrauch in 1939,[101] who reported that yields in the *Diels-Alder reaction* (**15-56**) were enhanced in aqueous detergent solutions. In an early study, Berson showed a clear relationship between the *endo*/*exo* product ratio and solvent polarity in the Diels-Alder reaction of cyclopentadiene and acrylates.[102] Breslow showed there was a hydrophobic acceleration for an intermolecular Diels-Alder reaction in which cyclopentadiene reacted with methyl

[95] Firestone, R.A.; Vitale, M.A. *J. Org. Chem.* ***1981***, *46*, 2160.

[96] *Organic Reactions in Water: Principles, Strategies and Applications*, Lindström, U.M. (ed.), Blackwell, Oxford, ***2007***; Chanda, A.; Fokin, V.V. *Chem. Rev.* ***2009***, *109*, 725.

[97] Chandrasekhar, S.; Prakash, S.J.; Rao, C.L. *J. Org. Chem.* ***2006***, *71*, 2196. PEG has also been used for the synthesis of β-amino sulfides. See Kamal, A.; Reddy, D.R.; Rajendar *Tetrahedron Lett.* ***2006***, *47*, 2261.

[98] Sun, H.; Wang, B.; DiMagno, S.G. *Org. Lett.* ***2008***, *10*, 4413.

[99] See Pirrung, M.C. *Chem. Eur. J.* ***2006***, *12*, 1312. *Water in Organic Synthesis, Workbench Edition* (*Science of Synthesis)* Kobayashi, S. (ed.), Geo Thieme Verlag, Stuttgart, ***2012***. Kobayashi, S. *Pure Appl. Chem.* ***2013***, *85*, 1089.

[100] Zuo, Y.-J.; Qu, J. *J. Org. Chem.* ***2014***, *79*, 6832.

[101] Hopff, H.; Rautenstrauch, C.W. *U.S. Patent* 2,262,002, ***1939*** [*Chem. Abstr. 36*: 10469, ***1942***].

[102] Berson, J.A.; Hamlet, Z.; Mueller, W.A. *J. Am. Chem. Soc.* ***1962***, *84*, 297.

vinyl ketone.[103] Clearly, there is an accelerating effect on some chemical reactions when done in water that is useful in organic chemistry.[104]

When nonpolar compounds are suspended in water their relative insolubility causes them to associate, diminishing the water–hydrocarbon interfacial area (a hydrophobic effect).[105] This association is greater in water than in methanol and brings the reactive partners into close proximity, increasing the rate of reaction. Any additive that increases the hydrophobic effect will increase the rate.[104]

Organic chemical reactions have been done is supercritical fluids, including supercritical water.[106] A supercritical fluid can be either liquid or gas, but it is used in a state above the temperature and pressure where gases and liquids can coexist. The properties of a supercritical fluid are different from those of either gases or liquids under standard conditions, with no distinct liquid and gas phases at temperatures and pressures above its critical point. The critical point is the temperature, pressure, etc. at which there are no phase boundaries. Carbon dioxide can be used as a reaction solvent when pressurized (supercritical carbon dioxide, $scCO_2$).[107] Carbon dioxide is nontoxic, inexpensive, abundant, and easily recycled. These properties have made it attractive as an extraction solvent.[108] The low critical temperature of CO_2 (T_c) 31.1 °C ensures that $scCO_2$ is a safe solvent for many applications.[109] There are solubility issues that suggest $scCO_2$ is a rather polar solvent.[110] For example, many systems with hydrocarbon chains are not very soluble in CO_2.[111] Water/carbon dioxide emulsions have also been employed.[112] The use of supercritical carbon dioxide ($scCO_2$) has been explored in many reactions,[113] including catalysis.[114] Some applications of this technique include the electrochemical synthesis of conducting polymers[115] and highly cross-linked polymers[116] in $scCO_2$, the synthesis of octyl palmitate,[117] the synthesis of carbonated fatty methyl esters,[118] and the synthesis of methyl carbamates.[119] A carbonylation reaction was done in $scCO_2$ in the course of a synthesis of trisubstituted cyclopentanes and

[103] Rideout, D.; Breslow, R. *J. Am. Chem. Soc.* ***1980***, *102*, 7816.

[104] Engberts, J.B.F.N.; Blandamer, M.J. *Chem. Commun.* ***2001***, 1701; Lindström, U.M. *Chem. Rev.* ***2002***, *102*, 2751; Ribe, S.; Wipf, P. *Chem. Commun.* ***2001***, 299.

[105] For a review of chemical reactions in aqueous media with a focus on C—C bond formation, see Li, C.-J. *Chem. Rev.* ***2005***, *105*, 3095. For microwave-assisted synthesis in water, see Dallinger, D.; Kappe, C.O. *Chem. Rev.* ***2007***, *107*, 2563.

[106] Weingärtner, H.; Franck, E.U. *Angew. Chem. Int. Ed.* ***2005***, *44*, 2672; Fraga-Dubreuil, J.; Poliakoff, M. *Pure Appl. Chem.* ***2006***, *78*, 1971. Kus, N.S. *Tetrahedron* ***2012***, *68*, 949.

[107] Parrott, A.J.; Bourne, R.A.; Akien, G.R.; Irvine, D.J.; Poliakoff, M. *Angew. Chem. Int, Ed.* ***2011***, *50*, 3788.

[108] See Raynie, D.E. *Anal. Chem.* ***2004***, *76*, 4659.

[109] Subramaniam, B.; Rajewski, R. A.; Snavely, K. *J. Pharm. Sci.* ***1997***, *86*, 885.

[110] Raveendran, P.; Ikushima, Y.; Wallen, S.L. *Acc. Chem. Res.* ***2005***, *38*, 478.

[111] Consani, K.A.; Smith, R.D.J. *Supercrit. Fluids* ***1990***, *3*, 51.

[112] Jacobson, G.B.; Lee Jr., C.T.; da Rocha, S.R.P.; Johnston, K.P. *J. Org. Chem.* ***1999***, *64*, 1207; Jacobson, G.B.; Lee Jr., C.T.; Johnston, K.P. *J. Org. Chem.* ***1999***, *64*, 1201.

[113] Gopalan, A.D.; Wai, C.M.; Jacobs, H.K. *Supercritical Carbon Dioxide: Separations and Processes*, American Chemical Society (distributed by Oxford University Press), Washington, DC. ***2003***; Beckman, E.J. *Ind. Eng. Chem. Res.* ***2003***, *42*, 1598; Wang, S.; Kienzle, F. *Ind. Eng. Chem. Res.* ***2000***, *39*, 4487.

[114] Leitner, W. *Acc. Chem. Res.* ***2002***, *35*, 746.

[115] Anderson, P.E.; Badlani, R.N.; Mayer, J.; Mabrouk, P.A. *J. Am. Chem. Soc.* ***2002***, *124*, 10284.

[116] Cooper, A.I.; Hems, W.P.; Holmes, A.B. *Macromolecules* ***1999***, *32*, 2156.

[117] Madras, G.; Kumar, R.; Modak, J. *Ind. Eng. Chem. Res.* ***2004***, *43*, 7697,1568.

[118] Doll, K.M.; Erhan, S.Z. *J. Agric. Food Chem.* ***2005***, *53*, 9608.

[119] Selva, M.; Tundo, P.; Perosa, A.; Dall'Acqua, F. *J. Org. Chem.* ***2005***, *70*, 2771.

cyclohexanes as key components of substance P antagonists.[120] A continuous flow acid-catalyzed dehydration of alcohols was accomplished in $scCO_2$.[121] Supercritical fluids are playing an increasingly important role in synthetic organic chemistry.[122]

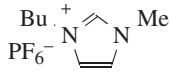
Other supercritical fluids can be used for chemical reactions, such as supercritical ammonia in the synthesis of labeled guanidines.[123]

9.G. IONIC LIQUID SOLVENTS

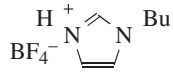
Environmentally friendly solvents,[124] which include ionic liquids, are of great interest.[125] An ionic liquid is a salt in which the ions are poorly coordinated, usually leading to their being liquid at <100 °C and sometimes at room temperature.[126] In such ionic species, there is usually at least one ion with a delocalized charge whereas the other component is usually organic. This combination inhibits the formation of a stable crystal lattice. The structure and solvation properties of solutes in ionic liquids have been studied.[127] It is known that ionic liquids form ideal solutions.[128] Hydrogen bonding is important.[129] A greener, halide-free synthesis of ionic liquids has been reported,[130] as well as a synthesis of tetramethylguanidinium cation-based ionic liquids.[131] Acidic ionic liquids have been reviewed.[132] It was discovered that some ionic liquids are suitable as a medium for chemical reactions.[133] Both methylimidazolium ions and pyridinium ions form the basis of common ionic liquids that have been used in organic chemistry.[134] Ionic liquids have been synthesized in both microstructured and stirred batch reactors, and a comparison made of the relative techniques.[135] There are coordinating chiral ionic liquids.[136] One of

[120] Kuethe, J.T.; Wong, A.; Wu, J.; Davies, I.W.; Dormer, P.G.; Welch, C.J.; Hillier, M.C.; Hughes, D.L.; Reider, P.J. *J. Org. Chem.* ***2002***, *67*, 5993.
[121] Gray, W.K.; Smail, F.R.; Hitzler, M.G.; Ross, S.K.; Poliakoff, M. *J. Am. Chem. Soc.* ***1999***, *121*, 10711.
[122] See Prajapati, D.; Gohain, M. *Tetrahedron* ***2004***, *60*, 815.
[123] Jacobson, G.B.; Westerberg, G.; Markides, K.E.; Langstrom, B. *J. Am. Chem. Soc.* ***1996***, *118*, 6868.
[124] *Alternative Solvents for Green Chemistry,* Kerton, F.M.; Clark J.M.; Kraus, G.A. Royal Society of Chemistry, Cambridge, ***2009***.
[125] But also see Scammells, P.J.; Scott, J.L.; Singer, R.D. *Austr. J. Chem.* ***2005***, *58*, 155.
[126] For a discussion of physical properties, see Ludwig, R.; Kragl, U. *Angew. Chem. Int. Ed. 2007*, *46*, 6582.
[127] Hardacre, C.; Holbrey, J.D.; Nieuwenhuyzen, M.; Youngs, T.G.A. *Acc. Chem. Res.* ***2007***, *40*, 1146; Greaves, T.L.; Drummond, C.J. *Chem. Rev.* ***2008***, *108*, 206. See also Lungwitz, R.; Strehmel, V.; Spange, S. *New J. Chem.* ***2010***, *34*, 1135. See Schmeisser, M.; Illner, P.; Puchta, R.; Zahl, A.; Rudi van Eldik, R. *Chem. Eur. J.* ***2012***, *18*, 10969.
[128] Abbott, A.P.; Frisch, G.; Garrett, H.; Hartley, J. *Chem. Commun.* ***2011***, *47*, 11876.
[129] Dong, K.; Zhang, S. *Chem. Eur. J.* ***2012***, *18*, 2748.
[130] Ferguson, J.L.; Holbrey, J.D.; Ng, S.; Plechkova, N.V.; Seddon, K.R.; Tomaszowska, A.A.; Wassell, D.F. *Pure Appl. Chem.* ***2012***, *84*, 723.
[131] Singh, A.P.; Sithambaram, D.; Sanghavi, R.; Gupta, P.K.; Verma, R.S.; Doble, M.; Gardas, R.L.; Senapati S. *New J. Chem.* ***2017***, *41*, 12268.
[132] Amarasekara, A.S. *Chem. Rev.* ***2016***, *116*, 6133.
[133] Earle, M.J.; Seddon, K.R. *Pure. Appl. Chem.* ***2000***, *72*, 1391; Wasserscheid, P.; Welton, T.; *Ionic Liquids in Synthesis*, Wiley-VCH, NY, ***2002***; Adams, D.J.; Dyson, P.J.; Taverner, S.J.; *Chemistry in Alternative Reaction Media*, Wiley, ***2003***. See Chiappe, C.; Malvaldi, M.; Pomelli, C.S. *Pure Appl. Chem.* ***2009***, ***81***, 767. See Hajipour, A.R.; Rafiee, F. *Org. Prep. Proceed. Int.* ***2015***, *47*, 249.
[134] Rogers, R.D.; Voth, G.A. A*cc. Chem. Res.* ***2007***, *40*,1077;
[135] Iken, H.; Guillen, F.; Chaumat, H.; Mazières, M.-R.; Plaquevent, J.-C.; Tzedakis, T. *Tetrahedron Lett.* ***2012***, *53*, 3474.
[136] Vasiloiu, M.; Leder, S.; Gaertner, P.; Mereiter, K.; Bica, K. *Org. Biomol. Chem.* ***2013***, *11*, 8092.

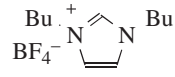
the most common ionic liquids used as a solvent is 1-butyl-3-methylimidazolium as the hexafluorophosopahte, **10** (Bmim PF_6).[137] Hydrogen butylimidazolium tetrafluoroborate (HBuIm, **11**) and 1,3-dibutylimidazolium, tetrafluoroborate (DiBuIm, **12**), for example,[138] have been reported to facilitate *Diels-Alder reactions* (**15-56**).[139] It is known that a proton on C2 of imidazolium cations such as **10-12** is relatively acidic.[140] Carbene formation is common and the anion generated by treatment with base can undergo substitution reactions.[141] These facts lead to a caution that undesired side reactions are possible when these ionic liquids are employed as solvents.[141] Pyridinium-based ionic liquids such as ethylpyridinium tetrafluoroborate (**13**) have also been used.[142] Several room temperature ionic liquids have been synthesized from amino acids.[143] The a.c. (alternating current) electrochemical stability of ionic liquids has been reported.[144]



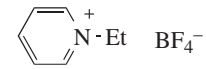
10



11



12



13

Ionic solvents have been used to facilitate heterocyclic reactions,[145] several catalytic reactions,[146] the *Heck reaction* (**13-9**)[147] and other Pd-catalyzed C—C bond-forming reactions,[148] the oxidation of alcohols with hypervalent iodine reagents (**19-3**),[149] and the catalytic asymmetric dihydroxylation of alkenes (**15-44**) using a recoverable and reusable Os/ligand complex.[150] The camphorsulfonate anion has been used as a counterion for imidazolium salts, and shown to increase the number of unsolvated imidazolium cations.[151] This ionic liquid was then shown to influence the *endo*/*exo* ratio in a stereoselective Diels-Alder reaction (**15-56**).[152] Other catalytic reactions in ionic liquids are known.[152] Other chiral ionic liquids are known.[153] Reactions performed in an ionic liquid are a rapidly growing

[137] Dupont, J.; Consorti, C.S.; Suarez, P.A.Z.; de Souza, R.F. *Org. Synth. Coll. Vol. X*, 184.
[138] For discussion of HBuIM and DiBuIm, see Harlow, K.J.; Hill, A.F.; Welton, T. *Synthesis* ***1996***, 697; Larsen, A.S.; Holbrey, J.D.; Tham, F.S.; Reed, C.A. *J. Am. Chem. Soc.* ***2000***, *122*, 7264.
[139] Jaegar, D.A.; Tucker, C.E. *Tetrahedron Lett.* ***1989***, *30*, 1785.
[140] Handy, S.T.; Okello, M. *J. Org. Chem.* ***2005***, *70*, 1915.
[141] See Chowdhury, S.; Mohan, R.S.; Scott, J.L. *Tetrahedron* ***2007***, *63*, 2363.
[142] See Xiao, Y.; Malhotra, S.V. *Tetrahedron Lett.* ***2004***, *45*, 8339.
[143] Fukumoto, K.; Yoshizawa, M.; Ohno, H. *J. Am. Chem. Soc.* ***2005***, *127*, 2398. Also see Chen, X.; Li, X.; Hu, A.; Wang, F. *Tetrahedron Asymmetry* ***2008***, *19*, 1.
[144] Yang, F.; Li, Z.; Zhang, S.; Zhang, Q.; Hu, X.; Zhang, X.; Deng, Y. *Chem. Lett.* ***2011***, *40*, 1423.
[145] Martins, M.A.P.; Frizzo, C.P.; Moreira, D.N.; Zanatta, N.; Bonacorso, H.G. *Chem. Rev.* ***2008***, *108*, 2015.
[146] See Toma, Š.; Mečiarová. M.; Šebesta, R. *Eur. J. Org. Chem.* ***2009***, 321. See Sarkar, A.; Roy, S.R.; Parikh, N.; Chakraborti, A.K. *J. Org. Chem.* ***2011***, *76*, 7132.
[147] Handy, S.T.; Okello, M.; Dickenson, G. *Org. Lett.* ***2003***, *5*, 2513.
[148] Calò, V.; Nacci, A.; Monopoli, A. *Eur. J. Org. Chem.* ***2006***, 3791.
[149] Yadav, J.S.; Reddy, B.V.S.; Basak, A.K.; Narsaiah, A.V. *Tetrahedron* ***2004***, *60*, 2131.
[150] Branco, L.C.; Afonso, C.A.M. *J. Org. Chem.* ***2004***, *69*, 4381.
[151] Nobuoka, K.; Kitaoka, S.; Kunimitsu, K.; Iio, M.; Harran, T.; Wakisaka, A.; Ishikawa, Y. *J. Org. Chem.* ***2005***, *70*, 10106.
[152] Pârvulescu, V.I.; Hardacre, C. *Chem. Rev.* ***2007***, *107*, 2615.
[153] Baudequin, C.; Brégeon, D.; Levillain, J.; Guillen, F.; Plaquevent, J.-C.; Gaumont, A.C. *Tetrahedron Asymmetry* ***2005***, *16*, 3921; Pernak, J.; Feder-Kubis, J. *Tetrahedron Asymmetry* ***2006***, *17*, 1728; Luo, S.-P.; Xu, D.-Q.; Yue, H.-D.; Wang, L.-P.; Yang, W.-L.; Xu, Z.-Y. *Tetrahedron Asymmetry* ***2006***, *17*, 2028.

area of organic chemistry, and one which has been expanded to include microwave reactions (Sec. 7.C) in ionic solvents.[154] The development and use of ionic solvents is a growth area of organic chemistry.[155] It is also noted that some ionic liquids are categorized as Lewis bases (Sec. 8.E), which will influence the acidity of dissolved compounds.[156] There are also acidic Brønsted ionic liquids.[157]

Deep eutectic solvents are an increasingly useful class of ionic solvents. Deep eutectic solvents are formed from a eutectic mixture of Lewis or Brønsted acids and bases that contain anionic and/or cationic species.[158] Examples are mixtures of quaternary ammonium salts with hydrogen bond donors: amines and carboxylic acids. Deep eutectic solvents are a class of ionic solvents. A specific example is a mixture of choline chloride and urea in a 1:2 mole ratio that has a melting point lower than that of choline or urea, and is a liquid at room temperature.[159] Four types of deep eutectic solvents have been identified: (i) a quaternary ammonium salt plus a metal chloride; (ii) a quaternary ammonium salt plus a metal chloride hydrate; (iii) a quaternary ammonium salt plus a hydrogen bond donor; and (iv) a metal chloride hydride plus a hydrogen bond donor.[160]

9.H. SOLVENTLESS REACTIONS

In some cases, it should be possible to accomplish a chemical transformation without the use of a solvent. Dry media reactions under microwave irradiation is an important area of study (Sec. 7.C).[161] There are several advantages of solventless reactions: (i) the possibility of direct formation of high purity compounds; (ii) the possibility of sequential reactions; (iii) fast kinetics; (iv) lower energy usage; (v) minimal need for preformed salts and metal–metalloid complexes; (vi) simplicity and low equipment cost; and (vii) the possibility of avoiding functional group protection–deprotection.[162] Potential difficulties include the possibility of hot spots and runaway reactions, and difficulties in handling solid or highly viscous materials.[163] An example of this approach is the aldol condensation, where a single aldol product was obtained in high yield.[164] 3-Carboxylcoumarins have been produced via a solventless aldol reaction.[163]

[154] See Leadbeater, N.E.; Torenius, H.M. *J. Org. Chem.* ***2002***, *67*, 3145.
[155] For studies to expand the polarity range of ionic solvents see Dzyuba, S.V.; Bartsch, R.A. *Tetrahedron Lett.* ***2002***, *43*, 4657. See *Ionic Liquids: From Knowledge to Application*, Plechkova, N.V.; Rogers, R.D.; Seddon, K.R. (Eds.), American Chemical Society, Washington, DC (distributed by Oxford University Press), ***2010***.
[156] MacFarlane, D.R.; Pringle, J.M.; Johansson, K.M.; Forsyth, S.A.; Forsyth, M. *Chem. Commun.* ***2006***, 1905.
[157] Hajipour, A.R.; Rafiee, F. *Org. Prep. Proceed. Int.* ***2010***, *42*, 285.
[158] Smith, E.L.; Abbott, A.P.; Ryder, K.S. *Chem. Rev*. ***2014***, *114*, 11060.
[159] Abbott, A.P.; Capper, G.; Davies, D.L.; Rasheed, R.K.; Tambyrajah, V. *Chem. Commun.* ***2003***, 70.
[160] Abbott, A.; Barron, J.; Ryder, K.; Wilson, D. *Chem. Eur. J*. ***2007***, *13*, 6495.
[161] Kidwai, M. *Pure Appl. Chem.* ***2001***, *73*, 147.
[162] Cave, G.W.V.; Raston, C.L.; Scott, J.L. *Chem. Commun.* ***2001***, 2159; Toda, F.; Tanaka, K. *Chem. Rev.* ***2000***, *100*, 1025.
[163] Raston, C.L. *Chemistry in Australia* ***2004***, 10.
[164] Toda, F.; Tanaka, K.; Hamai, K. *J. Chem. Soc., Perkin Trans. 1* ***1990***, 3207.

PART II

INTRODUCTION

Part II of this book will be directly concerned with organic reactions and their mechanisms. The reactions have been classified into 10 chapters, based primarily on reaction type: substitutions, additions to multiple bonds, eliminations, rearrangements, and oxidation-reduction reactions. Substitutions are classified on the basis of mechanism as well as substrate. Chapters 10 and 13 include nucleophilic substitutions at aliphatic and aromatic substrates, respectively. Chapters 12 and 11 deal with electrophilic substitutions at aliphatic and aromatic substrates, respectively. All free-radical substitutions are discussed in Chapter 14. Additions to multiple bonds are classified not according to mechanism, but according to the type of multiple bond. Additions to carbon-carbon multiple bonds are dealt with in Chapter 15; additions to other multiple bonds in Chapter 16. One chapter is devoted to each of the three remaining reaction types: Chapter 17, eliminations; Chapter 18, rearrangements; Chapter 19, oxidation-reduction reactions. This last chapter covers only those oxidation-reduction reactions that could not be conveniently treated in any of the other categories (except for oxidative eliminations).

Each chapter in Part 2 consists of two main sections. The first section of each chapter (except Chapter 19) deals with mechanism and reactivity. For each reaction type the various mechanisms are discussed in turn, with particular attention given to the evidence for each mechanism and to the factors that cause one mechanism rather than another to prevail in a given reaction. Following this, each chapter contains a section on reactivity, including, where pertinent, a consideration of orientation and the factors affecting it.

The second main section of each chapter is a treatment of the reactions belonging to the category indicated by the title of the chapter. It is not possible to discuss in a book of this nature all or nearly all known reactions. However, an attempt has been made to include all the important reactions of standard organic chemistry that can be used to prepare relatively pure compounds in reasonable yields. In order to present a well-rounded picture and to include some reactions that are traditionally discussed in textbooks, a number of reactions that do not fit into the above category have been included. However, certain special areas have been covered only lightly or not at all. Among these are polymerization reactions, and the preparation and reactions of heterocyclic compounds, carbohydrates, steroids, and compounds containing phosphorus, silicon, arsenic, boron, and mercury. The basic principles involved in these areas are of course no different from those in the areas more fully treated.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

Each reaction is discussed in its own numbered section.[1] These sections are numbered consecutively within a chapter, with each section number preceded by the chapter number, so that reaction **16-1** is the first reaction of Chapter 16 and reaction **13-21** is the twenty-first reaction of Chapter 13. The order in which the reactions are presented is not arbitrary, but is based on an orderly outline that depends on the type of reaction. Within each section, the scope and utility of the reaction are discussed and references are given to review articles, if any. If there are features of the mechanism that especially pertain to that reaction, these are also discussed within the section rather than in the first part of the chapter, as there the discussion of mechanism is more general.

II.A. IUPAC NOMENCLATURE FOR TRANSFORMATIONS

There has long been a need for a method of naming reactions. Many reactions have been given the names of their discoverers or those who popularized them (e.g., *Claisen*, *Diels-Alder*, *Stille*, *Wittig*, *Cope*, *Dess-Martin*). In the past, this was necessary because mechanisms were not well understood, and a *named reaction* was a convenient way to identify certain transformations. Nowadays, the reasons for assigning a name are less clear and there may be as many as 800–1000 named reactions. Some believe that this practice has gotten out of hand, while others believe it to be the best way to organize key reactions.

II.B. IUPAC SYSTEM FOR SYMBOLIC REPRESENTATION OF MECHANISMS

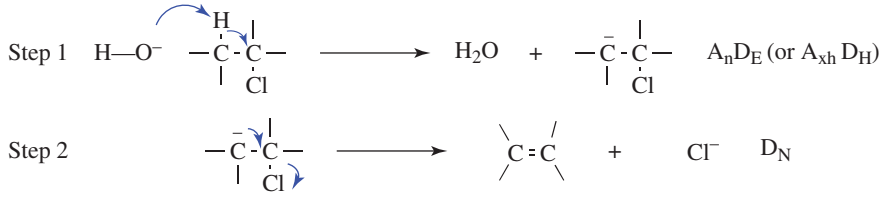
In addition to providing a system for naming transformations, the IUPAC Commission on Physical Organic Chemistry has also produced one for representing mechanisms.[2] As will be seen, many mechanisms (but by no means all) are commonly referred to by designations, such as S_N2, $A_{AC}2$, $E1_{cB}$, and $S_{RN}1$, many of them devised by C.K. Ingold and co-workers. While these designations have been useful (and they will continued to be used in this book), the sheer number of them can be confusing, especially since the symbols do not give a direct clue to what is happening. For example, there is no way to tell directly from the symbols how S_N2' is related to S_N2 (Sec. 10.A.i). The IUPAC system is based on a very simple description of bond changes.[3] The letter A represents formation of a bond (association) and D the breaking of a bond (dissociation). These are *primitive changes*. The basic description of a mechanism consists of these letters, with subscripts to indicate where the electrons are going. In any mechanism, the *core atoms* are defined as (i) the two atoms in a multiple bond that undergoes addition, or (ii) the two atoms that will be in a multiple bond after elimination, or (iii) the single atom at which substitution takes place.

[1] The classification of reactions into sections is, of course, to some degree arbitrary. Each individual reaction is different, and custom generally decides how we group them together. Individual preferences also play a part. No claim is made that the classification system used in this book is more valid than any other. For another way of classifying reactions, see Fujita, S. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 597.

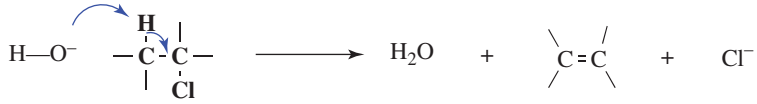
[2] Guthrie, R.D. *Pure Appl. Chem.* ***1989***, *61*, 23. For a briefer description, see Guthrie, R.D.; Jencks, W.P. *Acc. Chem. Res.* ***1989***, *22*, 343.

[3] There are actually two IUPAC systems. The one used in this book (Ref. 4) is intended for general use. A more detailed system, which describes every conceivable change happening in a system, and which is designed mostly for computer handling and storage, is given by Littler, J.S. *Pure Appl. Chem.* ***1989***, *61*, 57. The two systems are compatible; the Littler system uses the same symbols as the Guthrie system, but has additional symbols.

As an example of the system, this is how an $E1_{cB}$ mechanism (Sec. 17.A.iii) would be represented:



The overall designation is $A_nD_E + D_N$ (or $A_{xh}D_H + D_N$). In this case the overall reaction is:



and the core atoms are the two carbons atoms in boldface.

Step 1, First Symbol

A bond is being formed between O and H. Bond formation is represented by A. For this particular case the system gives two choices for subscript. In any process, the subscript is N if a core atom is forming a bond to a nucleophile (A_N) or breaking a bond to a nucleofuge (D_N). If a non-core atom is doing the same thing, lowercase n is used instead. Since H and O are non-core atoms, the lowercase n is used, and the formation of the O—H bond is designated by A_n. However, because involvement of H^+ is so common in organic mechanisms, the rules allow an alternative. The subscript H or h may replace N or n. The symbol xh denotes that the H^+ comes from or goes to an unspecified carrier atom X. Thus the term Axh means that a bond is being formed between H (moving without electrons) and an outside atom, in this case O. The same subscript, xh, would be used if the outside atom were any other nucleophilic atom, say N or S.

Step 1, Second Symbol

A bond is being broken between C and H. The symbol is D. In any process, the subscript is E if a core atom is forming a bond to an electrophile (A_E) or breaking a bond to an electrofuge (D_E). Since C is a core atom, the symbol here is D_E. Alternatively, the symbol could be D_H. The rules allow A_H or D_H to replace A_E or D_E if the electrophile or electrofuge is H^+. Because a core atom is involved in this primitive change the H in the subscript is capitalized.

Step 1, Combined Symbols

In step 1, two bond changes take place simultaneously. In such cases, they are written together with no space or punctuation: A_nD_E or $A_{xh}D_H$.

Step 2

Only one bond is broken in this step and no bonds are formed. (The movement of a pair of unshared electrons into the C—C bond, forming a double bond, is not designated by any symbol. In this system bond multiplicity changes are understood without being specified.) Thus the symbol is D. The broken bond is between a core atom (C) and a nucleofuge (Cl), so the designation is D_N.

Overall

The overall designation can be either $A_nD_N + D_N$ or $A_{xh}D_H + D_N$. The + symbol shows that there are two separate steps. If desired, rate-limiting steps can be shown by the symbol. In this case, if the first step is the slow step [old designation $(E1_{cB})_I$], the designation would be $A_nD_E + D_N$ or $A_{xh}D_H + D_N$.

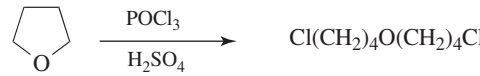
For most mechanisms (other than rearrangements), there will be only two A or D terms with uppercase subscripts, and the nature of the reaction can be immediately recognized by looking at them. If both are A, the reaction is an addition; if both are D (as in $A_nD_E + D_N$) it is an elimination. If one is A and the other D, the reaction is a substitution.

Here, we have given only a brief description of the system. Other IUPAC designations will be shown in Part II, where appropriate. For more details, further examples, and additional symbols, see Ref. 2.

II.C. ORGANIC SYNTHESES REFERENCES

At the end of many numbered sections in the Part II chapters there is a list of *Organic Syntheses* references (abbreviated OS). With the exception of a few very common reactions (**12-3**, **12-23**, **12-24**, and **12-37**), and to the extent that it is possible, the list includes *all* OS references for each reaction. The volumes of OS that have been covered are Collective Volumes **I–XI**. There are indices to OS.[4] *Organic Syntheses* can now be accessed online.[5]

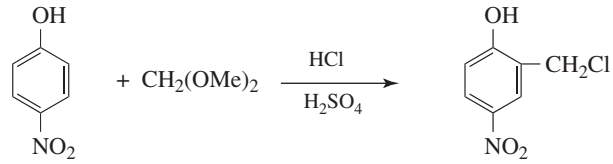
Certain ground rules were followed in assembling these lists. A reaction in which two parts of a molecule independently undergo simultaneous reaction is listed under both reactions. Similarly, if two reactions happen (or might happen) rapidly in succession without the isolation of an intermediate, the reactions are listed in both places. For example, at OS **IV**, 266 is:



[4] Smith, M.B. *Fieser and Fieser's Reagents For Organic Syntheses, Collective Index For Volumes 1–22*, Wiley, New York, ***2005***; Smith, J.G.; Fieser, M. *Fieser and Fieser's Reagents for Organic Synthesis: Collective Index for Volumes 1–12*, Wiley, New York, ***1990***; Liotta, D.C.; Volmer, M. *Organic Syntheses Reaction Guide*, Wiley, NY, ***1991***, which covers the series through Vol. 68. For an older index to *Organic Syntheses* (through Vol. 45), see Sugasawa, S.; Nakai, S. *Reaction Index of Organic Syntheses*, Wiley, NY, ***1967***.

[5] http://www.orgsyn.org/

This reaction is treated as **10-48** followed by **10-12** and is listed in both places. However, certain reactions are not listed because they are trivial examples. An instance of this is the reaction found at OS **III**, 468:



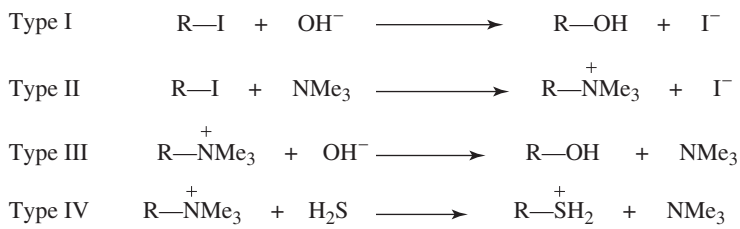
This is a chloromethylation reaction and is consequently listed in reaction **11-14**. However, in the course of the reaction formaldehyde is generated from the acetal. This reaction is not listed in reaction **10-6** (hydrolysis of acetals), because it is not really a preparation of formaldehyde.

CHAPTER 10

Aliphatic Substitution, Nucleophilic and Organometallic

In nucleophilic aliphatic substitution the attacking (electron donating) reagent (the nucleophile) brings an electron pair to the substrate, using this pair to form the new bond, and the leaving group (the nucleofuge) comes away with an electron pair:

As written, this equation says nothing about charges. Nucleophile Y may be neutral or negatively charged; RX may be neutral or positively charged; so there are four charge types, examples of which are



In all cases, Y must have an unshared pair of electrons, so that all nucleophiles are Lewis bases.[1] When Y is the solvent, the reaction is called *solvolysis*. Nucleophilic substitution at an aromatic carbon is considered in Chapter 13. There is a growing area of research that involves transition-metal catalyzed reactions at sp^3-hybridized carbon.[2]

Nucleophilic substitution at an alkyl carbon is said to *alkylate* the nucleophile. For example, the above reaction between RI and NMe_3 is an *alkylation* of trimethylamine. Nucleophilic substitution at an acyl carbon is an *acylation* of the nucleophile, and such reactions are found in Chapter 16.

[1] For a green protocol for nucleophilic substitution, see Liu, Y.; Xu, Y.; Jung, S.H.; Chae, J. *Synlett* ***2012***, *23*, 2692.

[2] Zhang, W.; Wang, N.-X.; Xing, Y. *Synlett* ***2015***, *26*, 2088. For a Cu-mediated reaction, see Cai, X.-h.; Xie, B. *Synthesis* ***2015***, *47*, 737.

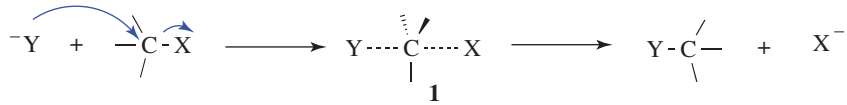
March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

10.A. MECHANISMS

Several distinct mechanisms are possible for aliphatic nucleophilic substitution reactions, depending on the substrate, nucleophile, leaving group, and reaction conditions. In all of them, however, the *attacking* reagent carries the electron pair with it. Mechanisms that occur at a saturated carbon atom are considered first.[3] By far the most common are the S_N1 and S_N2 mechanisms.

10.A.i. The S_N2 Mechanism

The designation S_N2 stands for *substitution nucleophilic bimolecular*.[4] The IUPAC designation is A_ND_N. In this mechanism, there is *back-side attack*,[5] which means that the nucleophile approaches the substrate from a position 180° away from the leaving group. This approach will minimize steric and electronic repulsion of the substrate and the incoming nucleophile. The reaction is a one-step process with no intermediate (see below, and Sec. 10.A.iv). The C—Y bond is formed as the C—X bond is broken to generate *pentacoordinate transition state* **1**.



1

The energy necessary to break the C—X bond is supplied by the collision of the nucleophile (Y) with the carbon bearing the leaving group (X). The top of the curve of free energy of activation is taken to be the transition state, and the position of the atoms for this reaction are shown in transition state **1**. The transition state is not a real structure, of course, but the energetic midpoint of the reaction. There are various computational methods to ascertain characteristics of a given transition state, and the experimental examination of kinetic isotope effects has been used to infer information about the transition state.[6] The group X must leave as the group Y comes in, because at no time can the carbon have more than eight electrons in its outer shell. When the transition state is reached, the central carbon atom has gone from its initial sp^3 hybridization to essentially sp^2 with an approximately perpendicular *p* orbital. One lobe of this *p* orbital overlaps with the nucleophile and the other with the leaving group. This is why a front-side S_N2 mechanism has never been observed. In a hypothetical front-side transition state, both the nucleophile and the leaving group would have to overlap with the same lobe of the *p* orbital. The back-side mechanism involves the maximum amount of overlap throughout the course of the reaction. At the energy point of

[3] See Hartshorn, S.R. *Aliphatic Nucleophilic Substitution*, Cambridge University Press, Cambridge, ***1973***; Katritzky, A.R.; Brycki, B.E. *Chem. Soc. Rev.* ***1990***, *19*, 83; Richard, J.P. *Adv. Carbocation Chem.* ***1989***, *1*, 121; Streitwieser, A. *Solvolytic Displacement Reactions*, McGraw-Hill, NY, ***1962***.

[4] Haddon, R.C.; Tian, Z.; Jiang, D. *J. Org. Chem.* ***2016***, *81*, 3648.

[5] See Sun, L.; Hase, W. L.; Song, K. *J. Am. Chem. Soc.* ***2001***, *123*, 5753. Nucleophlicity and leaving group ability for front-side and back-side attack have been studied: see Bento, A.P.; Bickelhaupt, F.M. *J. Org. Chem.* ***2008***, *73*, 7290.

[6] Hasanayn, F.; Streitwieser, A.; Al-Rifai, R. *J. Am. Chem. Soc.* ***2005***, *127*, 2249. See also Cruickshank, F.R.; Hyde, A.J.; Pugh, D. *J. Chem. Educ.* ***1977***, *54*, 288.

the transition state the three nonreacting substituents and the central carbon are approximately coplanar. They will be exactly coplanar if both the entering and the leaving group are the same.

There is a large amount of evidence for the S_N2 mechanism. First, there is the kinetic evidence.[7] Since both the nucleophile and the substrate are involved in the rate-determining step (the only step, in this case), the reaction should be first order in each component, second order overall, and satisfy the rate expression shown in Eq. (10-1).

$$\text{rate} = k\,[\text{RX}]\;[\text{Y}] \tag{10-1}$$

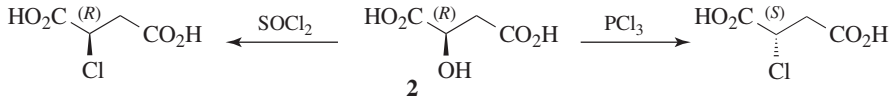
This rate law has been found to apply. Note that the 2 in S_N2 stands for bimolecular. It must be remembered that this is not always the same as second order (Sec. 6.J.vi). If a large excess of nucleophile is present (for example, if it is the solvent[8]) the mechanism may still be bimolecular, although the experimentally determined kinetics will be first order (Eq. 10-2).

$$\text{rate} = k\;[\text{RX}] \tag{10-2}$$

As previously mentioned (Sec. 6.J.vi), such kinetics are called *pseudo-first order*.

The kinetic evidence is a necessary but not a sufficient condition; other mechanisms will be encountered that are also consistent with these data. Much more convincing evidence is obtained from the fact that the mechanism predicts inversion of configuration when substitution occurs at a chiral carbon and this has been observed many times. This inversion of configuration (Sec. 4.E.ii) that proceeds through transition state **1** is called the *Walden inversion* and was observed long before the S_N2 mechanism was formulated by Hughes and Ingold.[9]

At this point it is useful to see just how it was originally proved that a given substitution reaction proceeds with inversion of configuration, even before the mechanism was known. Walden presented a number of examples[10] in which inversion *must* have taken place. For example, (+)-malic acid (**2**) could be converted to (+)-chlorosuccinic acid by thionyl chloride and converted to (−)-chlorosuccinic acid by PCl_3.



2

One was an inversion and the other a retention of configuration, but the question was which was which? The signs of rotation are of no help in answering this question since

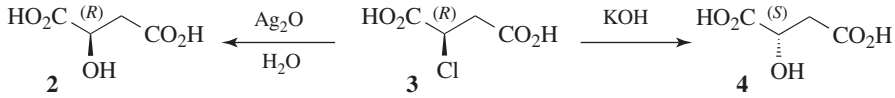
[7] For a theoretical investigation of a kinetic isotope effect, see Matsson, O.; Dybala-Defratyka, A.; Rostkowski, M.; Paneth, P.; Westaway, K.C. *J. Org. Chem.* ***2005***, *70*, 4022.

[8] For a discussion of this type of solvent effect, see Arnaut, L.G.; Formosinho, S.J. *Chem. Eur. J.* ***2007***, *13*, 8018.

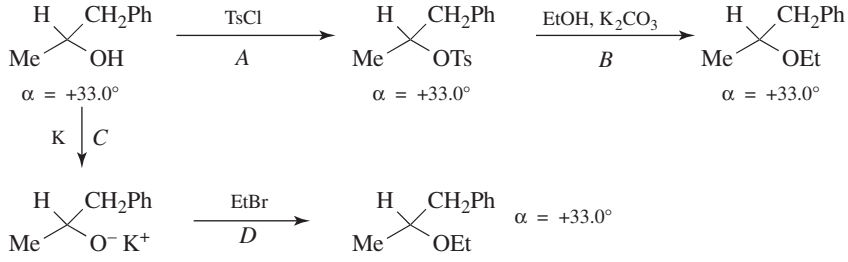
[9] Cowdrey, W.A.; Hughes, E.D.; Ingold, C.K.; Masterman, S.; Scott, A.D. *J. Chem. Soc.* ***1937***, 1252. The idea that the addition of one group and removal of the other are simultaneous was first suggested by Lewis, G.N. in *Valence and the Structure of Atoms and Molecules*, Chemical Catalog Company, NY, ***1923***, p. 113. The idea that a one-step substitution leads to inversion was proposed by Olsen, A.R. *J. Chem. Phys.* ***1933***, *1*, 418.

[10] Walden, P. *Ber.* ***1893***, *26*, 210; ***1896***, *29*, 133; ***1899***, *32*, 1855.

rotation need not be related to configuration (Sec. 4.F). Another example discovered by Walden is formation of **4** from **3**.[11]



A series of experiments designed to settle the matter of exactly where inversion takes place was performed by Phillips,[12] Kenyon,[13] and co-workers. In 1923, Phillips carried out the following cycle based on (+)-1-phenylpropan-2-ol. In this cycle, (+)-1-phenylpropan-2-ol is converted to its ethyl ether by two routes, path *AB* giving the (−) ether, and path *CD* giving the (+) ether. Therefore, at least one of the four steps must be an inversion. It is extremely unlikely that there is inversion in step *A*, *C*, or *D*, since in all these steps the C—O bond is unbroken, and in none of them could the oxygen of the bond have come from the reagent. There is a high probability that *A*, *C*, and *D* proceeded with retention, leaving *B* as the inversion. A number of other such cycles were carried out, always with nonconflicting results.[13] These experiments not only definitely showed that certain specific reactions proceed with inversion, but also established the configurations of many compounds.

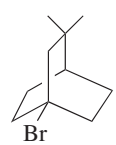


Walden inversion has been found at a primary carbon atom by the use of a chiral substrate containing a deuterium and a hydrogen atom at the carbon bearing the leaving group.[14] Inversion of configuration has also been found for S_N2 reactions proceeding in the gas phase.[15] High pressure mass spectrometry has been used to probe the energy surface for gas phase S_N2 reactions, which have two transition states (a "loose" transitions state and a "tight" transition state).[16]

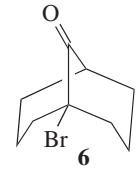
Another kind of evidence for the S_N2 mechanism comes from compounds with potential leaving groups at bridgehead carbons. If the S_N2 mechanism is correct, these compounds should not be able to react by this mechanism, since the nucleophile cannot approach from

[11] For a discussion, see Kryger, L.; Rasmussen, S.E. *Acta Chem. Scand.* ***1972***, *26*, 2349.
[12] Phillips, H. *J. Chem. Soc.* ***1923***, *123*, 44. See Garwood, D.C.; Cram, D.J. *J. Am. Chem. Soc.* ***1970***, *92*, 4575; Cram, D.J.; Cram, J.M. *Fortschr. Chem. Forsch.* ***1972***, *31*, 1.
[13] See Kenyon, J.; Phillips, H.; Shutt, G.R. *J. Chem. Soc.* ***1935***, 1663 and references cited therein.
[14] Streitwieser Jr., A. *J. Am. Chem. Soc.* ***1953***, *75*, 5014.
[15] Speranza, M.; Angelini, G. *J. Am. Chem. Soc.* ***1980***, *102*, 3115 and references cited therein; Kempf, B.; Hampel, N.; Ofial, A.R.; Mayr, H. *Chem. Eur. J.* ***2003***, *9*, 2209. See Riveros, J.M.; José, S.M.; Takashima, K. *Adv. Phys. Org. Chem.* ***1985***, *21*, 197.
[16] Li, C.; Ross, P.; Szulejko, J.E.; McMahon, T.B. *J. Am. Chem. Soc.* ***1996***, *118*, 9360.

the rear. Among the many known examples of unsuccessful reaction attempts at bridgeheads under S_N2 conditions[17] are treatment of the [2.2.2] system **5** with ethoxide ion[18] and treatment of the [3.3.1] system **6** with sodium iodide in acetone.[19] In these cases, open-chain analogs underwent the reactions readily.



5



6

As a final example of evidence for the S_N2 mechanism, the reaction between optically active 2-octyl iodide and radioactive iodide ion may be mentioned:

$$C_6H_{13}CHMeI + {}^*I^- \longrightarrow C_6H_{13}CHMe{}^*I + I^-$$

Racemization is expected in this reaction, since if the pure *R* isomer is the starting material each exchange will produce an *S* isomer. With increasing concentration of *S* isomer, it will begin to compete for I^- with the *R* isomer, until at the end a racemic mixture is left. The point investigated was a comparison of the rate of inversion with the rate of uptake of radioactive ${}^*I^-$. It was found[20] that the rates were identical within experimental error:

- rate of inversion: $2.88 \pm 0.03 \times 10^{-5}$
- rate of exchange: $3.00 \pm 0.25 \times 10^{-5}$

The rate of racemization was the parameter actually measured, which is twice the rate of inversion, since each inversion creates, in effect, two racemic molecules. The significance of this result is that it shows that every act of exchange is an act of inversion.

Eschenmoser and co-workers provided strong evidence that the transition state in an S_N2 reaction must be linear.[21] Base treatment of methyl α-tosyl-*o*-toluenesulfonate (**7**) gives the *o*-(l-tosylethyl)benzenesulfonate ion (**9**). The role of the base is to remove the benzylic proton α to the tosyl group to give the ion **8**. It might be supposed that the negatively charged carbon of **8** attacks the methyl group in an internal S_N2 process, but this is not the case. Crossover experiments[21] (see **11-27**) have shown that the negatively charged carbon attacks the methyl group of another molecule rather than the nearby one in the same molecule; that is, the reaction is intermolecular (see **8**) and not intramolecular, despite the more favorable entropy of the latter pathway (Sec. 6.D). It is likely that intramolecular attack does not take place because complete linearity cannot be attained. This behavior is in sharp contrast to

[17] See Müller, P.; Mareda, J. in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, ***1990***, pp. 189–217; Fort Jr., R.C.; Schleyer, P.v.R. *Adv. Alicyclic Chem.* ***1966***, *1*, 283.

[18] Doering, W. von E.; Levitz, M.; Sayigh, A.; Sprecher, M.; Whelan Jr., W.P. *J. Am. Chem. Soc.* ***1953***, *75*, 1008. Actually, a slow substitution was observed in this case, but not by an S_N2 mechanism.

[19] Cope, A.C.; Synerholm, M.E. *J. Am. Chem. Soc.* ***1950***, *72*, 5228.

[20] Hughes, E.D.; Juliusburger, F.; Masterman, S.; Topley, B.; Weiss, J. *J. Chem. Soc.* ***1935***, 1525.

[21] Tenud, L.; Farooq, S.; Seibl, J.; Eschenmoser, A. *Helv. Chim. Acta* ***1970***, *53*, 2059. See also, King, J.F.; McGarrity, M.J. *J. Chem. Soc., Chem. Commun.* ***1979***, 1140.

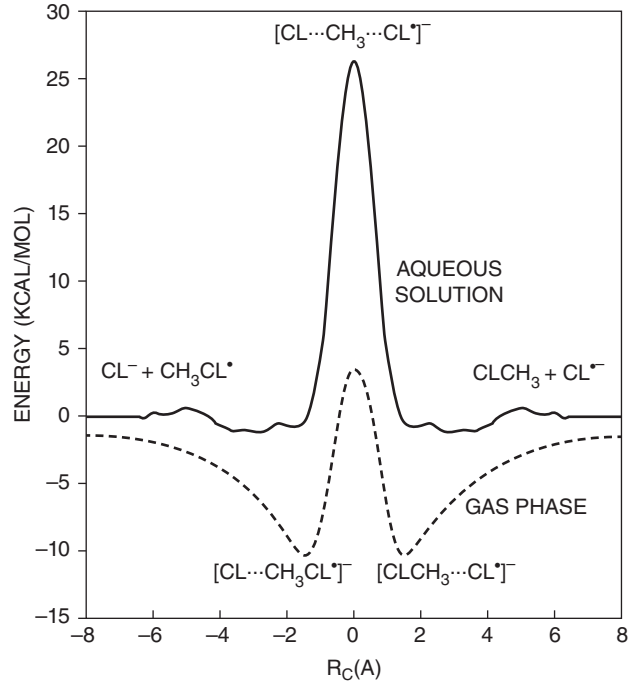
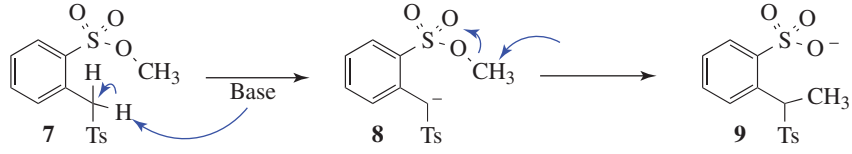


FIGURE 10.1. Free-energy profile for the gas phase (solid line) and aqueous solution (dashed line) S_N2 reaction between CH_3Cl and Cl^-, from molecular orbital calculations.[20]
Reprinted with permission from Chandrasekhar, J.; Smith, S.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***1985***, *107*, 154. Copyright 1985 American Chemical Society.

that in cases in which the leaving group is not constrained (Sec. 10.C), where intramolecular S_N2 mechanisms operate freely.



There is evidence, both experimental and theoretical, that there are intermediates in at least some S_N2 reactions in the gas phase, in charge type I reactions, where a negative ion nucleophile attacks a neutral substrate.[22] Two energy minima, one before and one after the transition state, appear in the reaction coordinate (Figure 10.1).[23]

The energy surface for the S_N2 *Menshutkin reaction* (**10-30**) has been examined and it was shown that charge separation was promoted by the solvent.[24] An *ab initio* study of the

[22] See Angel, L.A.; Ervin, K.M. *J. Am. Chem. Soc.* ***2003***, *125*, 1014.
[23] Taken from Chandrasekhar, J.; Smith, S.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***1985***, *107*,154.
[24] Gao, J.; Xia, X. *J. Am. Chem. Soc.* ***1993***, *115*, 9667.

S_N2 reaction at primary and secondary carbon centers has looked at the energy barrier (at the transition state) to the reaction.[25] The solvolytic behavior of aryl and alkyl carbonates has been examined, vis-à-vis the intrinsic barrier to their leaving-group ability.[26] These minima correspond to unsymmetrical ion–dipole complexes.[27] Theoretical calculations also show such minima in certain solvents (e.g., DMF), but not in water.[28] In general, polar aprotic solvents (those that do not have an acidic hydrogen, X—H where X = O, S, N, etc.), favor polarized transition state 1.[29] The rate of the reaction is generally slower in protic solvents such as alcohol or water. Liquid ammonia has been used as a dipolar aprotic solvent in these reactions.[30] The effect of alkyl groups on S_N2 reactivity has been discussed.[31] In many reactions, π conjugation has been invoked to enhance the rate of an S_N2 reaction, but work has shown substrate–nucleophile electrostatic interactions dictate S_N2 reaction rate trends.[32]

The S_N2 reactions can occur at atoms other than carbon, X (e.g., nitrogen or sulfur[33]). Analogous to the phenomenon observed for S_N2 reactions at carbon,[34] the valence of the element X controls the intrinsic barrier for the reaction in accord with the properties seen in the periodic table.[35] Nucleophilic substitution has been discussed for reactions at phosphorus[36] and at silicon.[37]

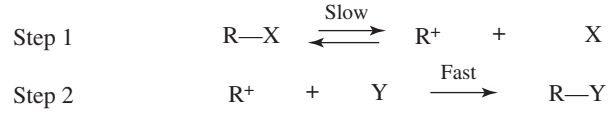
For a list of some of important reactions that operate by the S_N2 mechanism, see Sec. 10.G.i.

Note that in some reactions, such as bromine transfer between carbanions via nucleophilic attack on bromine, anomalous kinetic behavior is observed. The largest rate constants are associated with bromine transfer between cyano-activated carbanions and the smallest relate to the removal of bromine from the nitromethane and nitroethane moieties.[38] The Brønsted plot (log k vs. ΔpK_a) for this reaction shows that unlike any normal Brønsted plot, which by definition displays a positive slope, the plot for $MeNO_2$ and $EtNO_2$ is negative. In deprotonation reactions of carbon compounds, the reactivity of nitroethane and nitromethane were shown to be anomalous.[39] In the series nitromethane, ethane, and isopropane, compounds with higher acidity undergo slower deprotonation (i.e., the Brønsted plot displays a negative slope), contrary to expectations.[40]

[25] Lee, I.; Kim, C.K.; Chung, D.S.; Lee, B.-S. *J. Org. Chem.* ***1994***, *59*, 4490.
[26] Matić, M.; Katić, M.; Denegri, B.; Kronja, O. *J. Org. Chem.* ***2017***, *82*, 7820.
[27] Evanseck, J.D.; Blake, J.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***1987***, *109*, 2349; Kozaki, T.; Morihashi, K.; Kikuchi, O. *J. Am. Chem. Soc.* ***1989***, *111*, 1547; Jorgensen, W.L. *Acc. Chem. Res.* ***1989***, *22*, 184.
[28] Chandrasekhar, J.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***1985***, *107*, 2974.
[29] For a discussion of environmentally benign substitution reactions, see Vogel, P.; Figueira, S.; Muthukrishnan, S.; Mack, J. *Tetrahedron Lett.* ***2009***, *50*, 55.
[30] Ji, P.; Atherton, J.; Page, M.I. *J. Org. Chem.* ***2011***, *76*, 1425.
[31] Erden, I.; Gronert, S.; Keeffe, J.R.; Ma, J.; Ocal, N.; Gärtner, C.; Soukup, L.L. *J. Org. Chem.* ***2014***, *79*, 6410.
[32] Wu, C.-H.; Galabov, B.; Wu, J.I.-C.; Ilieva, S.; Schleyer, P.v.R.; Allen, W.D. *J. Am. Chem. Soc.* ***2014***, *136*, 3118.
[33] See reactions **10-60** to **10-68** and Bachrach, S.M.; Gailbreath, B.D. *J. Org. Chem.* ***2001***, *66*, 2005.
[34] Hoz, S.; Basch, H.; Wolk, J.L.; Hoz, T.; Rozental, E. *J. Am. Chem. Soc.* ***1999***, *121*, 7724.
[35] Yi, R.; Basch, H.; Hoz, S. *J. Org. Chem.* ***2002***, *67*, 5891.
[36] Van Bochove, M.A.; Swart, M.; Bickelhaupt, F.M. *J. Am. Chem. Soc.* ***2006***, *128*, 10738.
[37] Bento, A.P.; Bickelhaupt, F.M. *J. Org. Chem.* ***2007***, *72*, 2201.
[38] Grinblat, J.; Ben-Zion, M.; Hoz, S. *J. Am. Chem. Soc.* ***2001***, *123*, 10738.
[39] Pearson, R.G.; Dillon, R.L. *J. Am. Chem. Soc.* ***1953***, *75*, 2439.
[40] Yamataka, H.; Mishima, M. *J. Am. Chem. Soc.* ***1999***, *121*, 10223.

10.A.ii. The S_N1 Mechanism

The most ideal version of the S_N1 mechanism (*substitutional nucleophilic unimolecular*) consists of two steps[41] (once again, possible charges on the substrate and nucleophile are not shown):



The first step is a slow ionization of the substrate and is the rate-determining step. The second step is a rapid reaction between the intermediate carbocation and the nucleophile. There are, of course, transition states for both step 1 (R•••••••X) and step 2 (R^+•••••••Y).[42] The reactive nature of the carbocation can be expressed by its electrophilic character, or *electrophilicity*.[43] By contrast, the nucleophilic character of a nucleophile can be called the *nucleophilicity*.[44] A theoretical discussion concerning the origin of the electrophilicity concept was proposed by Parr et al.[45,46] In general, a good electrophile was characterized by having a high value of electronegativity (or a high value of electronic chemical potential), and a low value of chemical hardness (Sec. 8.E.i). The effect of substitution has been studied[47] in the context of superelectrophilicity (where carbocations are generated in superacidic media). Solvent effects have also been studied.[48] Electrophilicity scales have been proposed using other carbocations,[49] and there is an electrophilicity index.[50] Carbocation intermediates have been studied for the reaction $Ar_2CH{-}O_2CR \rightarrow Ar_2CH^+$, and the relative ionization rates with the same anionic leaving group do not correlate with the corresponding relative reactivities of the carbocation toward a common nucleophile.[51] The electrophilicity of 1,2-disubstituted ethylenes[52] and also indoles[53] has been examined. A density functional theory study has shown that nucleofugality appears related to group electrophilicity of the leaving group; electrofugality is related to the group nucleophilicity of the permanent group.[54] Note that a *nucleofuge* is a leaving group that retains the lone pair

[41] See Mayr, H.; Minegishi, S. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4493. For a discussion of dynamic processes associated with the SN1 mechanism, see Peters, K.S. *Chem. Rev.* ***2007***, *107*, 859.

[42] For a related computational study, see Ruff, F.; Farkas, Ö.; Kucsman, Á. *Eur. J. Org. Chem.* ***2006***, 5570.

[43] For an electrophilicity index, see Chattaraj, P.K.; Sarkar, U.; Roy, D.R. *Chem. Rev*. ***2006***, *106*, 2065; Chattaraj, P.K.; Roy, D.R. *Chem. Rev.* ***2007***, *107*, PR46; Chattaraj, P.K.; Giri, S.; Duley, S. *Chem. Rev.* ***2011***, *111*, PR43.

[44] For a discussion of the nucleophilicity (*N*) index, see Domingo, L.R.; Pérez, P. *Org. Biomol. Chem.* ***2011***, *9*, 7168. See also Bentley, T.W. *J. Phys. Org. Chem.* ***2013***, *26*, 977.

[45] Parr, R.G.; Szentpály, L.V.; Liu, S. *J. Am. Chem. Soc.* ***1999***, *121*, 1922. Also see Denekamp, C.; Sandlers, Y. *Angew. Chem. Int. Ed.* ***2006***, *45*, 2093.

[46] Parr's index has been used to describe both electrophilicity and nucleophilicity, see Kiyooka, S.-i.; Kaneno, D.; Fujiyama, R. *Tetrahedron Lett.* ***2013***, *54*, 339. Also see Kiyooka, S.-i.; Kaneno, D.; Fujiyama, R. *Tetrahedron* ***2013***, *69*, 4247.

[47] See Pérez, P. *J. Org. Chem.* ***2004***, *69*, 5048.

[48] Pérez, P.; Toro-Labbé, A.; Contreras, R. *J. Am. Chem. Soc.* ***2001***, *123*, 5527. For a discussion of the role of supercritical carbon dioxide, see Qiao, Y.X.; Theyssen, N.; Eifert, T.; Liauw, M.A.; Franciò, G.; Schenk, K.; Leitner, W.; Reetz, M.T. *Chem. Eur. J.* ***2017***, *23*, 3898.

[49] Pérez, P.; Toro-Labbé, A.; Aizman, A.; Contreras, R. *J. Org. Chem.* ***2002***, *67*, 4747.

[50] Chattaraj, P.K.; Sarkar, U.; Roy, D.R. *Chem. Rev.* ***2006***, *106*, 2065.

[51] Schaller, H.F.; Tishkov, A.A.; Feng, X.; Mayr, H. *J. Am. Chem. Soc.* ***2008***, *130*, 3012.

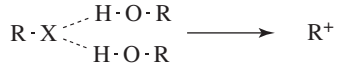
[52] Allgäuer, D.S.; Mayr, H. *Eur. J. Org. Chem.* ***2014***, 2956.

[53] Bandini, M. *Org. Biomol. Chem.* ***2013***, *11*, 5206.

[54] Ormazábal-Toledo, R.; Campodónico, P.R.; Contreras, R. *Org. Lett.* ***2011***, *13*, 822.

from its previous bond. An *electrofuge* is s a leaving group that does not retain the bonding pair of electrons from its previous bond.

Returning to the S_N1 mechanism, ionization of a leaving group to form the carbocation is always assisted by the solvent,[55] since the energy necessary to break the bond is largely recovered by solvation of R^+ and of X. For example, the ionization of *t*-BuCl to *t*-Bu^+ and Cl^- in the gas phase without a solvent requires 150 kcal mol^{-1} (630 kJ mol^{-1}). In the absence of a solvent, such a process simply would not take place, except at very high temperatures. In water, this ionization requires only 20 kcal mol^{-1} (84 kJ mol^{-1}). The difference is solvation energy. This means that the water is effectively "pulling" the leaving group away from the substrate. In cases where the role of the solvent is solely to assist the departure of the leaving group from the frontside, the mechanism is called *limiting* S_N1. In other words, there is a complete absence of backside (S_N2) participation by solvent molecules. There is kinetic and other evidence[56] that two molecules of a protic solvent form weak hydrogen bonds with X in order to pull the leaving group X away from RX.



In the IUPAC system, the S_N1 mechanism is $D_N + A_N$ or $D_N^{\ddagger} + A_N$ (where ‡ denotes the rate-determining step). The IUPAC designations for the S_N1 and S_N2 mechanisms thus clearly show the essential differences between them: A_ND_N indicates that bond breaking is concurrent with bond formation; $D_N + A_N$ shows that the former happens first.

In looking for evidence for the S_N1 mechanism, the first thought is that it should be a first-order reaction, following the rate law:

$$\text{rate} = k\,[\text{RX}] \tag{10-3}$$

Since the slow step involves only the substrate, the rate should be dependent only on the concentration of the substrate.[57] Although the solvent is necessary to assist in the process of ionization, it does not enter the rate expression, because it is present in large excess. However, the simple rate law given in Eq. (10-3) is not sufficient to account for all the data. Many cases are known where pure first-order kinetics are followed, but in many other cases more complicated kinetics are found. This fact can be explained by taking into account the reversibility of the first step. The X formed in this step competes with Y for the cation and the rate law must be modified as shown (see Chapter 6).

$$\begin{aligned} &\text{RX} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{R}^+ + \text{X} \\ &\text{R}^+ + \text{Y} \xrightarrow{k_2} \text{RY} \\ &\text{Rate} = \frac{k_1 k_2 [\text{RX}][\text{Y}]}{k_{-1}[\text{X}] + k_2[\text{Y}]} \end{aligned} \tag{10-4}$$

[55] See Okamoto, K. *Adv. Carbocation Chem.* ***1989***, *1*, 171. Also see Dvorko, G.F.; Ponomareva, E.A.; Kulik, N.I. *Russ. Chem. Rev.* ***1984***, *53*, 547.

[56] Blandamer, M.J.; Burgess, J.; Duce, P.P.; Symons, M.C.R.; Robertson, R.E.; Scott, J.M.W. *J. Chem. Res. (S)* ***1982***, 130.

[57] For a method of estimating the SN1 rate constant, see Matić, M.; Denegri, B.; Kronja, O. *J. Org. Chem.* ***2012***, *77*, 8986.

At the beginning of the reaction, when the concentration of X is very small, k_{-1}[X] is negligible compared with k_2[Y] and the rate law is reduced to Eq. (10-3). Indeed, S_N1 reactions generally do display simple first-order kinetics in their initial stages. Most kinetic studies of S_N1 reactions fall into this category. In the later stages of S_N1 solvolyses, [X] becomes large and Eq. (10-4) predicts that the rate should decrease. This is found to be the case for diarylmethyl halides,[58] although not for *tert*-butyl halides, which follow Eq. (10-3) for the entire reaction.[59] An explanation for this difference is that *tert*-butyl cations are less selective than the relatively stable diarylmethyl type (Sec. 5.A.ii). Although halide ion is a much more powerful nucleophile than water, there is much more water available since it is the solvent.[60] The selective diphenylmethyl cation survives many collisions with solvent molecules before combining with a reactive halide. However, some of the collisions with solvent lead to product, so despite the fact that the halide ion is more reactive, the slower reaction with solvents leads to product because of the overwhelming number of solvent molecules.

If the X formed during the reaction can decrease the rate, at least in some cases, it should be possible to *add* X from the outside and further decrease the rate in that way. This retardation of rate by addition of X is called the *common-ion effect* or the *mass-law effect*. Once again, addition of halide ions decreases the rate for diphenylmethyl but not for *tert*-butyl halides.

One factor that complicates the kinetic picture is the *salt effect*. An increase in ionic strength of the solution usually increases the rate of an S_N1 reaction (Sec. 10.G.iv). But when the reaction is of charge type II, where both Y and RX are neutral, so that X is negatively charged (and most solvolyses are of this charge type), the ionic strength increases as the reaction proceeds and this increases the rate. This effect must be taken into account in studying the kinetics. Incidentally, the fact that the addition of outside ions *increases* the rate of most S_N1 reactions makes especially impressive the *decrease* in rate caused by the common ion.

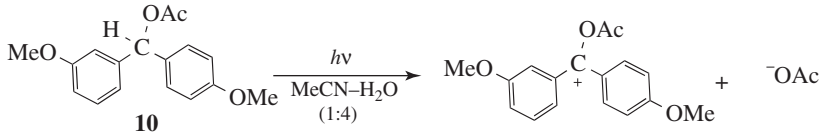
Note that the pseudo-first-order rate law for an S_N2 reaction in the presence of a large excess of Y (Eq. 10-1) is the same as that for an ordinary S_N1 reaction (Eq. 10-3). It is thus not possible to tell these cases apart by simple kinetic measurements. However, they can often be distinguished by the common-ion effect mentioned above. Addition of a common ion will not markedly affect the rate of an S_N2 reaction beyond the effect caused by other ions. Unfortunately, as seen above, not all S_N1 reactions show the common-ion effect, and this test fails for *tert*-butyl and similar cases.

Kinetic studies also provide other evidence for the S_N1 mechanism. One technique used ^{19}F NMR to follow the solvolysis of trifluoroacetyl esters.[61] If this mechanism operates essentially as shown above, the rate should be the same for a given substrate under a given set of conditions, *regardless of the identity of the nucleophile or its concentration*. In one experiment, benzhydryl chloride (Ph_2CHCl) was treated in SO_2 with the nucleophiles fluoride ion, pyridine, and triethylamine at several concentrations of each nucleophile.[62] In

[58] Benfey, O.T.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1952***, 2488.
[59] Bateman, L.C.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1940***, 960.
[60] In the experiments mentioned, the solvent was actually "70%" or "80%" aqueous acetone. The "80%" aqueous acetone consists of 4 volumes of dry acetone and 1 volume of water.
[61] Creary, X.; Wang, Y.-X. *J. Org. Chem.* ***1992***, *57*, 4761. Also see, Farcasiu, D.; Marino, G.; Harris, J.M.; Hovanes, B.A.; Hsu, C.S. *J. Org. Chem.* ***1994***, *59*, 154.
[62] Bateman, L.C.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1940***, 1011.

each case the initial rate of the reaction was approximately the same when corrections were made for the salt effect. The same type of behavior has been shown in a number of other cases, even when the reagents are as different in their nucleophilicities (Sec. 10.G.ii) as H_2O and HO^-.

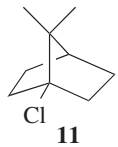
It is normally not possible to detect the carbocation intermediate of an S_N1 reaction directly, because its lifetime is very short. However, in the case of 3,4-dimethoxydiphenylmethyl acetate (**10**), and certain other substrates in polar solvents, it was possible to initiate the reaction photolytically, and under these conditions the UV spectra of the intermediate carbocations could be obtained,[63] providing additional evidence for the S_N1 mechanism. Further, addition of water to a colorless solution of $Ar_2CH{-}OAc$ (Ar = morpholinophenyl) in acetone, leads to direct observation of the intermediate carbocation.[64]



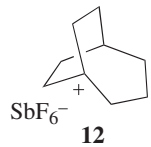
10

Further evidence for the S_N1 mechanism is that reactions run under S_N1 conditions fail or proceed very slowly at the bridgehead positions[13] of [2.2.1](norbornyl) systems[65] (e.g., 1-chloroapocamphane, **11**). If S_N1 reactions require carbocations and if carbocations must be planar or nearly planar, then it is no surprise that bridgehead 1-norbornyl carbon atoms, which cannot assume planarity, do not become the seat of carbocations. As an example, **11**, boiled for 21 hours with 30% KOH in 80% ethanol or for 48 hours with aqueous ethanolic silver nitrate gave no reaction in either case,[66] although analogous open-chain systems reacted readily. According to this theory, S_N1 reactions should be possible with larger rings, since near-planar carbocations might be expected there. This turns out to be the case. For example, [2.2.2] bicyclic systems undergo S_N1 reactions much faster than smaller bicyclic systems, although the reaction is still slower than with open-chain systems.[67] Proceeding to a still larger system, the bridgehead [3.2.2] cation **12** is actually stable enough to be kept in solution in $SbF_5{-}SO_3ClF$ at temperatures below $-50\ ^\circ C$[68] (see also Sec. 10.G, category 6). Other small bridgehead systems that undergo S_N1 reactions are the [3.1.1] (e.g., **13**)[69] and the cubyl (e.g., **14**)[70] systems. *Ab initio* calculations show that the cubyl cation, although it cannot be planar, requires less energy to form than the 1-norbornyl cation.[71] There are reactions where the cationic carbon is not coplanar with conjugating substituents (such as phenyl), and formation of the carbocation is more difficult but the reaction proceeds.[72]

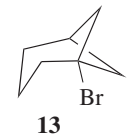
[63] McClelland, R.A.; Kanagasabapathy, V.M.; Steenken, S. *J. Am. Chem. Soc.* ***1988***, *110*, 6913.
[64] Schaller, H.F.; Mayr, H. *Angew. Chem. Int. Ed.* ***2008***, *47*, 3958.
[65] Fort Jr., R.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1973***, pp. 1783–1835.
[66] Bartlett, P.D.; Knox, L.H. *J. Am. Chem. Soc.* ***1939***, *61*, 3184.
[67] For synthetic examples, see Kraus, G.A.; Hon, Y. *J. Org. Chem.* ***1985***, *50*, 4605.
[68] Olah, G.A.; Liang, G.; Wiseman, J.R.; Chong, J.A. *J. Am. Chem. Soc.* ***1972***, *94*, 4927.
[69] Della, E.W.; Pigou, P.E.; Tsanaktsidis, J. *J. Chem. Soc., Chem. Commun.* ***1987***, 833.
[70] Eaton, P.E.; Yang, C.; Xiong, Y. *J. Am. Chem. Soc.* ***1990***, *112*, 3225; Moriarty, R.M.; Tuladhar, S.M.; Penmasta, R.; Awasthi, A.K. *J. Am. Chem. Soc.* ***1990***, *112*, 3228.
[71] Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* ***1990***, *112*, 3227.
[72] Lee, I.; Kim, N.D.; Kim, C.K. *Tetrahedron Lett.* ***1992***, *33*, 7881.



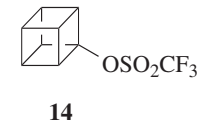
11



12

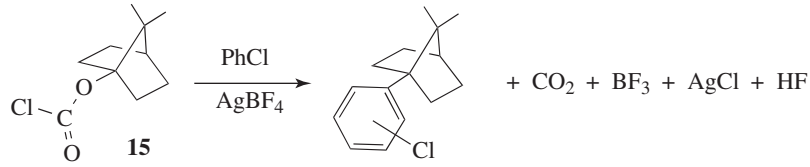


13



14

Certain nucleophilic substitution reactions that normally involve carbocations can take place at norbornyl bridgeheads[73] (though it is not certain that carbocations are actually involved in all cases) if the leaving group used is of the type that cannot function as a nucleophile (and thus come back) once it has gone. An example is the displacement of $ClCO_2$ in **15**. In this example,[74] chlorobenzene is the nucleophile (see **11-10**).



15

Additional evidence for the S_N1 mechanism, in particular, for the intermediacy of carbocations, is that solvolysis rates of alkyl chlorides in ethanol parallel carbocation stabilities, as determined by heats of ionization measured in superacid solutions (Sec. 5.A.ii).[75] It is important to note that some solvolysis reactions proceed by an S_N2 mechanism.[76]

10.A.iii. Ion Pairs in the S_N1 Mechanism[77]

As with the kinetic evidence, the stereochemical evidence for the S_N1 mechanism is less clear-cut than it is for the S_N2 mechanism.[78] If there is a free carbocation, it is planar (Sec. 5.A.ii), and the nucleophile should attack with equal facility from either side of the plane, resulting in complete racemization. Although many first-order substitutions do give complete racemization, many others do not. Typically there is 5–20% inversion, although in a few cases, a small amount of retention of configuration has been found. These and other results have led to the conclusion that in many S_N1 reactions at least some of the products are not formed from free carbocations but rather from *ion pairs*. According to this concept,[79] S_N1 reactions proceed in this manner:

16 **17** **18**

[73] White, E.H.; McGirk, R.H.; Aufdermarsh Jr., C.A.; Tiwari, H.P.; Todd, M.J. *J. Am. Chem. Soc.* ***1973***, *95*, 8107; Beak, P.; Harris, B.R. *J. Am. Chem. Soc.* ***1974***, *96*, 6363.

[74] For reactions with the OCOCl leaving group, see Beak, P. *Acc. Chem. Res.* ***1976***, *9*, 230.

[75] See Arnett, E.M.; Molter, K.E. *Acc. Chem. Res.* ***1985***, *18*, 339.

[76] Lee, I.; Lee, Y.S.; Lee, B.-S.; Lee, H.W. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 1441.

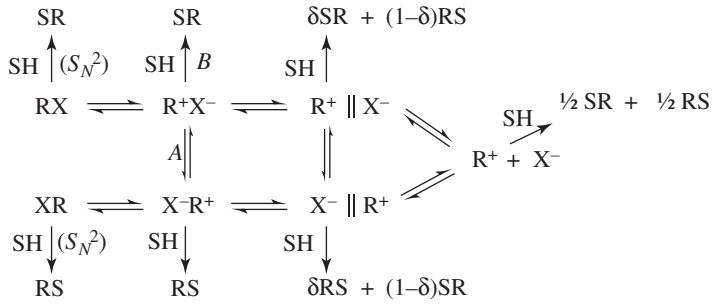
[77] See Beletskaya, I.P. *Russ. Chem. Rev.* ***1975***, *44*, 1067; Raber, D.J.; Harris, J.M.; Schleyer, P.v.R. in Szwarc, M. *Ions and Ion Pairs in Organic Reactions*, Vol. 2, Wiley, NY, ***1974***, pp. 247–374.

[78] For an alternative view, see Uggerud, E. *J. Org. Chem.* ***2001***, *66*, 7084.

[79] Proposed by Winstein, S.; Clippinger, E.; Fainberg, A.H.; Heck, R.; Robinson, G.C. *J. Am. Chem. Soc.* ***1956***, *78*, 328.

where **16** is an *intimate*, *contact*, or *tight ion pair*, **17** is a *loose*, or *solvent-separated ion pair*,[80] and **18** are the dissociated ions (which means that each ion is surrounded by molecules of solvent).[81] The reaction in which the intimate ion pair recombines to give the original substrate is referred to as *internal return*. The reaction products can result from attack by the nucleophile at any stage. In the intimate ion pair **16**, R^+ does not behave like the free cation of **18**. There is probably significant bonding between R^+ and X^- and asymmetry may well be maintained.[82] Here, X^- "solvates" the cation on the side from which it departed, while solvent molecules near **16** can only solvate it from the opposite side. Nucleophilic attack by a solvent molecule on **16** thus leads to inversion. It is noted that there is evidence for concerted pathways in some ion pairing reactions.[83]

Ignoring the possibilities of elimination or rearrangement (see Chapters 17 and 18), a complete picture of the possibilities for solvolysis reactions[84] in a solvent SH is represented by the scheme shown,[85] although in any particular case it is unlikely that all these reactions occur.



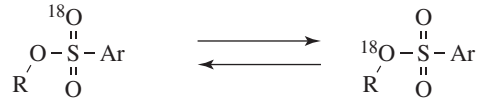
In this scheme RS and SR represent enantiomers, etc., and δ represents some fraction. The following are the possibilities. (i) Direct attack by SH on RX gives SR (complete inversion) in a straight S_N2 process. (ii) If the intimate ion pair $R^+ X^-$ is formed, the solvent can attack at this stage. This can lead to total inversion if reaction A does not take place or to a combination of inversion and racemization if there is competition between A and B. (iii) If the solvent-separated ion pair is formed, SH can attack here. The stereochemistry is not maintained as tightly and more racemization (perhaps total) is expected. (iv) Finally, if free R^+ is formed, it is planar, and attack by SH gives complete racemization.

The ion pair concept thus predicts that S_N1 reactions can display either complete racemization or partial inversion. The fact that this behavior is generally found is evidence that ion

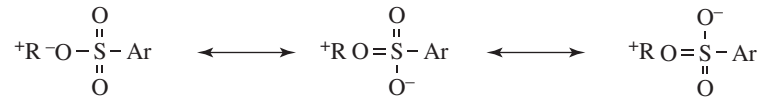
[80] Marcus, Y.; Hefter, G. *Chem. Rev.* ***2006***, *106*, 4585.
[81] See Kessler, H.; Feigel, M. *Acc. Chem. Res.* ***1982***, 15, 2.
[82] Fry, J.L.; Lancelot, C.J.; Lam, L.K.M.; Harris, J.M.; Bingham, R.C.; Raber, D.J.; Hall, R.E.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1970***, *92*, 2538.
[83] Savéant, J.-M. *J. Am. Chem. Soc.* ***2008***, *130*, 4732.
[84] See Richard, J.P.; Toteva, M.M.; Amyes, T.L. *Org. Lett.* ***2001***, *3*, 2225.
[85] Shiner Jr., V.J.; Fisher, R.D. *J. Am. Chem. Soc.* ***1971***, *93*, 2553.

pairs are involved in many S_N1 reactions. There is much other evidence for the intervention of ion pairs,[86] including ion–molecule pairs.[87]

1. The compound 2-octyl brosylate was labeled at the sulfone oxygen with ^{18}O and solvolyzed. The unreacted brosylate recovered at various stages of solvolysis had the ^{18}O considerably, although not completely, scrambled:[88]



In an intimate ion pair, the three oxygen atoms become equivalent:



Similar results were obtained with several other sulfonate esters.[89] The possibility must be considered that the scrambling resulted from ionization of one molecule of $ROSO_2Ar$ to R^+ and $ArSO_2O^-$ followed by attack by the $ArSO_2O^-$ ion on *another* carbocation or perhaps on a molecule of $ROSO_2Ar$ in an S_N2 process. However, this was ruled out by solvolyzing unlabeled substrate in the presence of labeled $HOSO_2Ar$. These experiments showed that there was some intermolecular exchange (3–20%), but not nearly enough to account for the amount of scrambling found in the original experiments. Similar scrambling was found in solvolysis of labeled carboxylic esters $R—^{18}O—COR'$, where the leaving group is $R'COO^-$.[90] In this case also, the external addition of $RCOO^-$ did not result in significant exchange. However, it has been proposed that the scrambling could result from a concerted process, not involving ion-pair intermediates, and there is some evidence for this view.[91]

2. The *special salt effect*. The addition of $LiClO_4$ or LiBr in the acetolysis of certain tosylates produced an initial steep rate acceleration that then decreased to the normal linear acceleration (caused by the ordinary salt effect).[92] This is interpreted as the ClO_4^- (or Br^-) trapping the solvent-separated ion pair to give $R^+ \,||\, ClO_4^-$, which, being unstable under these conditions, goes to product. Hence, the amount of solvent-separated ion pair that would have returned to the starting material is reduced, and the rate of the overall reaction is increased. The special salt effect has been directly observed by the use of picosecond absorption spectroscopy.[93]
3. The possibilities of racemization or inversion of the *product* RS of a solvolysis reaction were discussed previously. However, the formation of an ion pair followed

[86] See Ronco, G.; Petit, J.; Guyon, R.; Villa, P. *Helv. Chim. Acta* ***1988***, *71*, 648; Kevill, D.N.; Kyong, J.B.; Weitl, F.L. *J. Org. Chem.* ***1990***, *55*, 4304.
[87] Jia, Z.S.; Ottosson, H.; Zeng, X.; Thibblin, A. *J. Org. Chem.* ***2002***, *67*, 182.
[88] Diaz, A.F.; Lazdins, I.; Winstein, S. *J. Am. Chem. Soc.* ***1968***, *90*, 1904.
[89] See Fujio, M.; Sanematsu, F.; Tsuno, Y.; Sawada, M.; Takai, Y. *Tetrahedron Lett.* ***1988***, *29*, 93.
[90] Goering, H.L.; Hopf, H. *J. Am. Chem. Soc.* ***1971***, *93*, 1224 and references cited therein.
[91] Dietze, P.E.; Wojciechowski, M. *J. Am. Chem. Soc.* ***1990***, *112*, 5240.
[92] Cristol, S.J.; Noreen, A.L.; Nachtigall, G.W. *J. Am. Chem. Soc.* ***1972***, *94*, 2187.
[93] Simon, J.D.; Peters, K.S. *J. Am. Chem. Soc.* ***1982***, *104*, 6142.

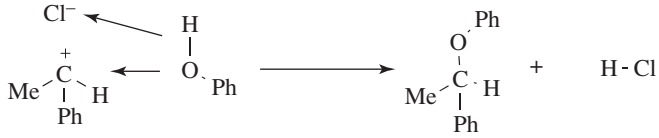
by internal return can also affect the stereochemistry of the *substrate* molecule RX. Cases have been found where internal return racemizes an original optically active RX, an example being solvolysis in aqueous acetone of α-*p*-anisylethyl *p*-nitrobenzoate,[94] while in other cases partial or complete retention is found, for example, solvolysis in aqueous acetone of *p*-chlorobenzhydryl *p*-nitrobenzoate.[95] Racemization of RX is presumably caused by the equilibrium pathway:

$$\text{R-X} \rightleftharpoons \text{R}^+\text{X}^- \rightleftharpoons \text{X}^-\text{R}^+ \rightleftharpoons \text{X-R}$$

Evidence for ion pairs includes some cases where internal return involves racemization; it has been shown that such racemization is *faster* than solvolysis. For example, optically active *p*-chlorobenzhydryl chloride racemizes ~30 times faster than it solvolyzes in acetic acid.[96]

Molecular orbital calculations[97] on *tert*-BuCl show that the C—Cl distance in the intimate ion pair is 2.9 Å and the onset of the solvent-separated ion pair takes place at about 5.5 Å (cf. the C—Cl bond length of 1.8 Å).

In a few cases, S_N1 reactions have been found to proceed with partial retention (20–50%) of configuration. Ion pairs have been invoked to explain some of these reactions.[98] For example, it has been proposed that the phenolysis of optically active α-phenylethyl chloride, in which the ether of net retained configuration is obtained, involves a four-center mechanism:



This conclusion is strengthened by the fact that partial retention was obtained in this system only with chloride or other neutral leaving groups; with leaving groups bearing a positive charge, which are much less likely to form hydrogen bonds with the solvent, no retention was found.[99] Partial retention can also arise when the ion pair is shielded at the back side by an additive such as acetonitrile, acetone, or aniline.[100]

The difference between the S_N1 and S_N2 mechanisms is in the timing of the steps. In the S_N1 mechanism, first X leaves, then Y attacks. In the S_N2 case, the two things happen simultaneously. One could imagine a third possibility: first the attack of Y and then the removal of X. This is not possible at a saturated carbon, since it would mean more than

[94] Goering, H.L.; Briody, R.G.; Sandrock, G. *J. Am. Chem. Soc.* ***1970***, *92*, 7401.
[95] Goering, H.L.; Briody, R.G.; Levy, J.F. *J. Am. Chem. Soc.* ***1963***, *85*, 3059.
[96] Winstein, S.; Gall, J.S.; Hojo, M.; Smith, S. *J. Am. Chem. Soc.* ***1960***, *82*, 1010. See also, Shiner Jr., V.J.; Hartshorn, S.R.; Vogel, P.C. *J. Org. Chem.* ***1973***, *38*, 3604.
[97] Jorgensen, W.L.; Buckner, J.K.; Huston, S.E.; Rossky, P.J. *J. Am. Chem. Soc.* ***1987***, *109*, 1891.
[98] Okamoto, K. *Pure Appl. Chem.* ***1984***, *56*, 1797. Also see Lee, I.; Kim, H.Y.; Lee, H.W.; Kim, I.C. *J. Phys. Org. Chem.* ***1989***, *2*, 35.
[99] Okamoto, K.; Kinoshita, T.; Shingu, H. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 1545.
[100] Kinoshita, T.; Ueno, T.; Ikai, K.; Fujiwara, M.; Okamoto, K. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 3273; Kinoshita, T.; Komatsu, K.; Ikai, K.; Kashimura, K.; Tanikawa, S.; Hatanaka, A.; Okamoto, K. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 1875.

eight electrons in the outer shell of carbon. However, this type of mechanism is possible and indeed occurs at other types of substrate (Sec. 10.F; Chapter 13).

10.A.iv. Mixed S_N1 and S_N2 Mechanisms

Some reactions of a given substrate under a given set of conditions display all the characteristics of S_N2 mechanisms; other reactions seem to proceed by S_N1 mechanisms, but cases are found that cannot be characterized so easily. There seems to be something in between, a mechanistic "borderline" region.[101] At least two broad theories have been devised to explain these phenomena. One theory holds that intermediate behavior is caused by a mechanism that is neither "pure" S_N1 nor "pure" S_N2, but some "in-between" type. According to the second theory, there is no intermediate mechanism at all, and borderline behavior is caused by simultaneous operation, in the same flask, of both the S_N1 and S_N2 mechanisms; that is, some molecules react by the S_N1, while others react by the S_N2 mechanism.

One formulation of the intermediate-mechanism theory is that of Sneen.[102] The formulation is in fact very broad and applies not only to borderline behavior, but to all nucleophilic substitutions at a saturated carbon.[103]

According to Sneen, all S_N1 and S_N2 reactions can be accommodated by one basic mechanism (the *ion-pair mechanism*). The substrate first ionizes to an intermediate ion pair that is then converted to products:

$$\mathrm{RX} \underset{}{\overset{k_1}{\rightleftharpoons}} \mathrm{R^+\ X^-} \overset{k_2}{\rightleftharpoons} \text{Products}$$

The difference between the S_N1 and S_N2 mechanisms is that in the former case the *formation* of the ion pair (k_1) is rate determining, while in the S_N2 mechanism its *destruction* (k_2) is rate determining. Borderline behavior is found where the rates of formation and destruction of the ion pair are of the same order of magnitude.[104] However, a number of investigators have asserted that these results could also be explained in other ways.[105]

There is evidence for the Sneen formulation where the leaving group has a positive charge. In this case, there is a cation–molecule pair ($\mathrm{RX^+ \rightarrow R^+\ X^-}$),[106] instead of the ion pair that would be present if the leaving group were uncharged. Katritzky and co-workers found that when such a reaction was run at varying high pressures, there was a minimum in the plot of rate constant versus pressure.[107] A minimum of this sort usually indicates a change in mechanism, and the interpretation in this case was that the normal S_N2 mechanism operates at higher pressures and the cation–molecule mechanism at lower pressures.

An alternative view that also favors an intermediate mechanism is that of Schleyer and co-workers,[108] who believe that the key to the problem is varying degrees of nucleophilic

[101] For borderline mechanisms in general, see Jencks, W.P. *Chem. Soc. Rev.* ***1982***, *10*, 345.
[102] Sneen, R.A.; Felt, G.R.; Dickason, W.C. *J. Am. Chem. Soc.* ***1973***, *95*, 638 and references cited therein; Sneen, R.A. *Acc. Chem. Res.* ***1973***, *6*, 46.
[103] See Kevill, D.N.; Degenhardt, C.R. *J. Am. Chem. Soc.* ***1979***, *101*, 1465.
[104] See Sneen, R.A. *Acc. Chem. Res.* ***1973***, *6*, 46; Stein, A.R. *Can. J. Chem.* ***1987***, *65*, 363.
[105] See McLennan, D.J. *Acc. Chem. Res.* ***1976***, *9*, 281; Katritzky, A.R.; Musumarra, G.; Sakizadeh, K. *J. Org. Chem.* ***1981***, *46*, 3831. For a reply, see Sneen, R.A.; Robbins, H.M. *J. Am. Chem. Soc.* ***1972***, *94*, 7868. See Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 442–450.
[106] See Thibblin, A. *J. Chem. Soc., Perkin Trans. 2* ***1987***, 1629.
[107] Katritzky, A.R.; Sakizadeh, K.; Gabrielsen, B.; le Noble, W.J. *J. Am. Chem. Soc.* ***1984***, *106*, 1879.
[108] Bentley, T.W.; Bowen, C.T.; Morten, D.H.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1981***, *103*, 5466.

solvent assistance to ion-pair formation. They have proposed an S_N2 (intermediate) mechanism.[109]

Among the experiments that have been cited for the viewpoint that borderline behavior results from simultaneous S_N1 and S_N2 mechanisms is the behavior of 4-methoxybenzyl chloride in 70% aqueous acetone.[110] In this solvent, hydrolysis[111] (that is, conversion to 4-methoxybenzyl alcohol) occurs by an S_N1 mechanism. When azide ions are added, the alcohol is still a product, but now 4-methoxybenzyl azide is another product. Addition of azide ions increases the rate of ionization (by the salt effect) but *decreases* the rate of hydrolysis. If more carbocations are produced but fewer go to the alcohol, then some azide must be formed by reaction with carbocations: an S_N1 process. However, the rate of ionization is always *less* than the total rate of reaction, so some azide must also form by an S_N2 mechanism.[110] Thus, the conclusion is that S_N1 and S_N2 mechanisms operate simultaneously.[112]

Some nucleophilic substitution reactions that seem to involve a "borderline" mechanism actually do not. Thus, one of the principal indications that a "borderline" mechanism is taking place has been the finding of partial racemization and partial inversion. However, this type of stereochemical behavior is quite consistent with a strictly S_N2 process.[113] The reaction of optically active 2-octyl brosylate in 75% aqueous dioxane gave inverted octan-2-ol in 77% optical purity[113] When sodium azide was added, 2-octyl azide was obtained along with the octan-2-ol, *but the latter was now 100% inverted*. It is apparent that, in the original case, octan-2-ol was produced by two different processes: an S_N2 reaction leading to inverted product, and another process in which some intermediate leads to racemization or retention. When azide ions were added, they scavenged this intermediate, so that the entire second process now went to produce azide, while the S_N2 reaction, unaffected by addition of azide, still went on to give inverted octan-2-ol. What is the nature of the intermediate in the second process? At first thought it is a carbocation, so that this would be another example of simultaneous S_N1 and S_N2 reactions. However, solvolysis of 2-octyl brosylate in pure methanol or of 2-octyl methanesulfonate in pure water, in the absence of azide ions, gave methyl 2-octyl ether or octan-2-ol, respectively, *with 100% inversion of configuration*, indicating that the mechanism in these solvents was pure S_N2. Since methanol and water are more polar than 75% aqueous dioxane and since an increase in polarity of solvent increases the rate of S_N1 reactions at the expense of S_N2 (Sec. 10.G.iii), it is extremely unlikely that any S_N1 process could occur in 75% aqueous dioxane. The intermediate in the second process is thus not a carbocation. Its nature is suggested by the fact that, in the absence of azide ions, the amount of inverted octan-2-ol decreased with an increasing percentage of dioxane in the solvent. Thus the intermediate is an oxonium ion (**19**) formed by an S_N2 attack *by dioxane*. This ion is not a stable product but reacts with water in another S_N2 process to produce octan-2-ol with retained configuration.

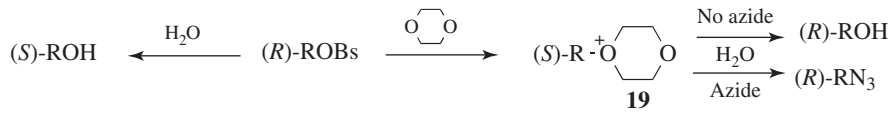
[109] Also see Laureillard, J.; Casadevall, A.; Casadevall, E. *Tetrahedron* ***1984***, *40*, 4921; *Helv. Chim. Acta* ***1984***, *67*, 352. For evidence against the SN2 (intermediate) mechanism, see Richard, J.P.; Amyes, T.L.; Vontor, T. *J. Am. Chem. Soc.* ***1991***, *113*, 5871.

[110] Amyes, T.L.; Richard, J.P. *J. Am. Chem. Soc.* ***1990***, *112*, 9507. Also see Katritzky, A.R.; Brycki, B.E. *J. Phys. Org. Chem.* ***1988***, *1*, 1; Stein, A.R. *Can. J. Chem.* ***1989***, *67*, 297.

[111] The relationship between electropilicity and rate coefficients is discussed in Aizman, A.; Contreras, R.; Pérez, P. *Tetrahedron* ***2005***, *61*, 889.

[112] See, however, Sneen, R.A.; Larsen, J.W. *J. Am. Chem. Soc.* ***1969***, *91*, 6031.

[113] Weiner, H.; Sneen, R.A. *J. Am. Chem. Soc.* ***1965***, *87*, 287.

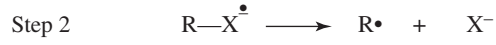


That part of the original reaction that resulted in retention of configuration[114] is thus seen to stem from two successive S_N2 reactions and not from any "borderline" behavior.[115]

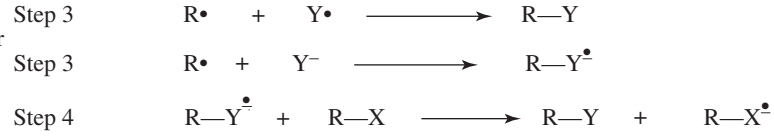
10.B. SET MECHANISMS

In certain reactions where nucleophilic substitutions would seem obviously indicated, there is evidence that radicals and/or radical ions are actually involved.[116] The first step in such a process is transfer of an electron from the nucleophile to the substrate to form a radical anion:

Mechanisms that begin this way are called SET *(single-electron transfer) mechanisms*.[117] Once formed, the radical ion cleaves:



The radicals formed in this way can go on to product by reacting with the Y• produced in Step 1 or with the original nucleophilic ion Y^-, in which case an additional step is necessary:



In the latter case, the radical ion $R{-}X^{\bullet-}$ is formed by Step 4 as well as by Step 1, so that a chain reaction (Sec. 14.A.i) can take place.

One type of evidence for an SET mechanism is the finding of some racemization. A free radical would likely result in a completely racemized product RY, but it has been suggested[118] that inversion can also take place in some SET processes. The suggestion is that

[114] According to this scheme, the configuration of the isolated RN_3 should be retained. It was, however, largely inverted, owing to a competing S_N2 reaction where N_3- directly attacks ROBs.

[115] See Streitwieser Jr., A.; Walsh, T.D.; Wolfe Jr., J.R. *J. Am. Chem. Soc.* ***1965***, *87*, 3682; Streitwieser Jr., A.; Walsh, T.D. *J. Am. Chem. Soc.* ***1965***, *87*, 3686; Beronius, P.; Nilsson, A.; Holmgren, A. *Acta Chem. Scand.* ***1972***, *26*, 3173. See also, Knier, B.L.; Jencks, W.P. *J. Am. Chem. Soc.* ***1980***, *102*, 6789.

[116] Bank, S.; Noyd, D.A. *J. Am. Chem. Soc.* ***1973***, *95*, 8203; Ashby, E.C.; Goel, A.B.; Park, W.S. *Tetrahedron Lett.* ***1981***, *22*, 4209. For discussions of the relationship between S_N2 and SET mechanisms, see Lewis, E.S. *J. Am. Chem. Soc.* ***1989***, *111*, 7576; Shaik, S.S. *Acta Chem. Scand.* ***1990***, *44*, 205.

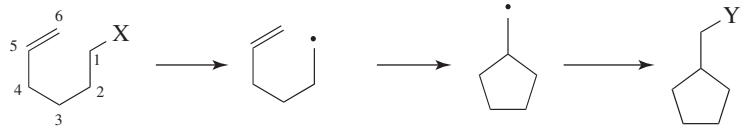
[117] See Savéant, J. *Adv. Phys. Org. Chem.* ***1990***, *26*, 1; Ashby, E.C. *Acc. Chem. Res.* ***1988***, *21*, 414. See also, Pross, A. *Acc. Chem. Res.* ***1985***, *18*, 212; Chanon, M. *Acc. Chem. Res.* ***1987***, *20*, 214; Rossi, R.A.; Pierini, A.B.; Peñéñory, A.B. *Chem. Rev.* ***2003***, *103*, 71.

[118] Daasbjerg, K.; Lund, T.; Lund, H. *Tetrahedron Lett.* ***1989***, *30*, 493.

in Step 1 the Y^- still approaches from the back side, even although an ordinary S_N2 mechanism will not follow, and that the radical R•, once formed, remains in a solvent cage with Y• still opposite X^-, so that Steps 1, 2, and 3 can lead to inversion. Reactions with SET mechanisms typically show predominant, although not 100%, inversion.

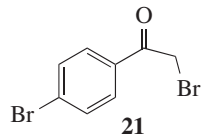
$$Y^- + R{-}X \longrightarrow \underbrace{\left[Y^\bullet\ R{-}X^{\bullet-}\right]}_{\text{solvent cage}} \longrightarrow \underbrace{\left[Y^\bullet\ R^\bullet\ X^-\right]}_{\text{solvent cage}} \longrightarrow Y{-}R + X^-$$

Other evidence cited[119] for SET mechanisms has been detection of radical or radical ion intermediates by ESR[120] or CIDNP; the finding that such reactions can take place at 1-norbornyl bridgeheads;[121] and the formation of cyclic side products when the substrate has a double bond in the 5,6 position (such substrates are called *radical probes*).



Free radicals with double bonds in this position are known to cyclize readily (Sec. 15.A.iii).[122]

20



21

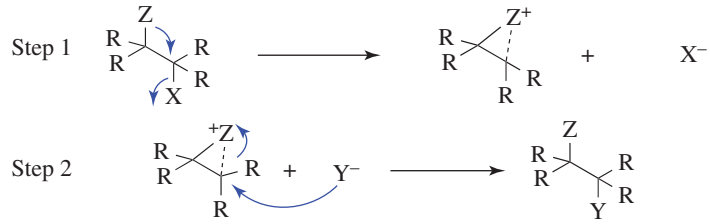
The SET mechanism is chiefly found where X = I or NO_2 (see **10-67**). A closely related mechanism, the $S_{RN}1$, takes place with aromatic substrates (Chapter 13).[123] In that mechanism the initial attack is by an electron donor, rather than a nucleophile. The $S_{RN}1$ mechanism has also been invoked for reactions of enolate anions with 2-iodobicyclo[4.1.0]heptane.[124] An example is the reaction of 1-iodobicyclo[2.2.1]heptane (**20**) with $NaSnMe_3$ or $LiPPh_2$, and some other nucleophiles, to give the substitution product.[125] Another is the reaction of bromo 4-bromoacetophenone (**21**) with Bu_4NBr in cumene.[126] The two mechanisms, S_N2 versus SET, have been compared and contrasted.[127] There are also reactions where it is reported that radical, carbanion, and carbene pathways occur simultaneously.[128]

[119] See also, Fuhlendorff, R.; Lund, T.; Lund, H.; Pedersen, J.A. *Tetrahedron Lett.* ***1987***, *28*, 5335.
[120] See, for example Russell, J.A.; Pecoraro, J.M. *J. Am. Chem. Soc.* ***1979***, *101*, 3331.
[121] Santiago, A.N.; Morris, D.G.; Rossi, R.A. *J. Chem. Soc., Chem. Commun.* ***1988***, 220.
[122] See Newcomb, M.; Curran, D.P. *Acc. Chem. Res.* ***1988***, *21*, 206; Newcomb, M. *Acta Chem. Scand.* ***1990***, *44*, 299. For replies to this criticism, see Ashby, E.C. *Acc. Chem. Res.* ***1988***, *21*, 414; Ashby, E.C.; Pham, T.N.; Amrollah-Madjdabadi, A.A. *J. Org. Chem.* ***1991***, *56*, 1596.
[123] In this book, there is a distinction between the SET and $S_{RN}1$ mechanisms. However, many workers use the designation SET to refer to the $S_{RN}1$, the chain version of the SET, or both.
[124] Nazareno, M.A.; Rossi, R.A. *J. Org. Chem.* ***1996***, *61*, 1645.
[125] Ashby, E.C.; Sun, X.; Duff, J.L. *J. Org. Chem.* ***1994***, *59*, 1270.
[126] Haberfield, P. *J. Am. Chem. Soc.* ***1995***, *117*, 3314.
[127] Shaik, S.S. *Acta Chem. Scand.* ***1990***, *44*, 205.
[128] Ashby, E.C.; Park, B.; Patil, G.S.; Gadru, K.; Gurumurthy, R. *J. Org. Chem.* ***1993***, *58*, 424.

The mechanisms so far considered can, in theory at least, operate on any type of saturated (or for that matter unsaturated) substrate. There are other mechanisms that are more limited in scope.

10.C. THE NEIGHBORING-GROUP MECHANISM[129]

It is occasionally found with certain substrates that (i) the rate of reaction is greater than expected and (ii) the configuration at a chiral carbon is *retained* and not inverted or racemized. In these cases, there is usually a group with an unshared pair of electrons β to the leaving group (or sometimes farther away). The mechanism operating in such cases is called the *neighboring-group mechanism* and consists essentially of two S_N2 substitutions, each causing an inversion so the net result is retention of configuration.[130] In the first step of this reaction, the neighboring group acts as a nucleophile, pushing out the leaving group but still retaining attachment to the molecule. In the second step, the external nucleophile displaces the neighboring group by a back-side attack.



The reaction obviously must go faster than if Y were attacking directly, since if the latter process were faster, *it* would be happening. The neighboring group Z is said to be lending *anchimeric assistance*. The rate law followed in the neighboring-group mechanism is the first-order law shown in Eq. (10-2) or (10-3); that is, Y does not take part in the rate-determining step.

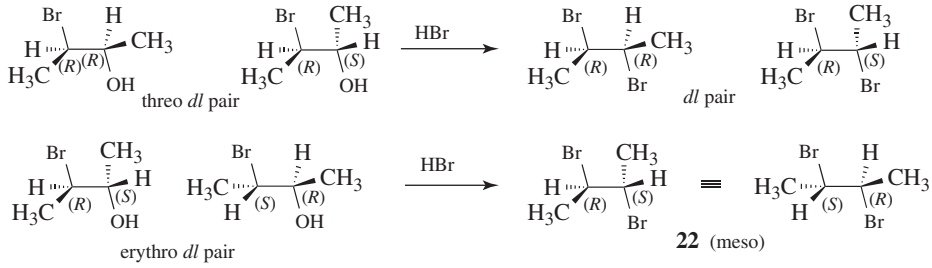
The reason attack by Z is faster than that by Y is that the group Z is more available. In order for Y to react, it must collide with the substrate, but Z is immediately available by virtue of its position. A reaction between the substrate and Y involves a large decrease in entropy of activation ($\Delta S^{\ddagger}$), since the reactants are far less free in the transition state than before. Reaction of Z involves a much smaller loss of $\Delta S^{\ddagger}$ (Sec. 6.D).[131]

It is not always easy to determine when a reaction rate has been increased by anchimeric assistance. In order to be certain, it is necessary to know what the rate would be without participation by the neighboring group. An obvious way to examine this question is to compare the rates of the reaction with and without the neighboring group, for example, $HOCH_2CH_2Br$ versus CH_3CH_2Br. However, this will certainly not give an accurate determination of the extent of participation, since the steric and field effects of H and OH are not the same. Furthermore, no matter what the solvent, the shell of solvent molecules that surrounds the polar protic OH group must differ greatly from that which surrounds the nonpolar hydrogen atom. Because of these considerations, it is desirable to have a large increase

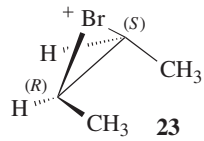
[129] See Capon, B.; McManus, S. *Neighboring Group Participation*, Vol. 1, Plenum, NY, ***1976***.
[130] McCortney, B.A.; Jacobson, B.M.; Vreeke, M.; Lewis, E.S. *J. Am. Chem. Soc.* ***1990***, *112*, 3554.
[131] See Page, M.I. *Chem. Soc. Rev.* ***1973***, *2*, 295.

in the rate, preferably > 50 fold, before a rate increase is attributed to neighboring-group participation.

The first important evidence for the existence of this mechanism was the demonstration that retention of configuration can occur if the substrate is suitable. It was shown that the *threo dl* pair of 3-bromobutan-2-ol when treated with HBr gave *dl*-2,3-dibromobutane, while the *erythro* pair gave the *meso* isomer (**22**).[132]

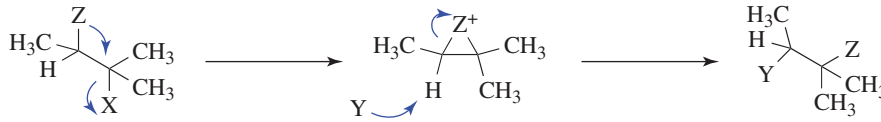


This result indicated that retention had taken place. Note that both products are optically inactive and so cannot be told apart by differences in rotation. The *meso* and *dl* dibromides have different boiling points and different indexes of refraction and were identified by these properties. Even more convincing evidence was that either of the two *threo* isomers alone gave not just one of the enantiomeric dibromides, but the *dl* pair. The reason for this is that the intermediate present after the attack by the neighboring group (**23**) is symmetrical, so the external nucleophile Br^- can attack both carbon atoms equally well. Intermediate **23** is a *bromonium ion*, the existence of which has been demonstrated in several types of reactions (see **15-35**).



23

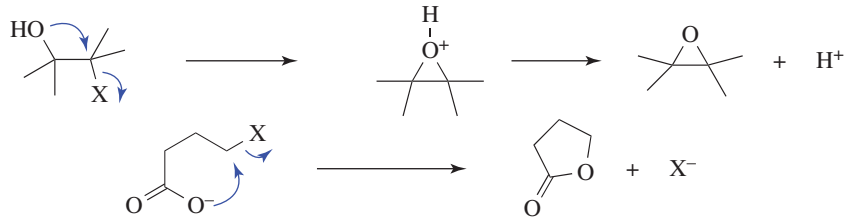
Although **23** is symmetrical, intermediates in most neighboring-group mechanisms are not, and it is therefore possible to get not a simple substitution product but a rearrangement. This will happen if Y attacks not the carbon atom from which X left, but the one to which Z was originally attached:



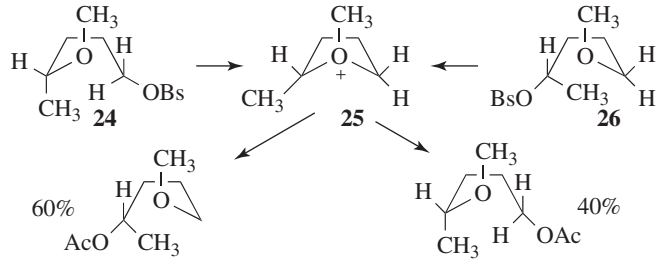
In such cases, substitution and rearrangement products are often produced together. For a discussion of rearrangements, see Chapter 18.

[132] Winstein, S.; Lucas, H.J. *J. Am. Chem. Soc.* ***1939***, *61*, 1576, 2845.

Another possibility is that the intermediate may be stable or may find some other way to stabilize itself. In such cases, Y never attacks at all and the product is cyclic. These are simple internal S_N2 reactions.[133] Two examples are formation of epoxides and lactones:



The fact that acetolysis of both 4-methoxy-1-pentyl brosylate (**24**) and 5-methoxy-2-pentyl brosylate (**26**) gave the same mixture of products is further evidence for participation by a neighboring group.[134] In this case, the intermediate **25** is common to both substrates.



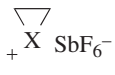
The neighboring-group mechanism operates only when the ring size is right for a particular type of Z. For example, for $MeO(CH_2)_nOBs$, neighboring-group participation was important for $n = 4$ or 5 (corresponding to a five- or six-membered intermediate), but not for $n = 2$, 3, or 6.[135] However, optimum ring size is not the same for all reactions, even with a particular Z. In general, the most rapid reactions occur when the ring size is three, five, or six, depending on the reaction type. The likelihood of four-membered ring neighboring-group participation is increased when there are alkyl groups α or β to the neighboring group.[136]

The following are some of the more important neighboring groups: COO^- (but not COOH), COOR, COAr, OCOR,[137] OR, OH, O^-,[138] NH_2, NHR, NR_2, NHCOR, SH, SR, S^-,[139] SO_2Ph,[140] I, Br, and Cl. The effectiveness of halogens as neighboring groups decreases in the order I > Br > Cl.[141] The Cl substituent is a very weak neighboring group,

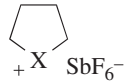
[133] For a theoretical treatment of strain energy release and intrinsic barriers for internal S_N2 reactions, see Wolk, J.L.; Rozental, E.; Basch, H.; Hoz, S. *J. Org. Chem.* ***2006***, *71*, 3876.
[134] Allred, E.L.; Winstein, S. *J. Am. Chem. Soc.* ***1967***, *89*, 3991, 3998.
[135] Allred, E.L.; Winstein, S. *J. Am. Chem. Soc.* ***1967***, *89*, 4012.
[136] Eliel, E.L.; Clawson, L.; Knox, D.E. *J. Org. Chem.* ***1985***, *50*, 2707; Eliel, E.L.; Knox, D.E. *J. Am. Chem. Soc.* ***1985***, *107*, 2946.
[137] See Wilen, S.H.; Delguzzo, L.; Saferstein, R. *Tetrahedron* ***1987***, *43*, 5089.
[138] See Perst, H. *Oxonium Ions in Organic Chemistry*, Verlag Chemie, Deerfield Beach, FL, ***1971***, pp. 100–127. Also see Francl, M.M.; Hansell, G.; Patel, B.P.; Swindell, C.S. *J. Am. Chem. Soc.* ***1990***, *112*, 3535.
[139] See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 141–145.
[140] Lambert, J.B.; Beadle, B.M.; Kuang, K. *J. Org. Chem.* ***1999***, *64*, 9241.
[141] Peterson, P.E. *Acc. Chem. Res.* ***1971***, *4*, 407, and references cited therein.

and can be shown to act in this way only when the solvent does not interfere. For example, when 5-chloro-2-hexyl tosylate is solvolyzed in acetic acid, there is little participation by the Cl, but when the solvent is changed to trifluoroacetic acid, which is much less nucleophilic, neighboring-group participation by the Cl becomes the major reaction pathway.[142] Thus, Cl acts as a neighboring group *only when there is need for it* (for other examples of the *principle of increasing electron demand*, see below, Sec. 10.C.i).

A number of intermediates of halogen participation (halonium ions),[143] for example, **27** and **28**, have been prepared as stable salts in SbF_5–SO_2 or SbF_5–SO_2ClF solutions.[144] Some have even been crystallized. Attempts to prepare four-membered homologs of **27** and **28** were not successful.[145] There is no evidence that F can act as a neighboring group.[136]

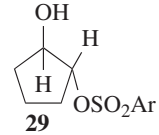


27



28

X = Br, Cl or I



29

The principle that a neighboring group lends assistance in proportion to the need for such assistance also applies to differences in leaving-group ability. Thus, *p*-$NO_2C_6H_4SO_2O$ (the nosylate group) is a better leaving group than *p*-$MeC_6H_4SO_2O$ (the tosylate group). Experiments have shown that the OH group in *trans*-2-hydroxycyclopentyl arenesulfonates **29** acts as a neighboring group when the leaving group is tosylate but not when it is nosylate, apparently because the nosylate group leaves so rapidly that it does not require assistance.[146]

10.C.i. Neighboring-Group Participation by π and σ Bonds: Nonclassical Carbocations[147]

For all the neighboring groups listed in the preceding section (Sec. 10.C), the nucleophilic attack is made by an atom with an unshared pair of electrons. In this section, neighboring-group participation by C═C π bonds and C─C and C─H σ bonds will be considered. There has been a great deal of controversy over whether such bonds can act as neighboring groups and about the existence and structure of the intermediates involved. These intermediates are called *nonclassical* (or *bridged*) carbocations. In *classical carbocations* (Chapter 5) the positive charge is *localized* on one carbon atom or delocalized by resonance involving an unshared pair of electrons or a double or triple bond in the allylic position. In a *nonclassical carbocation*[148] the positive charge is *delocalized* by a double or triple bond that is not in

[142] Peterson, P.E.; Bopp, R.J.; Chevli, D.M.; Curran, E.L.; Dillard, D.E.; Kamat, R.J. *J. Am. Chem. Soc.* ***1967***, *89*, 5902. See also, Reich, I.L.; Reich, H.J. *J. Am. Chem. Soc.* ***1974***, *96*, 2654.

[143] See Olah, G.A. *Halonium Ions*, Wiley, NY, ***1975***; Koster, G.F. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement D*, pt. 2, Wiley, NY, ***1983***, pp. 1265–1351.

[144] See Henrichs, P.M.; Peterson, P.E. *J. Org. Chem.* ***1976***, *41*, 362; Vancik, H.; Percac, K.; Sunko, D.E. *J. Chem. Soc., Chem. Commun.* ***1991***, 807.

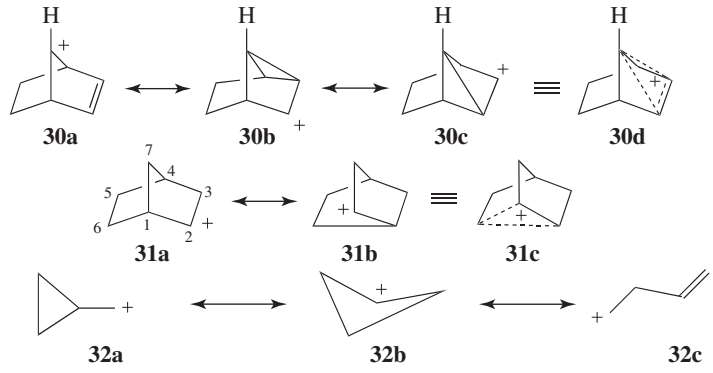
[145] Olah, G.A.; Bollinger, J.M.; Mo, Y.K.; Brinich, J.M. *J. Am. Chem. Soc.* ***1972***, *94*, 1164.

[146] Haupt, F.C.; Smith, M.R. *Tetrahedron Lett.* ***1974***, 4141.

[147] See Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***; Bartlett, P.D. *Nonclassical Ions*, W.A. Benjamin, NY, ***1965***. Barkhash, V.A. *Top. Curr. Chem.* ***1984***, *116/117*, 1; McManus, S.P.; Pittman Jr., C.U. in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 302–321.

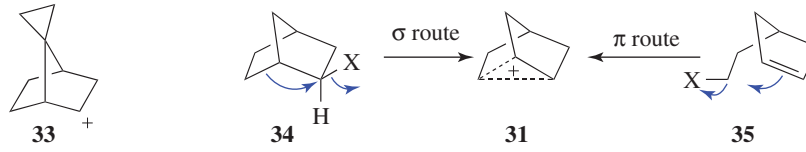
[148] Olah, G.A. *J. Org. Chem.* ***2005***, *70*, 2413.

the allylic position or by a single bond. Examples are the 7-norbornenyl cation (**30**), the norbornyl cation (**31**),[149] and the cyclopropylmethyl cation (**32**).



A cyclopropyl group (as in **33**) is capable of stabilizing the norbornyl cation, inhibiting this rearrangement.[150] Carbocation **30** is called a *homoallylic* carbocation, because in **30a** there is one carbon atom between the positively charged carbon and the double bond.

Many of these carbocations can be produced in more than one way if the proper substrates are chosen. For example, **31** can be generated by the departure of a leaving group from **34** or from **35**.[151]



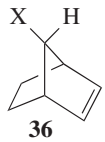
The first of these pathways is called the σ *route* to a nonclassical carbocation, because participation of a σ bond is involved. The second is called the π *route*.[152] The argument against the existence of nonclassical carbocations is essentially that the structures **30a** to **30c** (or **31a**, **31b**, etc.) are not canonical forms but real structures and that there is rapid equilibration among them. This debate remained an active area of interest for some reactions for many years.[153] In one study, the solvolysis and rearrangement of 2-bicyclo[3.2.2]nonanyl tosylate in methanol generated ethers derived from the 2-bicyclo[3.2.2]nonanyl and 2-bicyclo[3.3.1]nonanyl systems that were rationalized in terms of a classical carbocation.[154] Density functional and *ab initio* calculations indicated that the products of the 2-bicyclo[3.2.2]nonanyl tosylate solvolysis were found to have nonclassical structures.[155]

[149] Sieber, S.; Schleyer, P.v.R.; Vancik, H.; Mesic, M.; Sunko, D.E. *Angew. Chem. Int. Ed.* ***1993***, *32*, 1604; Schleyer, P.v.R.; Sieber, S. *Angew. Chem. Int. Ed.* ***1993***, *32*, 1606.
[150] Herrmann, R.; Kirmse, W. *Liebigs Ann. Chem.* ***1995***, 703.
[151] Bartlett, P.D.; Bank, S.; Crawford, R.J.; Schmid, G.H. *J. Am. Chem. Soc.* ***1965***, *87*, 1288.
[152] Winstein, S.; Carter, P. *J. Am. Chem. Soc.* ***1961***, *83*, 4485.
[153] For example, see Brunelle, P.; Sorensen, T.S.; Taeschler, C. *J. Org. Chem.* ***2001***, *66*, 7294.
[154] Okazaki, T.; Terakawa, E.; Kitagawa, T.; Takeuchi, K. *J. Org. Chem.* ***2000***, *65*, 1680.
[155] Smith, W.B. *J. Org. Chem.* ***2001***, *66*, 376.

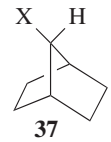
In discussing nonclassical carbocations, care must be taken to make the distinction between neighboring-group participation and the existence of nonclassical carbocations.[156] If a nonclassical carbocation exists in any reaction, then an ion with electron delocalization, as shown in the above examples, is a discrete reaction intermediate. If a carbon–carbon double bond or carbon–carbon single bond participates in the departure of the leaving group to form a carbocation, it may be that a nonclassical carbocation is involved, but there is no necessary relation. In any particular case either or both of these possibilities are possible.

In the following pages, some of the evidence bearing on the questions of the participation of π and σ bonds is considered, which bears on the existence of nonclassical carbocations,[157] although a thorough discussion is beyond the scope of this book.[116]

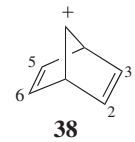
1. *C═C as a neighboring group.*[158] The most striking evidence that C═C can act as a neighboring group is that acetolysis of **36**-OTs is 10^{11} times faster than that of **37**-OTs and *proceeds with retention of configuration*.[159] The rate data alone do not necessarily prove that acetolysis of **36**-OTs involves a nonclassical intermediate (**30d**), but it is certainly strong evidence that the C═C group assists in the departure of the OTs. Evidence that **30** is indeed a nonclassical ion comes from an NMR study of the relatively stable norbornadienyl cation (**38**). The ^{1}H NMR spectrum shows that the 2 and 3 protons are not equivalent to the 5 and 6 protons.[160] Thus there is interaction between the charged carbon and one double bond, which is evidence for the existence of **30d**.[161]



36



37



38

In the case of **36**, the double bond is geometrically fixed in an especially favorable position for back-side attack on the carbon bearing the leaving group (hence the very large rate enhancement), but there is much evidence that other double bonds in the homoallylic position,[162] as well as in positions farther away,[163] can also lend anchimeric assistance, although generally with much lower rate ratios. One example of the latter is the compound β-(*syn*-7-norbornenyl)ethyl brosylate (**39**), which at

[156] This was pointed out by Cram, D.J. *J. Am. Chem. Soc.* ***1964***, *86*, 3767.

[157] See Brown, H.C. *The Nonclassical Ion Problem*, Plenum, NY, ***1977***. This book also includes rebuttals by Schleyer, P.v.R. See also, Brown, H.C. *Pure Appl. Chem.* ***1982***, *54*, 1783.

[158] See Story, P.R.; Clark Jr., B.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, pp. 1007–1060; Richey Jr., H.G. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 77–101.

[159] Winstein, S.; Shatavsky, M. *J. Am. Chem. Soc.* ***1956***, *78*, 592.

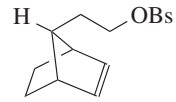
[160] Story, P.R.; Clark Jr., B.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, pp. 1026–1041; Lustgarten, R.K.; Brookhart, M.; Winstein, S. *J. Am. Chem. Soc.* ***1972***, *94*, 2347.

[161] See Gassman, P.G.; Doherty, M.M. *J. Am. Chem. Soc.* ***1982***, *104*, 3742 and references cited therein; Laube, T. *J. Am. Chem. Soc.* ***1989***, *111*, 9224.

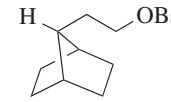
[162] See Schleyer, P.v.R.; Bentley, T.W.; Koch, W.; Kos, A.J.; Schwarz, H. *J. Am. Chem. Soc.* ***1987***, *109*, 6953; Fernández-Mateos, A.; Rentzsch, M.; Sánchez, L.R.; González, R.R. *Tetrahedron* ***2001***, *57*, 4873.

[163] See Ferber, P.H.; Gream, G.E. *Aust. J. Chem.* ***1981***, *34*, 1051; Orlovic, M.; Borcic, S.; Humski, K.; Kronja, O.; Imper, V.; Polla, E.; Shiner Jr., V.J. *J. Org. Chem.* ***1991***, *56*, 1874.

25 °C undergoes acetolysis ~140 000 times faster than the saturated analog **40**.[164] Triple bonds[165] and allenes[166] can also act as neighboring groups.

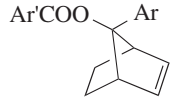


39

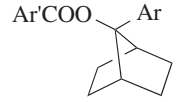


40

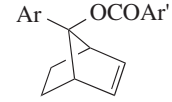
Evidence has been presented to show that participation by a potential neighboring group can be reduced or eliminated if an outside nucleophile is present that is more effective than the neighboring group in attacking the central carbon (see above), or if a sufficiently good leaving group is present (see above). In another example of the principle of increasing electron demand, Gassman and co-workers have shown that neighboring-group participation can also be reduced if the stability of the potential carbocation is increased. They found that the presence of a *p*-anisyl group at the 7 position of **36** and **37** exerts a powerful leveling effect on the rate differences. Thus, solvolysis in acetone–water at 85 °C of **38** was only ~2.5 times faster than that of the saturated compound **42**.[167] Furthermore, both **41** and its stereoisomer **43** gave the same mixture of solvolysis products, showing that the stereoselectivity in the solvolysis of **36** is not present here. The difference between **41** and **36** is that in the case of **41** the positive charge generated at the 7 position in the transition state is greatly stabilized by the *p*-anisyl group. Apparently, the stabilization by the *p*-anisyl group is so great that further stabilization that would come from participation by the C=C bond is not needed.[168] The use of a phenyl instead of a *p*-anisyl group is not sufficient to stop participation by the double bond completely, although it does reduce it.[169] These results essentially emphasize the previous conclusion that *a neighboring group lends anchimeric assistance only when there is sufficient demand for it*.[170] The π bond of a neighboring alkene group can assist solvolysis via π participation.[171]



41



42



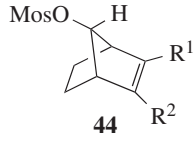
43

Ar = *p*-$MeOC_6H_4$
Ar' = *p*-$NO_2C_6H_4$

The ability of C=C to serve as a neighboring group can depend on its electron density. When the strongly electron-withdrawing CF_3 group was attached to a double bond carbon of **44**, the solvolysis rate was lowered by a factor of about 10^6.[172] A second CF_3 group had an equally strong effect. In this case, two CF_3 groups decrease

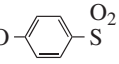
[164] Bly, R.S.; Bly, R.K.; Bedenbaugh, A.O.; Vail, O.R. *J. Am. Chem. Soc.* ***1967***, *89*, 880.
[165] See Peterson, P.E.; Vidrine, D.W. *J. Org. Chem.* ***1979***, *44*, 891; Rappoport, Z. *React. Intermed. (Plenum)* ***1983***, *3*, 440.
[166] Von Lehman, T.; Macomber, R. *J. Am. Chem. Soc.* ***1975***, *97*, 1531.
[167] Gassman, P.G.; Zeller, J.; Lamb, J.T. *Chem. Commun.* ***1968***, 69.
[168] See Olah, G.A.; Berrier, A.L.; Arvanaghi, M.; Prakash, G.K.S. *J. Am. Chem. Soc.* ***1981***, *103*, 1122.
[169] Gassman, P.G.; Fentiman Jr., A.F. *J. Am. Chem. Soc.* ***1969***, *91*, 1545; ***1970***, *92*, 2549.
[170] See Lambert, J.B.; Mark, H.W.; Holcomb, A.G.; Magyar, E.S. *Acc. Chem. Res.* ***1979***, *12*, 317.
[171] Malnar, I.; Juric, S.; Vrcek, V.; Gjuranovic, Z.; Mihalic, Z.; Kronja, O. *J. Org. Chem.* ***2002***, *67*, 1490.
[172] Gassman, P.G.; Hall, J.B. *J. Am. Chem. Soc.* ***1984***, *106*, 4267.

the electron density of the C=C bond to the point that the solvolysis rate for **44** ($R^1 = R^2 = CF_3$) was about the same as (actually ~17 times slower than) the rate for the saturated substrate **37** (X = OMos). Thus, the two CF_3 groups completely remove the ability of the C=C bond to act as a neighboring group.



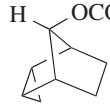
44

	Relative Rates
$R^1 = R^2 = H$	1.4×10^{12}
$R^1 = H, R^2 = CF_3$	1.5×10^{6}
$R^1 = R^2 = CF_3$	1

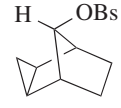
Mos = MeO  O_2S

2. *Cyclopropyl*[173] *as a neighboring group*.[174] In Sec. 4.Q.i the properties of a cyclopropane ring were shown to be similar to those of a double bond in some ways. Therefore it is not surprising that a suitably placed cyclopropyl ring can also be a neighboring group. Thus *endo-anti*-tricyclo[3.2.1.$0^{2,4}$]octan-8-yl *p*-nitrobenzoate (**45**) solvolyzed ~10^{14} times faster that the *p*-nitrobenzoate of **37**-OH.[175] Obviously, a suitably placed cyclopropyl ring can be even more effective[176] as a neighboring group than a double bond.[177] The need for suitable placement is emphasized by the fact that **47** solvolyzed only about five times faster than **37**-OBs,[178] while **46** solvolyzed three times *slower* than **37**-OBs.[179] In the case of **45** and of all other cases known where cyclopropyl lends considerable anchimeric assistance, the developing *p* orbital of the carbocation is orthogonal to the participating bond of the cyclopropane ring.[180]

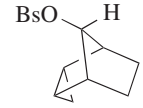
Ar = *p*-$NO_2C_6H_4$



45



46



47

An experiment designed to test whether a developing *p* orbital that would be parallel to the participating bond would be assisted by that bond showed no rate enhancement.[180] This is in contrast to the behavior of cyclopropane rings directly attached to positively charged carbons, where the *p* orbital is parallel to the plane of

[173] In this section, systems are considered in which at least one carbon separates the cyclopropyl ring from the carbon bearing the leaving group. For a discussion of systems in which the cyclopropyl group is directly attached to the leaving-group carbon, see below, category 4.b.

[174] For a review, see Haywood-Farmer, J. *Chem. Rev.* ***1974***, *74*, 315.

[175] Tanida, H.; Tsuji, T.; Irie, T. *J. Am. Chem. Soc.* ***1967***, *89*, 1953; Battiste, M.A.; Deyrup, C.L.; Pincock, R.E.; Haywood-Farmer, J. *J. Am. Chem. Soc.* ***1967***, *89*, 1954.

[176] For a competitive study of cyclopropyl versus double bond participation, see Lambert, J.B.; Jovanovich, A.P.; Hamersma, J.W.; Koeng, F.R.; Oliver, S.S. *J. Am. Chem. Soc.* ***1973***, *95*, 1570.

[177] Also see Gassman, P.G.; Creary, X. *J. Am. Chem. Soc.* ***1973***, *95*, 2729; Takakis, I.M.; Rhodes, Y.E. *Tetrahedron Lett.* ***1983***, *24*, 4959.

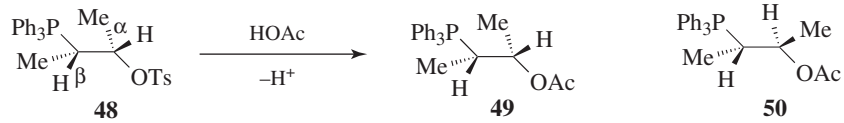
[178] Haywood-Farmer, J. *Chem. Rev.* ***1974***, *74*, 315.

[179] Haywood-Farmer, J.; Pincock, R.E. *J. Am. Chem. Soc.* ***1969***, *91*, 3020. Also see Rhodes, Y.E.; Takino, T. *J. Am. Chem. Soc.* ***1970***, *92*, 4469; Hanack, M.; Krause, P. *Liebigs Ann. Chem.* ***1972***, *760*, 17.

[180] Gassman, P.G.; Seter, J.; Williams, F.J. *J. Am. Chem. Soc.* ***1971***, *93*, 1673. See Chenier, P.J.; Jenson, T.M.; Wulff, W.D. *J. Org. Chem.* ***1982***, *47*, 770.

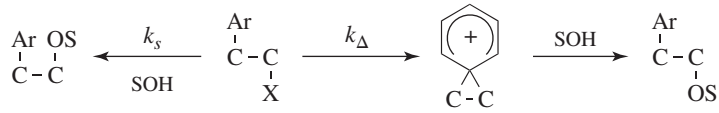
the ring (Sec. 5.A.ii, and category 4.b below). Rate enhancements, although considerably smaller, have also been reported for suitably placed cyclobutyl rings.[181]

3. *Aromatic rings as neighboring groups*.[182] There is a great deal of evidence that aromatic rings in the β position can function as neighboring groups.[183] Stereochemical evidence was obtained by solvolysis of L-*threo*-3-phenyl-2-butyl tosylate (**48**) in acetic acid.[184] Of the acetate product 96% was the *threo* isomer and only about 4% was *erythro*. Moreover, both the (+) and (−) *threo* isomers (**49** and **50**) were produced in approximately equal amounts (a racemic mixture).



48 **49** **50**

When solvolysis was conducted in formic acid, even less *erythro* isomer was obtained. This result is similar to that found on reaction of 3-bromobutan-2-ol with HBr (Sec. 10.C) and leads to the conclusion that configuration is retained because phenyl acts as a neighboring group. However, evidence from rate studies is not so simple. If β-aryl groups assist the departure of the leaving group, solvolysis rates should be enhanced. In general, they are not. However, solvolysis rate studies in 2-arylethyl systems are complicated by the fact that, for primary and secondary systems, two pathways can exist.[185] In one of these (designated k_Δ), the aryl, behaving as a neighboring group, pushes out the leaving group to give a bridged ion, called a *phenonium ion* (**51**), and is in turn pushed out by the solvent SOH, so the net result is substitution with retention of configuration (or rearrangement, if **51** is opened from the other side).



51

The other pathway (k_s) is simple S_N2 attack by the solvent at the leaving-group carbon. The net result is substitution with inversion and no possibility of rearrangement. Whether the leaving group is located at a primary or a secondary carbon, there is no crossover between these pathways; they are completely independent.[186] Both the k_Δ and k_s pathways are unimportant when the leaving group is at a tertiary carbon. In these cases the mechanism is S_N1 and open carbocations $ArCH_2CR_2^+$ are intermediates. This pathway is designated k_c. Which of the two pathways (k_s or

[181] See Ohkata, K.; Doecke, C.W.; Klein, G.; Paquette, L.A. *Tetrahedron Lett.* ***1980***, *21*, 3253.

[182] See Lancelot, L.A.; Cram, D.J.; Schleyer, P.v.R. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, pp. 1347–1483.

[183] Kevill, D.N.; D'Souza, M.J. *J. Chem. Soc., Perkin Trans. 2* ***1997***, 257.

[184] Cram, D.J. *J. Am. Chem. Soc.* ***1949***, *71*, 3863; ***1952***, *74*, 2129.

[185] Brookhart, M.; Anet, F.A.L.; Cram, D.J.; Winstein, S. *J. Am. Chem. Soc.* ***1966***, *88*, 5659; Lee, C.C.; Unger, D.; Vassie, S. *Can. J. Chem.* ***1972***, *50*, 1371.

[186] Brown, H.C.; Kim, C.J. *J. Am. Chem. Soc.* ***1971***, *93*, 5765.

TABLE 10.1 Approximate k_Δ/k_s ratios for acetolysis of p-$ZC_6H_4CH_2CH_2OTs$ at 90 °C[191]

Z	k_Δ/k_s
MeO	30
Me	11
H	1.3
Cl	0.3

Reprinted with permission from Jones, M.G.; Coke, J.L. *J. Am. Chem. Soc.* ***1969***, *91*, 4284. Copyright 1969 American Chemical Society.

k_Δ) predominates in any given case depends on the solvent and on the nature of the aryl group. As expected from the results we have seen for Cl as a neighboring group (see above), the k_Δ/k_s ratio is highest for solvents that are poor nucleophiles and so compete very poorly with the aryl group. For several common solvents the k_Δ/k_s ratio increases in the order $EtOH < CH_3CO_2H < HCO_2H < CF_3CO_2H$.[187] In accord with this, the following percentages of retention were obtained in solvolysis of 1-phenyl-2-propyl tosylate at 50 °C: solvolysis in EtOH 7%, CH_3CO_2H 35%, HCO_2H 85%.[187] This indicates that k_s predominates in EtOH (phenyl participates very little), while k_Δ predominates in HCO_2H. Trifluoroacetic acid is a solvent of particularly low nucleophilic power, and in this solvent the reaction proceeds entirely by k_Δ;[188] deuterium labeling showed 100% retention.[189] This case provides a clear example of neighboring-group rate enhancement by phenyl. The rate of solvolysis of $PhCH_2CH_2OTs$ at 75 °C in CF_3COOH is 3040 times the rate for CH_3CH_2OTs.[188]

With respect to the aromatic ring, the k_Δ pathway is electrophilic aromatic substitution (Chapter 11). Groups on the ring that activate that reaction (Sec. 11.B.i) are predicted to increase the rate of this pathway, and deactivating groups will decrease. This prediction has been borne out by several investigations. The *p*-nitro derivative of **48** solvolyzed in acetic acid 190 times slower than **48**, and there was much less retention of configuration; the acetate produced was only 7% *threo* and 93% *erythro*.[190] At 90 °C, acetolysis of p-$ZC_6H_4CH_2CH_2OTs$ gave the rate ratios shown in Table 10.1.[191] Throughout this series k_s is fairly constant, as it should be since it is affected only by the rather remote field effect of Z. It is k_Δ that changes substantially as Z is changed from activating to deactivating. The evidence is thus fairly clear that participation by aryl groups depends greatly on the nature of the group.

For some groups (e.g., *p*-nitrophenyl), in some solvents (e.g., acetic acid), there is essentially no neighboring-group participation at all,[192] while for others (e.g.,

[187] Diaz, A.; Winstein, S. *J. Am. Chem. Soc.* ***1969***, *91*, 4300. See also, Schadt, F.L.; Lancelot, C.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1978***, *100*, 228.

[188] Nordlander, J.E.; Kelly, W.J. *J. Am. Chem. Soc.* ***1969***, *91*, 996.

[189] Jablonski, R.J.; Snyder, E.I. *J. Am. Chem. Soc.* ***1969***, *91*, 4445.

[190] Thompson, J.A.; Cram, D.J. *J. Am. Chem. Soc.* ***1969***, *91*, 1778. See also Kingsbury, C.A.; Best, D.C. *Bull. Chem. Soc. Jpn.* ***1972***, *45*, 3440.

[191] Coke, J.L.; McFarlane, F.E.; Mourning, M.C.; Jones, M.G. *J. Am. Chem. Soc.* ***1969***, *91*, 1154; Jones, M.G.; Coke, J.L. *J. Am. Chem. Soc.* ***1969***, *91*, 4284. See also, Harris, J.M.; Schadt, F.L.; Schleyer, P.v.R.; Lancelot, C.J. *J. Am. Chem. Soc.* ***1969***, *91*, 7508.

[192] See Ando, T.; Shimizu, N.; Kim, S.; Tsuno, Y.; Yukawa, Y. *Tetrahedron Lett.* ***1973***, 117.

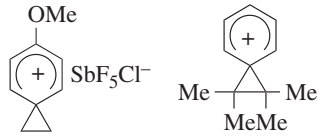
TABLE 10.2 Percent of product formed by the k_Δ pathway in solvolysis of *p*-$ZC_6H_4CH_2CH_2OTs$[193]

Z	Solvent	Percent by k_Δ
H	CH_3COOH	35–38
H	HCOOH	72–79
MeO	CH_3COOH	91–93
MeO	HCOOH	99

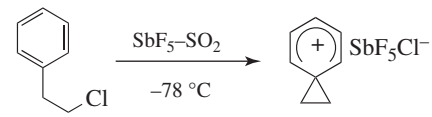
Reprinted with permission from Lancelot, C.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1969***, *91*, 4296. Copyright 1969 American Chemical Society.

p-methoxyphenyl), neighboring-group participation is substantial. The combined effect of solvent and structure is shown in Table 10.2,[193] where the figures shown were derived by three different methods. The decrease in neighboring-group effectiveness when aromatic rings are substituted by electron-withdrawing groups is reminiscent of the similar case of C=C bonds substituted by CF_3 groups (see above, category 1).

Several phenonium ions have been prepared as stable ions in solution where they can be studied by NMR, among them **52**,[194] **53**,[195] and the unsubstituted **51**.[196] These were prepared[197] by the method shown for **51**: treatment of the corresponding β-arylethyl chloride with SbF_5–SO_2 at low temperatures. These conditions are even more extreme than the solvolysis in CF_3COOH mentioned earlier. The absence of any nucleophile eliminates not only the k_s pathways but also nucleophilic attack on **51**. Although **51** is not in equilibrium with the open-chain ion $PhCH_2CH_2^+$ (which is primary and hence unstable), **53** is in equilibrium with the open-chain tertiary ions $PhCMe_2C^+Me_2$ and PhC^+MeCMe_3, although only **53** is present in appreciable concentration.



52 **53**



51

Proton and ^{13}C NMR show that **51**, **52**, and **53** are classical carbocations where the only resonance is in the six-membered ring. The three-membered ring is a normal cyclopropane ring that is influenced only to a relatively small extent by the positive charge on the adjacent ring. Nuclear magnetic resonance spectra show that the six-membered rings have no aromatic character but are similar in structure to the arenium

[193] Lancelot, C.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1969***, *91*, 4291, 4296; Lancelot, C.J.; Harper, J.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1969***, *91*, 4294; Schleyer, P.v.R.; Lancelot, C.J. *J. Am. Chem. Soc.* ***1969***, *91*, 4297.

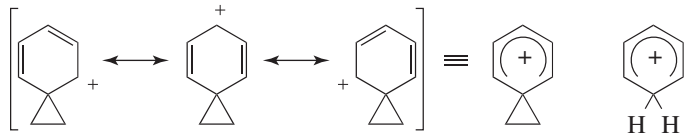
[194] Ramsey, B.; Cook Jr., J.A.; Manner, J.A. *J. Org. Chem.* ***1972***, *37*, 3310.

[195] Olah, G.A.; Comisarow, M.B.; Kim, C.J. *J. Am. Chem. Soc.* ***1969***, *91*, 1458. See, however, Ramsey, B.; Cook Jr., J.A.; Manner, J.A. *J. Org. Chem.* ***1972***, *37*, 3310.

[196] Olah, G.A.; Spear, R.J.; Forsyth, D.A. *J. Am. Chem. Soc.* ***1976***, *98*, 6284.

[197] See Olah, G.A.; Singh, B.P.; Liang, G. *J. Org. Chem.* ***1984***, *49*, 2922; Olah, G.A.; Singh, B.P. *J. Am. Chem. Soc.* ***1984***, *106*, 3265.

ions, for example **54**, that are intermediates in electrophilic aromatic substitution (Chapter 11).

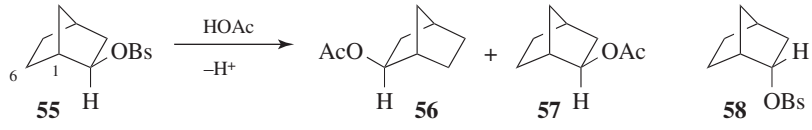


54

A number of phenonium ions, including **51**, have also been reported to be present in the gas phase, where their existence has been inferred from reaction products and from ^{13}C labeling.[198]

It is thus clear that β-aryl groups can function as neighboring groups.[199] Much less work has been done on aryl groups located in positions farther away from the leaving group, but there is evidence that these too can lend anchimeric assistance.[200]

4. *The carbon–carbon single bond as a neighboring group*.[201]
   a. *The 2-norbornyl system*. In the investigations to determine whether a C—C σ bond can act as a neighboring group, by far the greatest attention has been paid to the 2-norbornyl system.[202] Winstein and Trifan found that solvolysis in acetic acid of optically active *exo*-2-norbornyl brosylate (**55**; OBs = brosylate) gave a racemic mixture of the two *exo* acetates; no *endo* isomers were formed:[203]



55 **56** **57** **58**

Furthermore, **55** solvolyzed ~350 times faster than its *endo* isomer **58**. Similar high *exo*/*endo* rate ratios have been found in many other [2.2.1] systems. These two results (that solvolysis of an optically active *exo* isomer gave only racemic *exo* isomers and the high *exo*/*endo* rate ratio) were interpreted by Winstein, et al. as indicating that the 1,6 bond assists in the departure of the leaving group and that a nonclassical intermediate (**59**) is involved.

[198] Mishima, M.; Tsuno, Y.; Fujio, M. *Chem. Lett.* ***1990***, 2277.

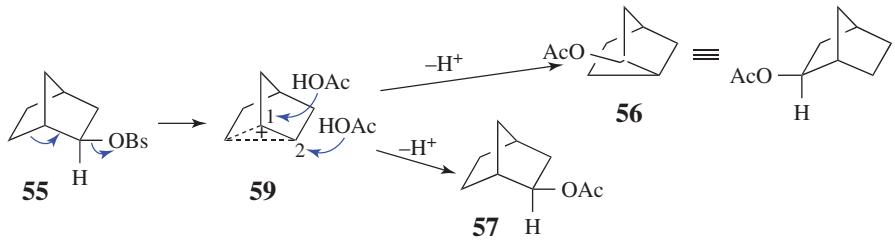
[199] See Tanida, H. *Acc. Chem. Res.* ***1968***, *1*, 239; Fujio, M.; Goto, M.; Seki, Y.; Mishima, M.; Tsuno, Y.; Sawada, M.; Takai, Y. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 1097. See Scheppele, S.E. *Chem. Rev.* ***1972***, *72*, 511 (p. 522).

[200] Jackman, L.M.; Haddon, V.R. *J. Am. Chem. Soc.* ***1974***, *96*, 5130; Gates, M.; Frank, D.L.; von Felten, W.C. *J. Am. Chem. Soc.* ***1974***, *96*, 5138; Ando, T.; Yamawaki, J.; Saito, Y. *Bull. Chem. Soc. Jpn.* ***1978***, *51*, 219.

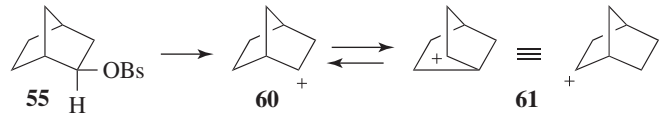
[201] See Olah, G.A. *Angew. Chem. Int. Ed.* ***1973***, *12*, 173 (pp. 192–198).

[202] See Olah, G.A.; Prakash, G.K.S.; Williams, R.E. *Hypercarbon Chemistry*, Wiley, NY, ***1987***, pp. 157–170; Grob, C.A. *Angew. Chem. Int. Ed.* ***1982***, *21*, 87; Sargent, G.D. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, pp. 1099–1200; Gream, G.E. *Rev. Pure Appl. Chem.* ***1966***, *16*, 25. Also see Kirmse, W. *Acc. Chem. Res.* ***1986***, *19*, 36. See also, Ref. 190.

[203] Winstein, S.; Clippinger, E.; Howe, R.; Vogelfanger, E. *J. Am. Chem. Soc.* ***1965***, *87*, 376.



They reasoned that solvolysis of the *endo* isomer **58** is not assisted by the 1,6 bond because it is not in a favorable position for back-side attack, and that consequently solvolysis of **58** takes place at a "normal" rate. Therefore the much faster rate for the solvolysis of **55** must be caused by anchimeric assistance. The stereochemistry of the product is also explained by the intermediacy of **59**, since in **59** the 1 and 2 positions are equivalent and would be attacked by the nucleophile with equal facility, but only from the *exo* direction in either case. Incidentally, acetolysis of **58** also leads exclusively to the *exo* acetates (**56** and **57**), so that in this case Winstein, et al. postulated that a classical ion (**60**) is first formed and then converted to the more stable **59**.



Evidence for this interpretation is that the product from solvolysis of **58** is not racemic but contains somewhat more **57** than **56** (corresponding to 3–13% inversion, depending on the solvent),[203] suggesting that when **60** is formed, some of it goes to give **57** before it can collapse to **59**.

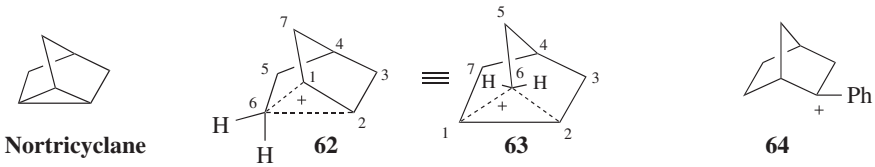
The concepts of σ participation and the nonclassical ion **59** were challenged by Herbert C. Brown,[157] who suggested that the two results can also be explained by postulating that **55** solvolyzes without participation of the 1,6 bond to give the classical ion **60** which is in rapid equilibrium with **61**. This rapid interconversion has been likened to the action of a windshield wiper.[204] Obviously, in going from **60** to **61** and back again, **59** must be present, but in Brown's view it is a transition state and not an intermediate. Brown's explanation for the stereochemical result was that exclusive *exo* attack is a property to be expected from any 2-norbornyl system, not only for the cation but even for reactions not involving cations, because of steric hindrance to attack from the *endo* side. There is a large body of data that shows *exo* attack on norbornyl systems is fairly general in many reactions. A racemic mixture will be obtained if **60** and **61** are present in equal amounts, since they are equivalent and *exo* attack on **60** and **61** gives, respectively, **57** and **56**. Brown explained the high *exo*/*endo* rate ratios by contending that it is the *exo* rate that is normal and the *endo* rate is abnormally *low*, because of steric hindrance to removal of the leaving group in that direction.[205]

[204] For another view, see Bielmann, R.; Fuso, F.; Grob, C.A. *Helv. Chim. Acta* ***1988***, *71*, 312; Flury, P.; Grob, C.A.; Wang, G.Y.; Lennartz, H.; Roth, W.R. *Helv. Chim. Acta* ***1988***, *71*, 1017.

[205] See Menger, F.M.; Perinis, M.; Jerkunica, J.M.; Glass, L.E. *J. Am. Chem. Soc.* ***1978***, *100*, 1503.

A vast amount of work has been done[206] on solvolysis of the 2-norbornyl system in an effort to determine whether the 1,6 bond participates and whether **59** is an intermediate. Most,[207] although not all,[208] chemists now accept the intermediacy of **59**.

Besides the work done on solvolysis of 2-norbornyl compounds, the 2-norbornyl cation has also been extensively studied at low temperatures; there is much evidence that under these conditions the ion is definitely nonclassical. Olah and co-workers have prepared the 2-norbornyl cation in stable solutions at temperatures below − 150 °C in SbF_5–SO_2 and FSO_3H–SbF_5–SO_2, where the structure is static and hydride shifts are absent.[209,210] Studies by proton and ^{13}C NMR, as well as by laser Raman spectra and X-ray electron spectroscopy, led to the conclusion[210] that under these conditions the ion is nonclassical.[211] A similar result has been reported for the 2-norbornyl cation in the solid state where at 77 K and even 5 K, ^{13}C NMR spectra gave no evidence of the freezing out of a single classical ion.[212]



Olah and co-workers represented the nonclassical structure as a corner-protonated nortricyclane (**62**); the symmetry is better seen when the ion is drawn as in **63**. Almost all the positive charge resides on C-1 and C-2 and very little on the bridging carbon C-6. Other evidence for the nonclassical nature of the 2-norbornyl cation in stable solutions comes from heat of reaction measurements that show that the 2-norbornyl cation is more stable (by ∼6–10 kcal mol^{-1} or 25–40 kJ mol^{-1}) than would be expected without the bridging.[213] Studies of IR spectra of the 2-norbornyl cation in the gas phase also show the nonclassical structure.[214] *Ab initio* calculations show that the nonclassical structure corresponds to an energy minimum.[215]

[206] See Lenoir, D.; Apeloig, Y.; Arad, D.; Schleyer, P.v.R. *J. Org. Chem.* ***1988***, *53*, 661; Grob, C.A. *Acc. Chem. Res.* ***1983***, *16*, 426; Brown, H.C. *Acc. Chem. Res.* ***1983***, *16*, 432; Walling, C. *Acc. Chem. Res.* ***1983***, *16*, 448.

[207] See Lajunen, M. *Acc. Chem. Res.* ***1985***, *18*, 254; Apeloig, Y.; Arad, D.; Schleyer, P.v.R. *J. Org. Chem.* ***1988***, *53*, 661.

[208] Also see Brown, H.C.; Ikegami, S.; Vander Jagt, D.L. *J. Org. Chem.* ***1985***, *50*, 1165; Nickon, A.; Swartz, T.D.; Sainsbury, D.M.; Toth, B.R. *J. Org. Chem.* ***1986***, *51*, 3736.

[209] The presence of hydride shifts (**18-1**) under solvolysis conditions has complicated the interpretation of the data.

[210] Olah, G.A. *Acc. Chem. Res.* ***1976***, *9*, 41; Saunders, M. *Acc. Chem. Res.* ***1983***, *16*, 440. See also, Johnson, S.A.; Clark, D.T. *J. Am. Chem. Soc.* ***1988***, *110*, 4112.

[211] See Kramer, G.M.; Scouten, C.G. *Adv. Carbocation Chem.* ***1989***, *1*, 93. See, however, Olah, G.A.; Prakash, G.K.S.; Farnum, D.G.; Clausen, T.P. *J. Org. Chem.* ***1983***, *48*, 2146.

[212] Myhre, P.C.; Webb, G.G.; Yannoni, C.S. *J. Am. Chem. Soc.* ***1990***, *112*, 8991.

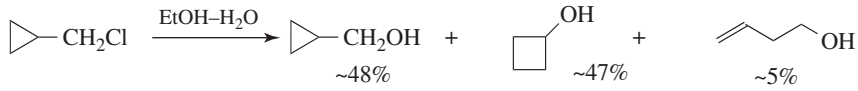
[213] See Lossing, F.P.; Holmes, J.L. *J. Am. Chem. Soc.* ***1984***, *106*, 6917 and references therein.

[214] Koch, W.; Liu, B.; DeFrees, D.J.; Sunko, D.E.; Vancik, H. *Angew. Chem. Int. Ed.* ***1990***, *29*, 183.

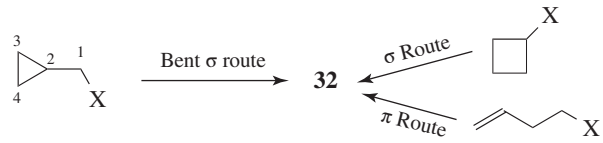
[215] See, for example Koch, W.; Liu, B.; DeFrees, D.J. *J. Am. Chem. Soc.* ***1989***, *111*, 1527.

The spectra of other norbornyl cations have also been investigated at low temperatures. Spectra of the tertiary 2-methyl- and 2-ethylnorbornyl cations show less delocalization,[216] and the 2-phenylnorbornyl cation (**64**) is essentially classical,[217] as are the 2-methoxy-[218] and 2-chloronorbornyl cations.[219] Recall (Sec. 5.A.ii) that methoxy and halo groups also stabilize a positive charge. The ^{13}C NMR data show that electron-withdrawing groups on the benzene ring of **64** cause the ion to become less classical, while electron-donating groups enhance the classical nature of the ion.[220]

b. *The cyclopropylmethyl system*. Apart from the 2-norbornyl system, the greatest amount of effort in the search for C—C participation has been devoted to the cyclopropylmethyl system.[221] It has long been known that cyclopropylmethyl substrates solvolyze with abnormally high rates and that the products often include not only unrearranged cyclopropylmethyl but also cyclobutyl and homoallylic compounds. An example is shown for cyclopropylcarbinyl chloride.[222]



Cyclobutyl substrates also solvolyze abnormally rapidly and give similar products. Indeed, computational studies on the cyclobutylmethyl cation suggest it is nonclassical. Furthermore, when the reactions are carried out with labeled substrates, considerable, although not complete, scrambling is observed. For these reasons, it has been suggested that a common intermediate (some kind of nonclassical intermediate, e.g., **32**, see above) is present in these cases. This common intermediate could then be obtained by three routes:



In recent years, much work has been devoted to the study of these systems, and it is apparent that matters are not so simple. Although there is much that is still not completely understood, some conclusions can be drawn.

[216] Olah, G.A.; DeMember, J.R.; Lui, C.Y.; White, A.M. *J. Am. Chem. Soc.* ***1969***, *91*, 3958. See also, Forsyth, D.A.; Panyachotipun, C. *J. Chem. Soc., Chem. Commun.* ***1988***, 1564.

[217] Olah, G.A. *Acc. Chem. Res.* ***1976***, *9*, 41. See also, Farnum, D.G.; Wolf, A.D. *J. Am. Chem. Soc.* ***1974***, *96*, 5166.

[218] Nickon, A.; Lin, Y. *J. Am. Chem. Soc.* ***1969***, *91*, 6861. See also, Montgomery, L.K.; Grendze, M.P.; Huffman, J.C. *J. Am. Chem. Soc.* ***1987***, *109*, 4749.

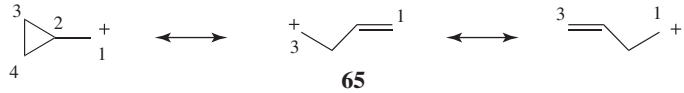
[219] Fry, A.J.; Farnham, W.B. *J. Org. Chem.* ***1969***, *34*, 2314.

[220] Farnum, W.B.; Botto, R.E.; Chambers, W.T.; Lam, B. *J. Am. Chem. Soc.* ***1978***, *100*, 3847. See also, Olah, G.A.; Berrier, A.L.; Prakash, G.K.S. *J. Org. Chem.* ***1982***, *47*, 3903.

[221] See in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, the articles by Richey Jr., H.G. pp. 1201–1294, and by Wiberg, K.B.; Hess Jr., B.A.; Ashe III, A.J. pp. 1295–1345; Sarel, S.; Yovell, J.; Sarel-Imber, M. *Angew. Chem. Int. Ed.* ***1968***, *7*, 577.

[222] Roberts, D.D.; Mazur, R.H. *J. Am. Chem. Soc.* ***1951***, *73*, 2509.

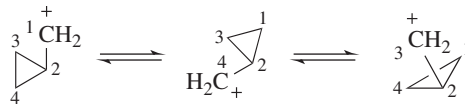
i. In the solvolysis of simple primary cyclopropylmethyl systems the rate is enhanced because of participation by the σ bonds of the ring.[223] The ion that forms initially is an unrearranged cyclopropylmethyl cation[224] that is *symmetrically* stabilized, that is, both the 2,3 and 2,4 σ bonds help stabilize the positive charge. As seen previously (Sec. 5.A.ii), a cyclopropyl group stabilizes an adjacent positive charge even better than a phenyl group. One way of representing the structure of this cation is as shown in **65**. Among the evidence that **65** is a symmetrical ion is that substitution of one or more methyl groups in the 3 and 4 positions increases the rate of solvolysis of cyclopropylcarbinyl 3,5-dinitrobenzoates by approximately a factor of 10 for *each* methyl group.[225] If only one of the σ bonds (say, the 2,3 bond) stabilizes the cation, then methyl substitution at the 3 position should increase the rate, and a second methyl group at the 3 position should increase it still more, but a second methyl group at the 4 position should have little effect.[226]



65

ii. The most stable geometry of simple cyclopropylmethyl cations is the bisected one shown in Sec. 5.A.ii. There is much evidence that in systems where this geometry cannot be obtained, solvolysis is greatly slowed.[227]

iii. Once a cyclopropylmethyl cation is formed, it can rearrange to two other cyclopropylmethyl cations:



This rearrangement, which accounts for the scrambling, is completely stereospecific.[228] The rearrangements probably take place through a nonplanar cyclobutyl cation intermediate or transition state. The formation of cyclobutyl and homoallylic products from a cyclopropylmethyl cation is also completely stereospecific. These products may arise by direct attack of the nucleophile on **65** or on the cyclobutyl cation intermediate.[229] A planar cyclobutyl cation is ruled out in both cases because it would be symmetrical and the stereospecificity would be lost.

[223] See Roberts, D.D.; Snyder Jr., R.C. *J. Org. Chem.* ***1979***, *44*, 2860, and references cited therein.

[224] Wiberg, K.B.; Ashe III, A.J. *J. Am. Chem. Soc.* ***1968***, *90*, 63.

[225] Schleyer, P.v.R.; van Dine, G.W. *J. Am. Chem. Soc.* ***1966***, *88*, 2321. See also, Kevill, D.N.; Abduljaber, M.H. *J. Org. Chem.* ***2000***, *65*, 2548.

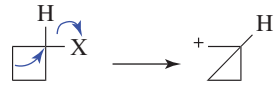
[226] See Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, the article by Wiberg, K.B.; Hess Jr., B.A.; Ashe III, A.J. pp. 1300–1303.

[227] See Rhodes, Y.E.; DiFate, V.G. *J. Am. Chem. Soc.* ***1972***, *94*, 7582. See, however, Brown, H.C.; Peters, E.N. *J. Am. Chem. Soc.* ***1975***, *97*, 1927.

[228] Majerski, Z.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1971***, *93*, 665.

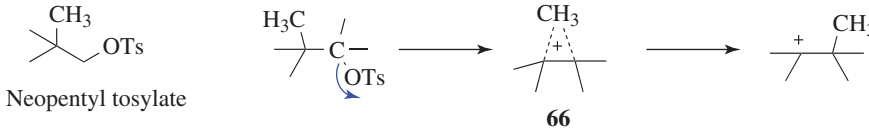
[229] Koch, W.; Liu, B.; DeFrees, D.J. *J. Am. Chem. Soc.* ***1988***, *110*, 7325; Saunders, M.; Laidig, K.E.; Wiberg, K.B.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1988***, *110*, 7652.

iv. The rate enhancement in the solvolysis of secondary cyclobutyl substrates is probably caused by participation by a bond leading directly to **65**, which accounts for the fact that solvolysis of cyclobutyl and of cyclopropylmethyl substrates often gives similar product mixtures. There is no evidence that requires cyclobutyl cations to be intermediates in most secondary cyclobutyl systems, although tertiary cyclobutyl cations can be solvolysis intermediates.



v. The unsubstituted cyclopropylmethyl cation has been generated in superacid solutions at low temperatures, where ^{13}C NMR spectra have led to the conclusion that it consists of a mixture of the bicyclobutonium ion **32** and the bisected cyclopropylmethyl cation **65**, in equilibrium with **32**.[230] Molecular orbital calculations show that these two species are energy minima, and that both have nearly the same energy.[229]

c. *Methyl as a neighboring group*. Both the 2-norbornyl and cyclopropylmethyl system contain a σ bond that is geometrically constrained to be in a particularly favorable position for participation as a neighboring group. However, there have been a number of investigations to determine whether a C—C bond can lend anchimeric assistance even in a simple open-chain compound, such as neopentyl tosylate.



Neopentyl tosylate

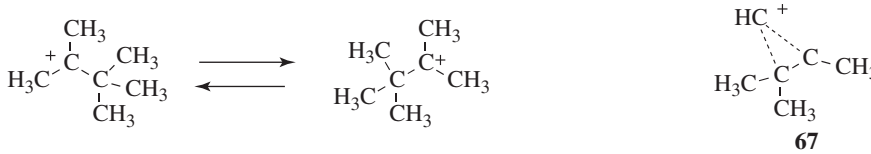
66

On solvolysis, neopentyl systems undergo almost exclusive rearrangement and **66** must lie on the reaction path, but the two questions that have been asked are: (i) is the departure of the leaving group concerted with the formation of the CH_3—C bond (e.g., does the methyl participate)? and (ii) is **66** an intermediate or only a transition state? With respect to the first question, there is evidence, chiefly from isotope effect studies, that indicates that the methyl group in the neopentyl system does indeed participate,[231] although it may not greatly enhance the rate. As to the second question, evidence that **66** is an intermediate is that small amounts of cyclopropanes (10–15%) can be isolated in these reactions.[232]

[230] Staral, J.S.; Yavari, I.; Roberts, J.D.; Prakash, G.K.S.; Donovan, D.J.; Olah, G.A. *J. Am. Chem. Soc.* ***1978***, *100*, 8016. See Myhre, P.C.; Webb, G.G.; Yannoni, C.S. *J. Am. Chem. Soc.* ***1990***, *112*, 8992.

[231] See Yamataka, H.; Ando, T.; Nagase, S.; Hanamura, M.; Morokuma, K. *J. Org. Chem.* ***1984***, *49*, 631. For an opposing view, see Zamashchikov, V.V.; Rudakov, E.S.; Bezbozhnaya, T.V.; Matveev, A.A. *J. Org. Chem. USSR* ***1984***, *20*, 11.

[232] Silver, M.S.; Meek, A.G. *Tetrahedron Lett.* ***1971***, 3579; Dupuy, W.E.; Hudson, H.R. *J. Chem. Soc., Perkin Trans. 2* ***1972***, 1715.

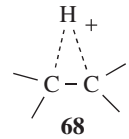


67

Cation **66** is a protonated cyclopropane and would give cyclopropane on loss of a proton.[233] In an effort to isolate a species that has structure **66**, the 2,3,3-trimethyl-2-butyl cation was prepared in superacid solutions at low temperatures.[234] However, ^{1}H and ^{13}C NMR, as well as Raman spectra, showed this to be a pair of rapidly equilibrating open ions. Of course, **67** must lie on the reaction path connecting the two open ions, but it is evidently a transition state and not an intermediate. However, evidence from X-ray photoelectron spectroscopy (XPS) showed that the 2-butyl cation is substantially methyl bridged.[235]

d. *Silylalkyl as a neighboring group.* Rates of solvolysis are enhanced in molecules that contain a silylalkyl or silylaryl group β to the carbon bearing the leaving group. This is attributed to formation of a cyclic transition state involving the silicon.[236]

5. *Hydrogen as a neighboring group*. The questions relating to hydrogen are similar to those relating to methyl. There is no question that hydride can migrate, but the two questions are: (i) does the hydrogen atom participate in the departure of the leaving group? and (ii) is **68** an intermediate or only a transition state?



68

There is some evidence that a β hydrogen can participate.[237] Evidence that **68** can be an intermediate in solvolysis reactions comes from a study of the solvolysis in trifluoroacetic acid of deuterated *sec*-butyl tosylate **69**. In this solvent of very low nucleophilic power, the products were an equimolar mixture of **70** and **71**,[238] but *no* **72** or **73** was found.

[233] For further discussions of protonated cyclopropanes, see Sec. **15.B.iv** and Sec. **18.A.ii**.

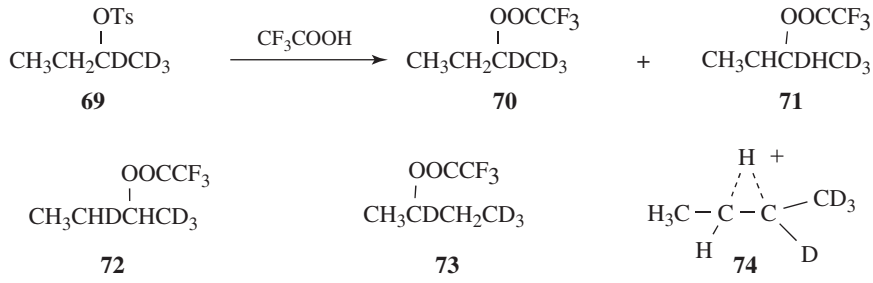
[234] Olah, G.A.; DeMember, J.R.; Commeyras, A.; Bribes, J.L. *J. Am. Chem. Soc.* ***1971***, *93*, 459.

[235] Johnson, S.A.; Clark, D.T. *J. Am. Chem. Soc.* ***1988***, *110*, 4112. See also, Carneiro, J.W.; Schleyer, P.v.R.; Koch, W.; Raghavachari, K. *J. Am. Chem. Soc.* ***1990***, *112*, 4064.

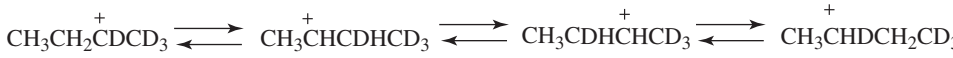
[236] Fujiyama, R.; Munechika, T. *Tetrahedron Lett.* ***1993***, *34*, 5907.

[237] See Buzek, P.; Schleyer, P.v.R.; Sieber, S.; Koch, W.; Carneiro, J.W. de M.; Vancik, H.; Sunko, D.E. *J. Chem. Soc., Chem. Commun.* ***1991***, 671; Imhoff, M.A.; Ragain, R.M.; Moore, K.; Shiner, V.J. *J. Org. Chem.* ***1991***, *56*, 3542.

[238] Dannenberg, J.J.; Barton, J.K.; Bunch, B.; Goldberg, B.J.; Kowalski, T. *J. Org. Chem.* ***1983***, *48*, 4524; Allen, A.D.; Ambidge, I.C.; Tidwell, T.T. *J. Org. Chem.* ***1983***, *48*, 4527.



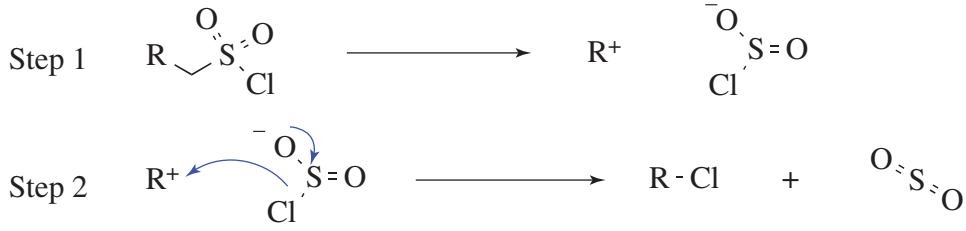
If this reaction did not involve neighboring hydrogen at all (pure S_N2 or S_N1), the product would be only **70**. On the other hand, if hydrogen does migrate, but only open cations are involved, then there should be an equilibrium among these four cations:



leading not only to **70** and **71**, but also to **72** and **73**. The results are most easily compatible with the intermediacy of the bridged ion **74**, which can then be attacked by the solvent equally at the 2 and 3 positions. Attempts to prepare **68** as a stable ion in superacid solutions at low temperatures have not been successful.[237]

10.D. THE S_Ni MECHANISM

In a few reactions, nucleophilic substitution proceeds with retention of configuration, even where there is no possibility of a neighboring-group effect. In the S_Ni mechanism (*substitution nucleophilic internal*), part of the leaving group must be able to attack the substrate, detaching itself from the rest of the leaving group in the process. The IUPAC designation is $D_N + A_ND_e$. The first step is the same as the very first step of the S_N1 mechanism: dissociation into an intimate ion pair.[239] But in the second step part of the leaving group attacks, necessarily from the front since it is unable to get to the rear, which results in retention of configuration.



[239] Lee, C.C.; Clayton, J.W.; Lee, C.C.; Finlayson, A.J. *Tetrahedron* ***1962***, *18*, 1395.

The example shown is the most important case of this mechanism yet discovered, since the reaction of alcohols with thionyl chloride to give alkyl halides usually proceeds in this way, with the first step in this case being

$$ROH + SOCl_2 \rightarrow ROSOCl$$

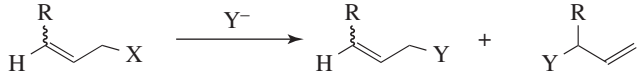
and these alkyl chlorosulfites can be isolated.

Evidence for this mechanism is as follows: the addition of pyridine to the mixture of alcohol and thionyl chloride results in the formation of alkyl halide with *inverted* configuration. Inversion results because the pyridine reacts with ROSOCl to give $ROSONC_5H_5$ before anything further can take place. The Cl^- freed in this process now attacks from the rear. The reaction between alcohols and thionyl chloride is second order, which is predicted by this mechanism, but the decomposition by simple heating of ROSOCl is first order.[240]

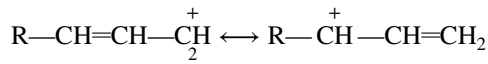
The S_Ni mechanism is relatively rare. Another example is the decomposition of ROCOCl (alkyl chloroformates) into RCl and CO_2.[241]

10.E. NUCLEOPHILIC SUBSTITUTION AT AN ALLYLIC CARBON: ALLYLIC REARRANGEMENTS

Allylic substrates rapidly undergo nucleophilic substitution reactions (Sec. 10.G.i, category 3),[242] but they will be discussed in a separate section because they are commonly accompanied by an *allylic rearrangement*.[243] When allylic substrates are treated with nucleophiles under S_N1 conditions, two products are usually obtained: the normal one and a rearranged one.



Two products are formed because an allylic type of carbocation is a resonance hybrid so that C-1 and C-3 each carry a partial positive charge and both are attacked by Y.



Of course, an allylic rearrangement is undetectable in the case of symmetrical allylic cations, as in the case where R = H, unless isotopic labeling is used. This mechanism has been called the S_N1' mechanism. The IUPAC designation is $1/D_N + 3/A_N$, with the numbers

[240] Lewis, E.S.; Boozer, C.E. *J. Am. Chem. Soc.* ***1952***, *74*, 308.

[241] Lewis, E.S.; Witte, K. *J. Chem. Soc. B* ***1968***, 1198. Also see Cohen, T.; Solash, J. *Tetrahedron Lett.* ***1973***, 2513; Verrinder, D.J.; Hourigan, M.J.; Prokipcak, J.M. *Can. J. Chem.* ***1978***, *56*, 2582.

[242] Baeza, A.; Nájera, C. *Synthesis* ***2014***, *46*, 25.

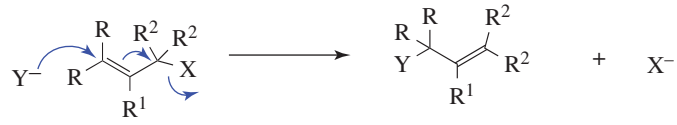
[243] See DeWolfe, R.H. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 417–437. For comprehensive older reviews, see DeWolfe, R.H.; Young, W.G. *Chem. Rev.* ***1956***, *56*, 753; or sections in Patai, S. *The Chemistry of Alkenes*, Wiley, NY, ***1964*** by Mackenzie, K. pp. 436–453 and DeWolfe, R.H.; Young, W.G. pp. 681–738.

1 and 3 signifying the *relative* positions where the nucleophile attacks and from which the nucleofuge leaves.

$CH_3CH{=}CHCH_2Cl$ **75** and $CH_3CHClCH{=}CH_2$ **76**

As with other S_N1 reactions, there is clear evidence that S_N1' reactions can involve ion pairs. If the intermediate attacked by the nucleophile is a completely free carbocation, then it should give the same mixture of alcohols when reacting with hydroxide ion, since the carbocation from each should be the same. When treated with 0.8 M aq. NaOH at 25 °C, **75** gave 60% $CH_3CH{=}CHCH_2OH$ and 40% $CH_3CHOHCH{=}CH_2$, while **76** gave the products in yields of 38% and 62%, respectively.[244] This phenomenon is called the *product spread*. In this case, and in most others, the product spread is in the direction of the starting compound. With increasing polarity of solvent,[245] the product spread decreases and in some cases is entirely absent. It is evident that in such cases the high polarity of the solvent stabilizes completely free carbocations. There is other evidence for the intervention of ion pairs in many of these reactions. When $H_2C{=}CHCMe_2Cl$ was treated with acetic acid, both acetates were obtained, but also some $ClCH_2CH{=}CMe_3$,[246] and the isomerization was faster than the acetate formation. This could not have arisen from a completely free Cl^- returning to the carbon, since the rate of formation of the rearranged chloride was unaffected by the addition of external Cl^-. All these facts indicate that the first step in these reactions is the formation of an unsymmetrical intimate ion pair that undergoes a considerable amount of internal return and in which the counterion remains close to the carbon from which it departed. Thus, **75** and **76**, for example, give rise to two *different* intimate ion pairs. The field of the anion polarizes the allylic cation, making the nearby carbon atom more electrophilic, so that it has a greater chance of attracting the nucleophile.[247]

Nucleophilic substitution at an allylic carbon can also take place by an S_N2 mechanism, in which case no allylic rearrangement usually takes place. However, allylic rearrangements can also take place under S_N2 conditions, by the following mechanism, in which the nucleophile attacks at the γ carbon rather than the usual position:[248]



S_N2' Mechanism

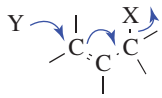
The IUPAC designation is $3/1/A_ND_N$. This mechanism is a second-order allylic rearrangement; it usually comes about where S_N2 conditions hold but where a substitution sterically retards the normal S_N2 mechanism.[249] There are a few well-established cases of the S_N2' mechanism on substrates of the type $C{=}C{-}CH_2X$, but compounds of the form

[244] DeWolfe, R.H.; Young, W.G. *Chem. Rev.* ***1956***, *56*, 753 give several dozen such examples.
[245] Katritzky, A.R.; Fara, D.C.; Yang, H.; Tämm, K.; Tamm, T.; Karelson, M. *Chem. Rev.* ***2004***, *104*, 175.
[246] Young, W.G.; Winstein, S.; Goering, H.L. *J. Am. Chem. Soc.* ***1951***, *73*, 1958.
[247] See Kantner, S.S.; Humski, K.; Goering, H.L. *J. Am. Chem. Soc.* ***1982***, *104*, 1693; Thibblin, A. *J. Chem. Soc., Perkin Trans. 2* ***1986***, 313.
[248] See Magid, R.M. *Tetrahedron* ***1980***, *36*, 1901 (pp. 1901–1910).
[249] Streitwieser, A.; Jayasree, E.G.; Leung, S.S.-H.; Choy, G.S.-C. *J. Org. Chem.* ***2005***, *70*, 8486.

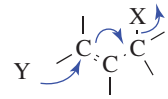
C=C–CR_2X give the S_N2' rearrangement almost exclusively[250] when they give bimolecular reactions at all. Increasing the size of the nucleophile can also increase the extent of the S_N2' reaction at the expense of the S_N2.[250] In certain cases, the leaving group can also have an affect on whether the rearrangement occurs. Thus PhCH=$CHCH_2X$, treated with $LiAlH_4$, gave 100% S_N2 reaction (no rearrangement) when X = Br or Cl, but 100% S_N2' when X = PPh_3^+ Br^-.[251] The solvent also plays a role in some cases, with more polar solvents giving more S_N2' product.[252]

The S_N2' mechanism as shown above involves the simultaneous movement of three pairs of electrons. However, Bordwell has contended that there is no evidence that requires that this bond making and bond breaking be in fact concerted,[253] and that a true S_N2' mechanism is a myth. There is evidence both for[254] and against[255] this proposal. There is also a review of the S_N' reaction.[256]

The stereochemistry of S_N2' reactions has been investigated. It has been found that both *syn*[257] (the nucleophile enters on the side from which the leaving group departs) and *anti*[258] reactions can take place, depending on the nature of X and Y,[259] although the *syn* pathway predominates in most cases.

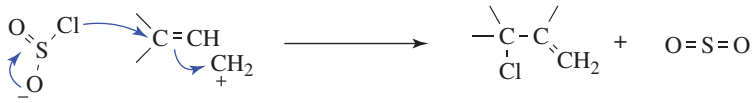


Syn



Anti

When a molecule has a nucleofuge capable of giving the S_Ni reaction in an allylic position, it is possible for the nucleophile to attack at the γ position instead of the α position. This is called the S_Ni' mechanism[260] and has been demonstrated on 2-buten-1-ol and 3-buten-2-ol, both of which gave 100% allylic rearrangement when treated with thionyl chloride in ether.[261]



[250] Bordwell, F.G.; Clemens, A.H.; Cheng, J. *J. Am. Chem. Soc.* ***1987***, *109*, 1773. Also see, Young, J.-j; Jung, L.-j.; Cheng, K.-m. *Tetrahedron Lett.* ***2000***, *41*, 3411; Bizet, V.; Lefebvre, V.; Baudoux, J.; Lasne, M.-C.; Boulangé, A.; Leleu, S.; Franck, X.; Rouden, J. *Eur. J. Org. Chem.* ***2011***, 4170.

[251] Hirab, T.; Nojima, M.; Kusabayashi, S. *J. Org. Chem.* ***1984***, *49*, 4084.

[252] Hirashita, T.; Hayashi, Y.; Mitsui, K.; Araki, S. *Tetrahedron Lett.* ***2004***, *45*, 3225.

[253] Bordwell, F.G.; Mecca, T.G. *J. Am. Chem. Soc.* ***1972***, *94*, 5829. See also Dewar, M.J.S. *J. Am. Chem. Soc.* ***1984***, *106*, 209.

[254] See Uebel, J.J.; Milaszewski, R.F.; Arlt, R.E. *J. Org. Chem.* ***1977***, *42*, 585.

[255] See Fry, A. *Pure Appl. Chem.* ***1964***, *8*, 409; Georgoulis, C.; Ville, G. *Bull. Soc. Chim. Fr.* ***1985***, 485; Meislich, H.; Jasne, S.J. *J. Org. Chem.* ***1982***, *47*, 2517.

[256] Paquette, L.A.; Stirling, C.J.M. *Tetrahedron* ***1992***, *48*, 7383.

[257] See Magid, R.M.; Fruchey, O.S. *J. Am. Chem. Soc.* ***1979***, *101*, 2107; Bäckvall, J.E.; Vågberg, J.O.; Genêt, J.P. *J. Chem. Soc., Chem. Commun.* ***1987***, 159.

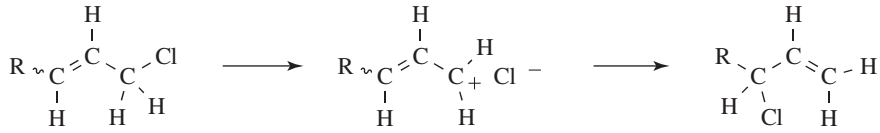
[258] See Stork, G.; Schoofs, A.R. *J. Am. Chem. Soc.* ***1979***, *101*, 5081.

[259] Bach, R.D.; Wolber, G.J. *J. Am. Chem. Soc.* ***1985***, *107*, 1352; Stohrer, W. *Angew. Chem. Int. Ed.* ***1983***, *22*, 613.

[260] For S_Ni' reaction with main group organometallics, see Devambatla, R.K.V.; Velagaleti, R.; Yarravarapu, N.; Fleming, F.F. *Tetrahedron* ***2012***, *68*, 2925.

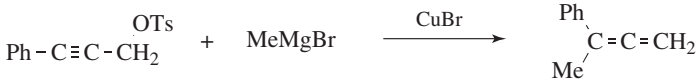
[261] Young, W.G. *J. Chem. Educ.* ***1962***, *39*, 456. See Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* ***1984***, *25*, 3055.

Ordinary allylic rearrangements (S_N1') or S_N2' mechanisms could not be expected to give 100% rearrangement in *both* cases. In the case shown, the nucleophile is only part of the leaving group, not the whole. But it is also possible to have reactions in which a simple leaving group, such as Cl, comes off to form an ion pair[262] and then returns not to the position whence it came but to the allylic position:



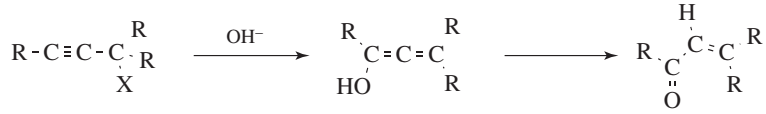
Most S_Ni' reactions are of this type.

Allylic rearrangements can also give triple-bond compounds, for example,



(Reaction **19-67**)

The product in this case is an allene,[263] but such shifts can also give triple-bond compounds or, if Y = OH, an enol will be obtained that tautomerizes to an α,β-unsaturated aldehyde or ketone. When X = OH, this conversion of acetylenic alcohols to unsaturated aldehydes or ketones is called the *Meyer-Schuster rearrangement*.[264]



The propargyl rearrangement can also go the other way; that is, 1-haloalkenes, treated with organocopper compounds, give alkynes.[265]

The S_N2' reaction has been shown to predominate in reactions of mixed cuprates (reaction **10-58**) with allylic mesylates,[266] and in ring-opening reactions of aziridines.[267] A related reaction is the opening of cyclopropylcarbinyl halides with organocuprates, where the cyclopropane ring reacts similarly to the C—C unit of an alkene to give a homoallylic substituted product.[268] This latter reaction is interesting since the reaction of **77** with

[262] For a theoretical study, see Streitwieser, A.; Jayasree, E.G.; Hasanayn, F.; Leung, S.S.-H. *J. Org. Chem.* ***2008***, *73*, 9426.

[263] See Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 12–19, 26–30; Taylor, D.R. *Chem. Rev.* ***1967***, *67*, 317 (pp. 324–328). See Larock, R.C.; Reddy, Ch.K. *Org. Lett.* ***2000***, *2*, 3325.

[264] See Swaminathan, S.; Narayanan, K.V. *Chem. Rev.* ***1971***, *71*, 429; Andres, J.; Cardenas, R.; Silla, E.; Tapi, O. *J. Am. Chem. Soc.* ***1988***, *110*, 666.

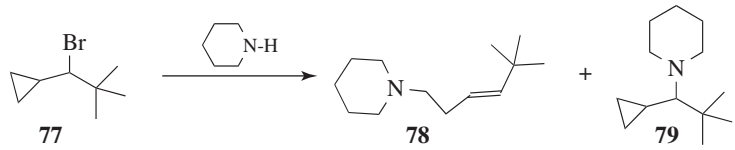
[265] Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* ***1984***, *25*, 3059, 3063.

[266] Ibuka, T.; Taga, T.; Habashita, H.; Nakai, K.; Tamamura, H.; Fujii, N.; Chounan, Y.; Nemoto, H.; Yamamoto, Y. *J. Org. Chem.* ***1993***, *58*, 1207.

[267] Wipf, P.; Fritch, P.C. *J. Org. Chem.* ***1994***, *59*, 4875.

[268] Smith, M.B.; Hrubiec, R.T. *Tetrahedron* ***1984***, *40*, 1457; Hrubiec, R.T.; Smith, M.B. *J. Org. Chem.* ***1984***, *49*, 385.

piperidine leads to the S_N2' product (**78**) in ~87% yield, but there is ~8% of the direct substitution product, **79**. Since the carbon bearing the bromine is very hindered, formation of **79** is somewhat unusual under these conditions. As Bordwell has suggested (see above), this may not be a true S_N2 process.



77 **78** **79**

The organocatalytic activation of the leaving group in intramolecular S_N2' reactions has been discussed.[269]

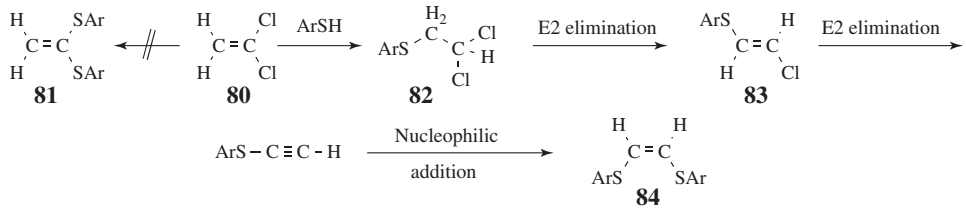
10.F. NUCLEOPHILIC SUBSTITUTION AT AN ALIPHATIC TRIGONAL CARBON: THE TETRAHEDRAL MECHANISM

All the mechanisms so far discussed take place at a saturated carbon atom. Nucleophilic substitution is also important at trigonal carbons, especially when the carbon is double bonded to an oxygen, a sulfur, or a nitrogen. These reactions are discussed in Chapter 16. Nucleophilic substitution at vinylic carbons is considered in this section and at aromatic carbons is considered in Chapter 13.

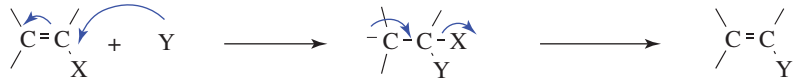
Nucleophilic substitution at a vinylic carbon[270] is difficult (Sec. 10.G.i), but many examples are known. Vinylic compounds have also been used as alkylating agents.[271] The reactivity at vinylic carbon has been discussed in what is known as nucleophilic vinylic substitution (S_NV), specifically the $S_NV\pi$ versus the $S_NV\sigma$ mechanisms.[272] The most common mechanisms are the tetrahedral mechanism and the closely related *addition–elimination mechanism*. Both of these mechanisms are impossible at a saturated substrate.

The addition–elimination mechanism has been demonstrated for the reaction between 1,1-dichloroethene (**80**) and ArS^- catalyzed by ^-OEt.[273] The product was not the 1,1-dithiophenoxy compound **81** but the "rearranged" compound **84**. Isolation of **82** and **83** showed that an addition–elimination mechanism had taken place. In the first step ArSH adds to the double bond (nucleophilic addition, Sec. 15.A.ii) to give the saturated **82**. The second step is an E2 elimination reaction (Sec. 17.A.i) to give the alkene **83**. A second elimination and addition give **84**.

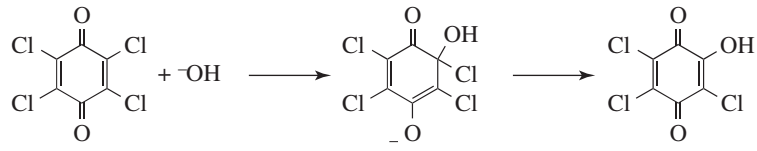
[269] Kuroda, Y.; Harada, S.; Oonishi, A.; Yamaoka, Y.; Yamada, K.; Takasu, K. *Angew. Chem. Int. Ed.* ***2015***, *54*, 8263.
[270] See Rappoport, Z. *Recl. Trav. Chim. Pays-Bas* ***1986***, *104*, 309; Shainyan, B.A. *Russ. Chem. Rev.* ***1986***, *55*, 511; Modena, G. *Acc. Chem. Res.* ***1971***, *4*, 73.
[271] Céspedes-Camacho, I.F.; Manso, J.A.; González-Jiménez, M.; Calle, E.; Casado, J. *Monatsh. Chem.* ***2012***, *143*, 723.
[272] Fernández, I.; Bickelhaupt, F.M.; Uggerud, E. *J. Org. Chem.* ***2013***, *78*, 8574.
[273] Truce, W.E.; Boudakian, M.M. *J. Am. Chem. Soc.* ***1956***, *78*, 2748.



The tetrahedral mechanism, often also called addition–elimination (*AdN-E*), takes place with much less facility than with carbonyl groups, since the negative charge of the intermediate must be borne by a carbon, which is less electronegative than oxygen, sulfur, or nitrogen:



Such an intermediate can also stabilize itself by combining with a positive species. When it does, the reaction is nucleophilic addition to a C═C double bond (see Chapter 15). It is not surprising that with vinylic substrates addition and substitution often compete. For chloroquinones, where the charge is spread by resonance, tetrahedral intermediates have been isolated:[274]



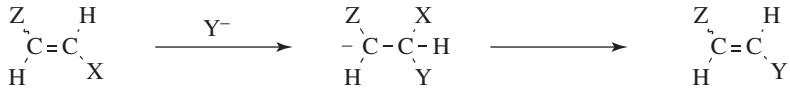
In the case of $Ph(MeO)C{=}C(NO_2)Ph + RS^-$, the intermediate lived long enough to be detected by UV spectroscopy.[275]

Since both the tetrahedral and addition–elimination mechanisms begin the same way, it is usually difficult to tell them apart, and often no attempt is made to do so. The strongest kind of evidence for the addition–elimination sequence is the occurrence of a "rearrangement," but of course the mechanism could still take place even if no rearrangement is found. Evidence[276] that a tetrahedral or an addition–elimination mechanism takes place in certain cases (as opposed, e.g., to an S_N1 or S_N2 mechanism) is that the reaction rate increases when the leaving group is changed from Br to Cl to F (this is called the *element effect*).[277] This clearly demonstrates that the carbon–halogen bond does not break in the rate-determining step (as it would in both the S_N1 and S_N2 mechanisms), because fluorine is by far the poorest leaving group[278] among the halogens in both the S_N1 and S_N2 reactions (Sec. 10.G.iii). The rate is faster with fluorides in the cases cited, because the superior electron-withdrawing

[274] Hancock, J.W.; Morrell, C.E.; Rhom, D. *Tetrahedron Lett.* ***1962***, 987.
[275] Bernasconi, C.F.; Fassberg, J.; Killion Jr., R.B.; Rappoport, Z. *J. Org. Chem.* ***1990***, *55*, 4568.
[276] See Rappoport, Z.; Peled, P. *J. Am. Chem. Soc.* ***1979***, *101*, 2682, and references cited therein.
[277] Avramovitch, B.; Weyerstahl, P.; Rappoport, Z. *J. Am. Chem. Soc.* ***1987***, *109*, 6687.
[278] See Chatalova-Sazepin, C.; Hemelaere, R.; Paquin, J.-F.; Sammis, G.M. *Synthesis* ***2015***, *47*, 2554.

character of the fluorine makes the carbon of the C—F bond more positive and hence more susceptible to nucleophilic attack.

Ordinary vinylic substrates react very poorly, if at all, by these mechanisms, but substitution is greatly enhanced in substrates of the type ZCH=CHX, where Z is an electron-withdrawing group such as HCO, RCO,[279] EtOOC, $ArSO_2$, NC, F, etc., since these β groups stabilize the carbanion:



Many such examples are known. In most cases where the stereochemistry has been investigated, retention of configuration is observed,[280] but stereoconvergence [the same product mixture from an (*E*) or (*Z*) substrate] has also been observed,[281] especially where the carbanionic carbon bears two electron-withdrawing groups.

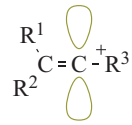
Although rare, nucleophilic substitution with inversion has also been reported, as in the intramolecular substitution of the C—Br bond of 2-bromobut-2-enylamines by the pendant nitrogen atom, giving 2-ethylene aziridines by way of stereochemical inversion.[282] It is not immediately apparent why the tetrahedral mechanism should lead to retention, but this behavior has been ascribed, on the basis of molecular orbital calculations, to hyperconjugation involving the carbanionic electron pair and the substituents on the adjacent carbon.[283]

Vinylic substrates are in general very reluctant to undergo S_N1 reactions, but they can be made to do so in two ways.[284]

1. *By the use of an a group that stabilizes the vinylic cation*. For example, α-aryl vinylic halides $ArBrC{=}CR'_2$ have often been shown to give S_N1 reactions.[285] The S_N1 reactions have also been demonstrated with other stabilizing groups: cyclopropyl,[286] vinylic,[287] alkynyl,[288] and an adjacent double bond ($R_2C{=}C{=}CR'X$).[289]
2. *Even without a stabilization, by the use of a very good leaving group*, e.g., OSO_2CF_3 (triflate).[290] The stereochemical outcome of S_N1 reactions at a vinylic substrate is often randomization,[291] that is, either a *cis* or a *trans* substrate gives a 1:1 mixture of *cis* and *trans* products, indicating that vinylic cations are linear. Another indication

[279] See Rybinskaya, M.I.; Nesmeyanov, A.N.; Kochetkov, N.K. *Russ. Chem. Rev.* ***1969***, *38*, 433.
[280] Rappoport, Z. *Adv. Phys. Org. Chem.* ***1969***, *7*, see pp. 31–62; Shainyan, B.A. *Russ. Chem. Rev.* ***1986***, *55*, 516. See also, Rappoport, Z.; Gazit, A. *J. Am. Chem. Soc.* ***1987***, *109*, 6698.
[281] See Rappoport, Z.; Gazit, A. *J. Am. Chem. Soc.* ***1987***, *109*, 6698; Park, K.P.; Ha, H. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 3006.
[282] Shiers, J.J.; Shipman, M.; Hayes, J.-F.; Slawin, A.M.Z. *J. Am. Chem. Soc.* ***2004***, *126*, 6868.
[283] Apeloig, Y.; Rappoport, Z. *J. Am. Chem. Soc.* ***1979***, *101*, 5095.
[284] See Stang, P.J.; Rappoport, Z.; Hanack, H.; Subramanian, L.R. *Vinyl Cations*, Chapter 5, Academic Press, NY, ***1979***; Stang, P.J. *Acc. Chem. Res.* ***1978***, *11*, 107; Rappoport, Z. *Acc. Chem. Res.* ***1976***, *9*, 265.
[285] See Stang, P.J.; Rappoport, Z.; Hanack, H.; Subramanian, L.R. *Vinyl Cations*, Chapter. 6, Academic Press, NY, ***1979***.
[286] Hanack, M.; Bässler, T.; Eymann, W.; Heyd, W.E.; Kopp, R. *J. Am. Chem. Soc.* ***1974***, *96*, 6686.
[287] Grob, C.A.; Spaar, R. *Helv. Chim. Acta* ***1970***, *53*, 2119.
[288] Hassdenteufel, J.R.; Hanack, M. *Tetrahedron Lett.* ***1980***, 503. See also, Kobayashi, S.; Nishi, T.; Koyama, I.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* ***1980***, 103.
[289] Schiavelli, M.D.; Gilbert, R.P.; Boynton, W.A.; Boswell, C.J. *J. Am. Chem. Soc.* ***1972***, *94*, 5061.
[290] See Hanack, M.; Märkl, R.; Martinez, A.G. *Chem. Ber.* ***1982***, *115*, 772.
[291] Kelsey, D.R.; Bergman, R.G. *J. Am. Chem. Soc.* ***1971***, *93*, 1941.

that vinylic cations prefer to be linear is the fact that reactivity in cycloalkenyl systems decreases with decreasing ring size.[292] However, a linear vinylic cation need not give random products.[293] The empty *p* orbital lies in the plane of the double bond, so entry of the nucleophile can be and often is influenced by the relative size of R^1 and R^2.[294] It must be emphasized that even where vinylic substrates do give S_N1 reactions, the rates are generally lower than those of the corresponding saturated compounds.

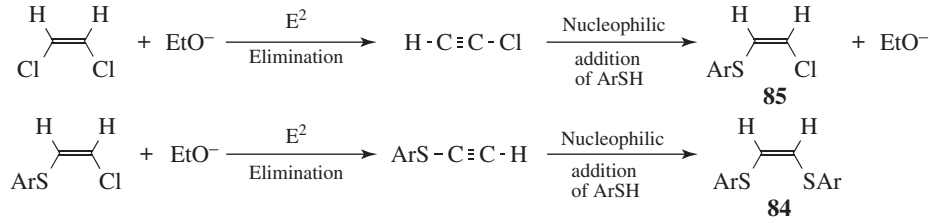


Alkynyl cations are so unstable that they cannot be generated even with very good leaving groups. However, one way in which they have been generated was by formation of a tritiated substrate.

$$R{-}C{\equiv}C{-}T \xrightarrow{\beta\ \text{Decay}} R{-}C{\equiv}C{-}{}^3He \xrightarrow[\text{fast}]{\text{Very}} R{-}C{\equiv}C^+ + {}^3He$$

When the tritium (half-life 12.26 years) decays it is converted to the helium-3 isotope, which, of course, does not form covalent bonds, and so immediately departs, leaving behind the alkynyl cation. When this was done in the presence of benzene, $RC{\equiv}CC_6H_5$ was isolated.[295] The tritium-decay technique has also been used to generate vinylic and aryl cations.[296]

In addition to the mechanisms already discussed, another mechanism, involving an *elimination–addition* sequence, has been observed in vinylic systems (a similar mechanism is known for aromatic substrates, Sec. 13.A.iii). An example of a reaction involving this mechanism is the reaction of 1,2-dichloroethane with ArS^- and ^-OEt to produce **85**. The mechanism may be formulated as shown. The steps are the same as in the addition–elimination mechanism, but in reverse order.



[292] Pfeifer, W.D.; Bahn, C.A.; Schleyer, P.v.R.; Bocher, S.; Harding, C.E.; Hummel, K.; Hanack, M.; Stang, P.J. *J. Am. Chem. Soc.* ***1971***, *93*, 1513.

[293] See Clarke, T.C.; Bergman, R.G. *J. Am. Chem. Soc.* ***1974***, *96*, 7934; Summerville, R.H.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1972***, *94*, 3629; ***1974***, *96*, 1110.

[294] Maroni, R.; Melloni, G.; Modena, G. *J. Chem. Soc., Chem. Commun.* ***1972***, 857.

[295] Angelini, G.; Hanack, M.; Vermehren, J.; Speranza, M. *J. Am. Chem. Soc.* ***1988***, *110*, 1298.

[296] See Cacace, F. *Adv. Phys. Org. Chem.* ***1970***, *8*, 79. See also, Fornarini, S.; Speranza, M. *J. Am. Chem. Soc.* ***1985***, *107*, 5358.

Evidence for this sequence[297] is as follows. (i) The reaction does not proceed without ethoxide ion, and the rate is dependent on the concentration of this ion and not on that of ArS^-. (ii) Under the same reaction conditions, chloroacetylene gave **85** and then **84**. (iii) Compound **85** gave no reaction when treated with ArS^-, but **84** was obtained when EtO^- was added. It is interesting that the elimination–addition mechanism has even been shown to occur in five- and six-membered cyclic systems, where triple bonds are greatly strained.[298] Note that both the addition–elimination and elimination–addition sequences, as shown above, lead to overall retention of configuration, since in each case both addition and elimination are *anti*.

The elimination–addition sequence has also been demonstrated for certain reactions of saturated substrates, e.g., $ArSO_2CH_2CH_2SO_2Ar$.[299] Treatment of this with ethoxide proceeds as follows:

$$ArSO_2CH_2CH_2SO_2Ar \xrightarrow[E^2\ \text{Elmination}]{EtO^-} ArSO_2CH=CH_2 \xrightarrow[\text{Addition}]{EtO^-} ArSO_2CH_2CH_2OEt$$

Mannich bases (see **16-17**) of the type $RCOCH_2CH_2NR_2$ similarly undergo nucleophilic substitution by the elimination–addition mechanism.[300] The nucleophile replaces the NR_2 group.

The simple S_N2 mechanism has never been convincingly demonstrated for vinylic substrates.[301]

Vinylic halides can react by a $S_{RN}1$ mechanism (Sec. 13.A.iv) in some cases. An example is the $FeCl_2$-catalyzed reaction of 1-bromo-2-phenylethene and the enolate anion of pinacolone (t-$BuCOCH_2^-$), which gave a low yield of substitution products along with alkynes.[302]

10.G. REACTIVITY

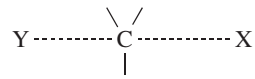
A large amount of work has been done in this area. Although a great deal is known, much is still poorly understood, and many results are anomalous and hard to explain. In this section, only approximate generalizations are attempted. The work discussed here, and the conclusions reached, pertain to reactions taking place in solution. Some investigations have also been carried out in the gas phase.[303]

10.G.i. The Effect of Substrate Structure

The effect on the reactivity of a change in substrate structure depends on the mechanism.

[297] Flynn Jr., J.; Badiger, V.V.; Truce, W.E. *J. Org. Chem.* ***1963***, *28*, 2298. See also, Shainyan, B.A.; Mirskova, A.N. *J. Org. Chem. USSR* ***1984***, *20*, 885, 1989; ***1985***, *21*, 283.
[298] Bottini, A.T.; Corson, F.P.; Fitzgerald, R.; Frost II, K.A. *Tetrahedron* ***1972***, *28*, 4883.
[299] See Popov, A.F.; Piskunova, Z.; Matvienko, V.N. *J. Org. Chem. USSR* ***1986***, *22*, 1299.
[300] See Andrisano, R.; Angeloni, A.S.; De Maria, P.; Tramontini, M. *J. Chem. Soc. C* ***1967***, 2307.
[301] See Rappoport, Z. *Acc. Chem. Res.* ***1981***, *14*, 7; Rappoport, Z.; Avramovitch, B. *J. Org. Chem.* ***1982***, *47*, 1397.
[302] Galli, C.; Gentili, P.; Rappoport, Z. *J. Org. Chem.* ***1994***, *59*, 6786.
[303] See DePuy, C.H.; Gronert, S.; Mullin, A.; Bierbaum, V.M. *J. Am. Chem. Soc.* ***1990***, *112*, 8650.

1. *Branching at the* α *and* β *carbons*. For the S_N2 mechanism, branching at either the α or the β carbons decreases the rate. Tertiary systems seldom[304] react by the S_N2 mechanism and neopentyl systems react so slowly as to make such reactions, in general, synthetically useless.[305] Experiments show that methyl halides react 30 times faster than ethyl halides, whereas isopropyl halides react 40 times slower than ethyl halides.[306] The presence of π bonds accelerates the rate, as illustrated by the fact that allyl halides react 40 times faster than ethyl halides, and benzyl halides react 120 times faster.[306] The reason for the low rates for secondary and especially tertiary is almost certainly steric, and this statement includes the primary neopentyl halides, which react 20 000 times slower than ethyl halides[307] The transition state **1** is more crowded when larger groups are close to the central carbon.[308]



1

The tetrahedral mechanism for substitution at a carbonyl carbon (Chapter 16) is also slowed or blocked completely by α or β branching, for similar reasons. Solvolysis in such systems is linked to relief of B strain, but solvent participation can overshadow this as steric hindrance increases.[309] Severe steric strain can cause distortion from coplanarity in the carbocation intermediate,[310] although there seems to be no loss of resonance stability.[311] Adding electron-donating substituents to such molecules improves coplanarity in the cation.[312] For example, esters of the formula R_3CCOOR' cannot generally be hydrolyzed by the tetrahedral mechanism (see **16-59**), nor can acids R_3CCO_2H be easily esterified.[313] Synthetic advantage can be taken of this fact, for example, when in a molecule containing two ester groups only the less hindered one is hydrolyzed.

For the S_N1 mechanism, branching at the α carbon increases the rate, as shown by rate data for alkyl bromides.[314] The secondary bromide isopropyl bromide reacts 11.6 times faster than bromoethane in water at 50 °C, and *tert*-butyl bromide (a tertiary halide) reacts 1.2×10^6 times faster.[314] This is explained by the stability order of alkyl cations (tertiary > secondary > primary). Of course, the rates are not actually dependent on the stability of the ions, but on the difference in free energy between the starting compounds and the transition states. The *Hammond postulate* (Sec. 6.G) is used to make the assumption that the transition states resemble the cations and that

[304] For a reported example, see Edwards, O.E.; Grieco, C. *Can. J. Chem.* ***1974***, *52*, 3561.
[305] See Anderson, P.H.; Stephenson, B.; Mosher, H.S. *J. Am. Chem. Soc.* ***1974***, *96*, 3171.
[306] See Streitwieser, A. *Solvolytic Displacement Reactions*, McGraw-Hill, NY, ***1962***, p. 13.
[307] For evidence, see Caldwell, G.; Magnera, T.F.; Kebarle, P. *J. Am. Chem. Soc.* ***1984***, *106*, 959.
[308] For a discussion of the interplay between steric and electronic effects, see Fernández, I.; Frenking, G.; Uggerud, E. *Chem. Eur. J.* ***2009***, *15*, 2166.
[309] Liu, K.-T.; Hou, S.-J.; Tsao, K.-L. *J. Org. Chem.* ***1998***, *63*, 1360.
[310] Fujio, M.; Nomura, H.; Nakata, K.; Saeki, Y.; Mishima, M.; Kobayashi, S.; Matsushita, T.; Nishimoto, K.; Tsuno, Y. *Tetrahedron Lett.* ***1994***, *35*, 5005.
[311] Fujio, M.; Nakata, K.; Kuwamura, T.; Nakamura, H.; Saeki, Y.; Mishima, M.; Kobayashi, S.; Tsuno, Y. *Tetrahedron Lett.* ***1992***, *34*, 8309.
[312] Liu, K.T.; Tsao, M.-L.; Chao, I. *Tetrahedron Lett.* ***1996***, *37*, 4173.
[313] See DeTar, D.F.; Binzet, S.; Darba, P. *J. Org. Chem.* ***1987***, *52*, 2074.
[314] See Streitwieser, A. *Solvolytic Displacement Reactions*, McGraw-Hill, NY, ***1962***, p. 43.

anything (e.g., branching) that lowers the free energy of the ions also lowers it for the transition states. For simple alkyl groups, the S_N1 mechanism is important under all conditions only for tertiary substrates.[315] As previously indicated (Sec. 10.A.iv), secondary substrates generally react by the S_N2 mechanism,[316] except that the S_N1 mechanism may become important at high solvent polarities. Isopropyl bromide reacts less than twice as fast as ethyl bromide in the relatively nonpolar 60% ethanol (compare this with the 10^4 ratio for *tert*-butyl bromide, where the mechanism is certainly S_N1), but in the more polar water the rate ratio is 11.6.[314] The 2-adamantyl system is an exception; it is a secondary system that reacts by the S_N1 mechanism because back-side attack is hindered for steric reasons.[317] Because there is no S_N2 component, this system provides an opportunity for comparing the pure S_N1 reactivity of secondary and tertiary substrates. It has been found that substitution of a methyl group for a hydrogen of 2-adamantyl substrates (thus changing a secondary to a tertiary system) increases solvolysis rates by a factor of $\sim 10^8$.[318] Simple primary substrates react by the S_N2 mechanism (or with participation by neighboring alkyl or hydrogen) but not by the S_N1 mechanism, even when solvolyzed in solvents of very low nucleophilicity[319] (e.g., trifluoroacetic acid or trifluoroethanol[320]), and even when very good leaving groups (e.g., OSO_2F) are present[321] (see, however, Sec. 10.G.iii).

For some tertiary substrates, the rate of S_N1 reactions is greatly increased by the relief of B strain in the formation of the carbocation (Sec. 9.B). Except where B strain is involved, β branching has little effect on the S_N1 mechanism, except that carbocations with β branching undergo rearrangements readily. Of course, isobutyl and neopentyl are primary substrates, and for this reason react very slowly by the S_N1 mechanism, but not more slowly than the corresponding ethyl or propyl compounds.

To sum up, primary and secondary substrates generally react by the S_N2 mechanism and tertiary by the S_N1 mechanism. However, tertiary substrates seldom undergo nucleophilic substitution at all. Elimination is always a possible side reaction of nucleophilic substitutions (wherever a β hydrogen is present), and with tertiary substrates it usually predominates. With a few exceptions, nucleophilic substitutions at a tertiary carbon have little or no preparative value. However, tertiary substrates that can react by the SET mechanism (e.g., p-$NO_2C_6H_4CMe_2Cl$) give very good yields of substitution products when treated with a variety of nucleophiles.[322]

[315] See Zamashchikov, V.V.; Bezbozhnaya, T.V.; Chanysheva, I.R. *J. Org. Chem. USSR* ***1986***, *22*, 1029.

[316] See Dietze, P.E.; Hariri, R.; Khattak, J. *J. Org. Chem.* ***1989***, *54*, 3317.

[317] Fry, J.L.; Harris, J.M.; Bingham, R.C.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1970***, *92*, 2540; Schleyer, P.v.R.; Fry, J.L.; Lam, L.K.M.; Lancelot, C.J. *J. Am. Chem. Soc.* ***1970***, *92*, 2542. Also see Dutler, R.; Rauk, A.; Sorensen, T.S.; Whitworth, S.M. *J. Am. Chem. Soc.* ***1989***, *111*, 9024.

[318] Fry, J.L.; Engler, E.M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1972***, *94*, 4628. See also, Gassman, P.G.; Pascone, J.M. *J. Am. Chem. Soc.* ***1973***, *95*, 7801.

[319] See Minegishi, S.; Kobayashi, S.; Mayr, H. *J. Am. Chem. Soc.* ***2004***, *126*, 5174; Kevill, D.N. in Charton, M. *Advances in Quantitative Structure–Property Relationships*, Vol. 1, JAI Press, Greenwich, CT, ***1996***, pp. 81–115; Schadt, F.L.; Bentley, T.W.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1976***, *98*, 7667.

[320] Dafforn, G.A.; Streitwieser Jr., A. *Tetrahedron Lett.* ***1970***, 3159.

[321] Cafferata, L.F.R.; Desvard, O.E.; Sicre, J.E. *J. Chem. Soc., Perkin Trans. 2* ***1981***, 940.

[322] Kornblum, N.; Cheng, L.; Davies, T.M.; Earl, G.W.; Holy, N.L.; Kerber, R.C.; Kestner, M.M.; Manthey, J.W.; Musser, M.T.; Pinnick, H.W.; Snow, D.H.; Stuchal, F.W.; Swiger, R.T. *J. Org. Chem.* ***1987***, *52*, 196.

2. *Unsaturation at the* α *carbon*. Vinylic, acetylenic,[323] and aryl substrates are very unreactive toward nucleophilic substitutions. For these systems, both the S_N1 and S_N2 mechanisms are greatly slowed or stopped altogether. One reason that has been suggested for this is that sp^2 (and, even more, *sp*) carbon atoms have a higher electronegativity than sp^3 carbons and thus a greater attraction for the electrons of the bond. As seen previously (Sec. 8.F, category 7), an *sp*—H bond has a higher acidity than an sp^3—H bond, with that of an sp^2—H bond in between. This is reasonable; the carbon retains the electrons when the proton is lost and an *sp* carbon, which has the greatest hold on the electrons, loses the proton most easily. But in nucleophilic substitution, the leaving group *carries off* the electron pair, so the situation is reversed and it is the sp^3 carbon that loses the leaving group and the electron pair most easily. It may be recalled (Sec. 1.J) that bond distances decrease with increasing *s* character. Thus the bond length for a vinylic or aryl C—Cl bond is 1.73 Å compared with 1.78 Å for a saturated C—Cl bond. Other things being equal, a shorter bond is a stronger bond.

   Of course it has been seen (Sec. 10.F) that S_N1 reactions at vinylic substrates can be accelerated by α substituents that stabilize that cation, and that reactions by the tetrahedral mechanism can be accelerated by β substituents that stabilize the carbanion. Also, reactions at vinylic substrates can in certain cases proceed by addition–elimination or elimination–addition sequences (Sec. 10.F).

   In contrast to such systems, substrates of the type RCOX are usually much *more* reactive than the corresponding RCH_2X. Of course, the mechanism here is almost always the tetrahedral one. Three reasons can be given for the enhanced reactivity of RCOX: (i) the carbonyl carbon has a sizable partial positive charge that makes it very attractive to nucleophiles; (ii) in an S_N2 reaction, a σ bond must break in the rate-determining step, which requires more energy than the shift of a pair of π electrons, which is what happens in a tetrahedral mechanism; (iii) a trigonal carbon offers less steric hindrance to a nucleophile than a tetrahedral carbon.

   For reactivity in aryl systems, see Chapter 13.

3. *Unsaturation at the* β *carbon*. The S_N1 rates are increased when there is a double bond in the β position, so that allylic and benzylic substrates react rapidly (allylic tosylates react more than 30 times faster than ethyl tosylate).[324] The reason is that allylic (Sec. 5.A.ii) and benzylic[325] (Sec. 5.A.ii) cations are stabilized by resonance. The presence of a second or a third phenyl group increases the rate still more (10^5 and 10^{10} times faster, respectively), because these carbocations are more stable yet.[324] Remember that allylic rearrangements are possible with allylic systems.

   In general, S_N1 rates at an allylic substrate are increased by any substituent in the 1 or 3 position that can stabilize the carbocation by resonance or hyperconjugation.[326] Among these are alkyl, aryl, and halo groups.

   The S_N2 rates for allylic and benzylic systems are also increased (see above), probably owing to resonance possibilities in the transition state. Evidence for this

[323] See Miller, S.I.; Dickstein, J.I. *Acc. Chem. Res.* ***1976***, *9*, 358.
[324] See Streitwieser, A. *Solvolytic Displacement Reactions*, McGraw-Hill, NY, ***1962***, p. 75.
[325] For a Grunwald-Winstein correlation analysis of the solvolysis of benzyl bromide, see Liu, K.-T.; Hou, I.-J. *Tetrahedron* ***2001***, *57*, 3343.
[326] See DeWolfe, R.H.; Young, W.G. in Patai, S. *The Chemistry of Alkenes*, Wiley, NY, ***1964***, pp. 683–688, 695–697.

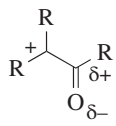
in **86** is that the rate of the reaction was 8000 times slower than the rate with $(PhCH_2)_2SEt^+$.[327] The cyclic compound **86** does not have the proper geometry for conjugation in the transition state.

86

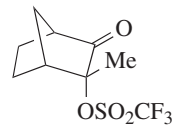
Triple bonds in the β position (in propargyl systems) have about the same effect as double bonds.[328] Alkyl, aryl, halo, and cyano groups, among others, in the 3 position of allylic substrates increase S_N2 rates, owing to increased resonance in the transition state, but alkyl and halo groups in the 1 position decrease the rates because of steric hindrance.

4. α *substitution*. Compounds of the formula ZCH_2X, where Z = RO, RS, or R_2N, undergo S_N1 reactions very rapidly,[329] because of the increased resonance in the carbocation. These groups have an unshared electron pair on an atom directly attached to the positive carbon, which stabilizes the carbocation (Sec. 5.A.ii). The field effects of these groups would be expected to decrease S_N1 rates (Sec. 10.G.i, category 6), so the resonance effect is far more important.

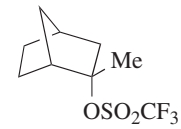
   When Z in ZCH_2X is RCO,[330] HCO, ROCO, NH_2CO, NC, or F_3C,[331] S_N1 rates are decreased compared to CH_3X, owing to the electron-withdrawing field effects of these groups. Furthermore, carbocations[332] with a CO or CN group are greatly destabilized because of the partial positive charge on the adjacent carbon (**87**). The S_N1 reactions have been carried out on such compounds,[333] but the rates are very low. For example, from a comparison of the solvolysis rates of **88** and **89**, a rate-retarding effect of $10^{7.3}$ was estimated for the C=O group.[334]



87



88



89

[327] King, J.F.; Tsang, G.T.Y.; Abdel-Malik, M.M.; Payne, N.C. *J. Am. Chem. Soc.* ***1985***, *107*, 3224.
[328] Jacobs, T.L.; Brill, W.F. *J. Am. Chem. Soc.* ***1953***, *75*, 1314.
[329] See Gross, H.; Höft, E. *Angew. Chem. Int. Ed.* ***1967***, *6*, 335.
[330] See De Kimpe, N.; Verhé, R. *The Chemistry of α-Haloketones, α-Haloaldehydes, and α-Haloimines*, Wiley, NY, ***1988***, pp. 225–368.
[331] Allen, A.D.; Kanagasabapathy, V.M.; Richard, J.P. *J. Am. Chem. Soc.* ***1989***, *111*, 1455.
[332] For reviews of such carbocations, see Bégué, J.; Charpentier-Morize, M. *Acc. Chem. Res.* ***1980***, *13*, 207; Charpentier-Morize, M. *Bull. Soc. Chim. Fr.* ***1974***, 343.
[333] For reviews, see Creary, X. *Acc. Chem. Res.* ***1985***, *18*, 3; Creary, X.; Hopkinson, A.C.; Lee-Ruff, E. *Adv. Carbocation Chem.* ***1989***, *1*, 45; Charpentier-Morize, M.; Bonnet-Delpon, D. *Adv. Carbocation Chem.* ***1989***, *1*, 219.
[334] Creary, X. *J. Org. Chem.* ***1979***, *44*, 3938.

However, when a different kind of comparison is made ($RCOCR'_2X$ versus HCR'_2X, where X = a leaving group), the RCO had only a small or negligible rate-retarding effect, indicating that resonance[335] may be offsetting the inductive destabilization for this group.[336] For a CN group also, the rate-retarding effect is reduced by this kind of resonance.[337] A carbocation with an COR group has been isolated.[338] When S_N2 reactions are carried out on these substrates, rates are greatly increased for certain nucleophiles (e.g., halide or halide-like ions), but decreased or essentially unaffected by others.[339] For example, α-chloroacetophenone ($PhCOCH_2Cl$) reacts with KI in acetone at 75 °C ~32 000 times faster than 1-chlorobutane,[340] but α-bromoacetophenone reacts with the nucleophile triethylamine 0.14 times as fast as iodomethane.[339] The reasons for this varying behavior are not clear, but those nucleophiles that form a "tight" transition state (one in which bond making and bond breaking have proceeded to about the same extent) are more likely to accelerate the reaction.[341]

When Z is SOR or SO_2R (e.g., α-halo sulfoxides and sulfones), nucleophilic substitution is retarded.[342] The S_N1 mechanism is slowed by the electron-withdrawing effect of the SOR or SO_2R group,[343] and the S_N2 mechanism presumably by the steric effect.

5. β *substitution*. For compounds of the type ZCH_2CH_2X, where Z is any of the groups listed in the previous section as well as halogen[344] or phenyl, S_N1 rates are lower than for unsubstituted systems, because the resonance effects mentioned in item 4 are absent, but the field effects are still there, although smaller. These groups in the β position do not have much effect on S_N2 rates unless they behave as neighboring groups and enhance the rate through anchimeric assistance,[345] or unless their size causes the rates to decrease for steric reasons.[346] It has been shown that silicon exerts a β effect, and that tin exerts a γ effect.[347] Silicon can also exert a γ effect.[348]
6. *The effect of electron-donating and electron-withdrawing groups*. If substitution rates for a series of compounds $p\text{-}ZC_6H_4CH_2X$ are measured, it is possible to study the electronic effects of groups Z on the reaction. Steric effects of Z are minimized

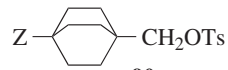
[335] The resonance contributor that has the positive charge on the more electronegative atom is less stable according to rule c in Sec. 2.E, but it nevertheless seems to be contributing in this case.
[336] Creary, X. *J. Am. Chem. Soc.* ***1984***, *106*, 5568. See, however, Takeuchi, K.; Yoshida, M.; Ohga,Y.; Tsugeno, A.; Kitagawa, T. *J. Org. Chem.* ***1990***, *55*, 6063.
[337] Gassman, P.G.; Saito, K.; Talley, J.J. *J. Am. Chem. Soc.* ***1980***, *102*, 7613.
[338] Takeuchi, K.; Kitagawa, T.; Okamoto, K. *J. Chem. Soc., Chem. Commun.* ***1983***, 7. See also, Dao, L.H.; Maleki, M.; Hopkinson, A.C.; Lee-Ruff, E. *J. Am. Chem. Soc.* ***1986***, *108*, 5237.
[339] Halvorsen, A.; Songstad, J. *J. Chem. Soc., Chem. Commun.* ***1978***, 327.
[340] Bordwell, F.G.; Brannen Jr., W.T. *J. Am. Chem. Soc.* ***1964***, *86*, 4645. Sisti, A.J.; Lowell, S. *Can. J. Chem.* ***1964***, *42*, 1896.
[341] See Lee, I.; Shim, C.S.; Chung, S.Y.; Lee, H.W. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 975; Yoh, S.; Lee, H.W. *Tetrahedron Lett.* ***1988***, *29*, 4431.
[342] Cinquini, M.; Colonna, S.; Landini, D.; Maia, A.M. *J. Chem. Soc., Perkin Trans. 2* ***1976***, 996.
[343] See Creary, X.; Mehrsheikh-Mohammadi, M.E.; Eggers, M.D. *J. Am. Chem. Soc.* ***1987***, *109*, 2435.
[344] See Gronert, S.; Pratt, L.M.; Mogali, S. *J. Am. Chem. Soc.* ***2001***, *123*, 3081.
[345] See Sedaghat-Herati, M.R.; McManus, S.P.; Harris, J.M. *J. Org. Chem.* ***1988***, *53*, 2539.
[346] See, for example, Okamoto, K.; Kita, T.; Araki, K.; Shingu, H. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 1913.
[347] Sugawara, M.; Yoshida, J.-i. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 1253.
[348] Nakashima, T.; Fujiyama, R.; Kim, H.-J.; Fujio, M.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 429.

or eliminated, because Z is so far from the reaction site. For S_N1 reactions, electron-withdrawing Z groups decrease the rate and electron-donating Z groups increase it.[349] This is because the latter decrease the energy of the transition state (and of the carbocation) by spreading the positive charge, for example,

while electron-withdrawing groups concentrate the charge. The Hammett σ ρ relationship[350] (Sec. 9.C) correlates fairly successfully the rates of many of these reactions (with σ^+ instead of σ). ρ values are generally about -4, which is what is expected for a reaction where a positive charge is created in the transition state.

For S_N2 reactions, no such simple correlations are found.[351] In this mechanism, bond breaking is about as important as bond making in the rate-determining step, and substituents have an effect on both processes, often in opposite directions. The unsubstituted benzyl chloride and benzyl bromide solvolyze by the S_N2 mechanism.[343] For Z = alkyl, the *Baker-Nathan order* (Sec. 2.M) is usually observed both for S_N1 and S_N2 reactions.

In *para*-substituted benzyl systems, steric effects have been removed, but resonance and field effects are still present. However, Holtz and Stock studied a system that removes not only steric effects but also resonance effects. This is the 4-substituted bicyclo[2.2.2]octylmethyl tosylate system (**90**).[352] In this system steric effects are completely absent owing to the rigidity of the molecules, and only field effects operate. By this means, Holtz and Stock showed that electron-withdrawing groups increase the rate of S_N2 reactions. This can be ascribed to stabilization of the transition state by withdrawal of some of the electron density.



90

For substrates that react by the tetrahedral mechanism, electron-withdrawing groups increase the rate and electron-donating groups decrease it.

7. *Cyclic substrates*. Cyclopropyl substrates are extremely resistant to nucleophilic attack.[353] For example, cyclopropyl tosylate solvolyzes $\sim 10^6$ times more slowly than cyclobutyl tosylate in acetic acid at 60 °C.[354] When such attack does take place, the result is generally not normal substitution but ring opening,[347] though exceptions are known,[355] especially when an α stabilizing group such as aryl or alkoxy is present:

[349] Jorge, J.A.L.; Kiyan, N.Z.; Miyata, Y.; Miller, J. *J. Chem. Soc., Perkin Trans. 2* ***1981***, 100; Vitullo, V.P.; Grabowski, J.; Sridharan, S. *J. Chem. Soc., Chem. Commun.* ***1981***, 737.

[350] See Fernández, I.; Frenking, G. *J. Org. Chem.* ***2006***, *71*, 2251.

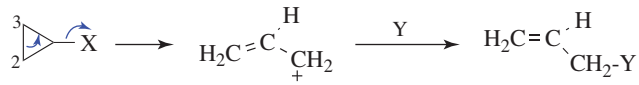
[351] See Lee, I.; Sohn, S.C.; Oh, Y.J.; Lee, B.C. *Tetrahedron* ***1986***, *42*, 4713.

[352] Holtz, H.D.; Stock, L.M. *J. Am. Chem. Soc.* ***1965***, *87*, 2404.

[353] See Friedrich, E.C. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, ***1987***, pp. 633–700; Aksenov, V.S.; Terent'eva, G.A.; Savinykh, Yu.V. *Russ. Chem. Rev.* ***1980***, *49*, 549.

[354] Roberts, J.D.; Chambers, V.C. *J. Am. Chem. Soc.* ***1951***, *73*, 5034.

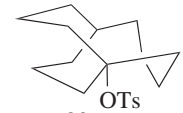
[355] See Banert, K. *Chem. Ber.* ***1985***, *118*, 1564; Vilsmaier, E.; Weber, S.; Weidner, J. *J. Org. Chem.* ***1987***, *52*, 4921.



There is much evidence that the ring opening is usually concerted with the departure of the leaving group[356] (as in the similar case of cyclobutyl substrates, Sec. 10.C.i, category 4.b.iv), from which we can conclude that if the 2,3 bond of the cyclopropane ring did not assist, the rates would be lower still. Strain plays a role in the ring-opening process.[357] It has been estimated[358] that without this assistance the rates of these already slow reactions would be further reduced by a factor of perhaps 10^{12}. For a discussion of the stereochemistry of the ring opening, see **18-27**, Sec. B. For larger rings, we have seen (Sec. 9.A) that, because of I strain, cyclohexyl substrates solvolyze slower than analogous compounds in which the leaving group is attached to a ring of 5 members or of from 7 to 11 members.

8. *Bridgeheads*.[17] The S_N2 mechanism is impossible at most bridgehead compounds (Sec. 10.A.i). Nucleophilic attack in [1.1.1]propellane has been reported, however.[359] In general, a relatively large ring is required for an S_N1 reaction to take place (Sec. 10.A.ii).[360] The S_N1 reactions have been claimed to occur for 1-iodobicyclo[1.1.1]pentane via the bicyclo[1.1.1]pentyl cation,[361] but this has been disputed and the bicyclo[1.1.0]butylcarbinyl cation was calculated to be the real intermediate.[362]

91



92

Solvolytic reactivity at bridgehead positions spans a wide range; for example, from $k = 4 \times 10^{-17}$ s^{-1} for **91** (very slow) to 3×10^{6} s^{-1} for the [3.3.3] compound **92** (very fast);[363] a range of 22 orders of magnitude. Molecular mechanics calculations show that S_N1 bridgehead reactivity is determined by strain changes between the substrate and the carbocation intermediate.[364]

9. *Deuterium substitution*. Both α and β secondary isotope effects affect the rate in various ways (Sec. 6.J.vii). The measurement of a secondary isotope effect provides a means of distinguishing between S_N1 and S_N2 mechanisms, since for S_N2 reactions the values range from 0.95 to 1.06 per α D, while for S_N1 reactions the values are

[356] See Jefford, C.W.; Wojnarowski, W. *Tetrahedron* ***1969***, *25*, 2089; Hausser, J.W.; Uchic, J.T. *J. Org. Chem.* ***1972***, *37*, 4087.
[357] See Wolk, J.L.; Hoz, T.; Basch, H.; Hoz, S. *J. Org. Chem.* ***2001***, *66*, 915.
[358] Brown, H.C.; Rao, C.G.; Ravindranathan, M. *J. Am. Chem. Soc.* ***1978***, *100*, 7946.
[359] Sella, A.; Basch, H.; Hoz, S. *Tetrahedron Lett.* ***1996***, *37*, 5573.
[360] See Kraus, G.A.; Hon, Y.; Thomas, P.J.; Laramay, S.; Liras, S.; Hanson, J. *Chem. Rev.* ***1989***, *89*, 1591.
[361] Adcock. J.L.; Gakh, A.A. *Tetrahedron Lett.* ***1992***, *33*, 4875.
[362] Wiberg, K.B.; McMurdie, N. *J. Org. Chem.* ***1993***, *58*, 5603.
[363] Bentley, T.W.; Roberts, K. *J. Org. Chem.* ***1988***, *50*, 5852.
[364] Bingham, R.C.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1971***, *93*, 3189; Müller, P.; Mareda, J. *Helv. Chim. Acta* ***1987***, *70*, 1017.

TABLE 10.3 List of groups in approximately descending order of reactivity towards S_N1 and S_N2 reactions[a]

S_N1 reactivity	S_N2 reactivity
Ar_3CX	Ar_3CX
Ar_2CHX	Ar_2CHX
$ROCH_2X$, $RSCH_2X$, R_2NCH_2X	$ArCH_2X$
R_3CX	ZCH_2X
$ArCH_2X$	$-C=C-CH_2X$
$-C=C-CH_2X$	$RCH_2X \approx RCHDX \approx RCHDCH_2X$
R_2CHX	R_2CHX
$RCH_2X \approx R_3CCH_2X$	R_3CX
RCHDX	ZCH_2CH_2X
$RCHDCH_2X$	R_3CCH_2X
$-C=C-C-X$	$-C=C-C-X$
ZCH_2X	
ZCH_2CH_2X	ArX
ArX	Bridgehead–X
[2.2.1] Bridgehead–X	

[a] Z is RCO, HCO, ROCO, NH_2CO, NC, or a similar group.

higher.[365] This method is especially good because it provides the minimum of perturbation of the system under study; changing from α H to α D hardly affects the reaction, while other probes, such as changing a substituent or the polarity of the solvent, may have a much more complex effect.

Table 10.3 is an approximate listing of groups in order of S_N1 and S_N2 reactivity. Table 10.4 shows the main reactions that proceed by the S_N2 mechanism (if R = primary or, often, secondary alkyl).

10.G.ii. The Effect of the Attacking Nucleophile[366]

Any species that has an unshared pair (i.e., any Lewis base) can, in principle, be a nucleophile, whether it is neutral or has a negative charge. The rates of S_N1 reactions are independent of the identity of the nucleophile, since the nucleophile does not appear in the rate-determining step.[367] This may be illustrated by the effect of changing the nucleophile from H_2O to ^-OH for a primary substrate and a tertiary substrate. For methyl bromide, which reacts by an S_N2 mechanism, the rate is multiplied > 5000 by the change to the more powerful nucleophile ^-OH, but for *tert*-butylbromide, which reacts by an S_N1 mechanism, the rate is unaffected.[368] A change in nucleophile can, however, change the *product* of an

[365] Shiner Jr., V.J.; Fisher, R.D. *J. Am. Chem. Soc.* ***1971***, *93*, 2553. For a review of secondary isotope effects in S_N2 reactions, see Westaway, K.C. *Isot. Org. Chem.* ***1987***, *7*, 275.

[366] Harris, J.M.; McManus, S.P. *Nucleophilicity*, American Chemical Society, Washington, DC, ***1987***; Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 145–167, 181–186; Hudson, R.F. in Klopman, G. *Chemical Reactivity and Reaction Paths*, Wiley, NY, ***1974***, pp. 167–252.

[367] See Ritchie, C.D.; Minasz, R.J.; Kamego, A.A.; Sawada, M. *J. Am. Chem. Soc.* ***1977***, *99*, 3747; McClelland, R.A.; Banait, N.; Steenken, S. *J. Am. Chem. Soc.* ***1986***, *108*, 7023.

[368] Bateman, L.C.; Cooper, K.A.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1940***, 925.

TABLE 10.4 The more important synthetic reactions of Chapter 10 that take place by S_N2 mechanism[a] (Catalysts are not shown.[b])

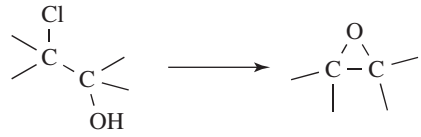
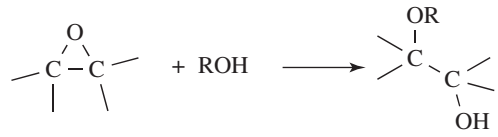
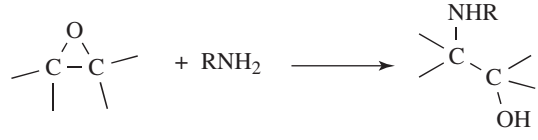
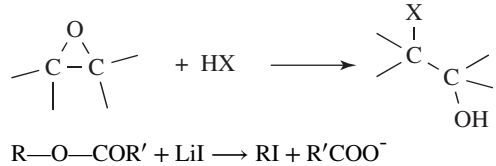
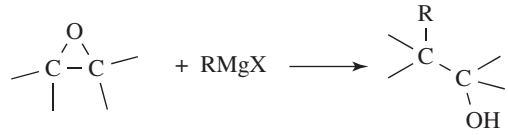
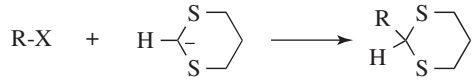
10-1	$RX + OH^- \longrightarrow ROH$
10-8	$RX + OR^- \longrightarrow ROR'$
10-9	
10-10	$R{-}OSO_2OR'' + OR^- \longrightarrow ROR'$
10-12	$2ROH \longrightarrow ROR$
10-14	
10-15	$R_3O^+ + R'OH \longrightarrow ROR'$
10-17	$RX + R'COO^- \longrightarrow R'COOR$
10-21	$RX + OOH^- \longrightarrow ROOH$
10-25	$RX + SH^- \longrightarrow RSH$
10-26	$RX + R'S^- \longrightarrow RSR'$
10-27	$RX + S_2^{2-} \longrightarrow RSSR$
10-30	$RX + SCN^- \longrightarrow RSCN$
10-31	$RX + R_2^-NH \longrightarrow RR_2'N$
10-31	$RX + R_3^{-'}N \longrightarrow RR_3'N^+X^-$
10-35	
10-41	$RX + R'CONH^- \longrightarrow RNHCOR'$
10-42	$RX + NO_2^- \longrightarrow RNO_2 + RONO$
10-43	$RX + N_3^- \longrightarrow RN_3$
10-44	$RX + NCO^- \longrightarrow RNCO$
10-44	$RX + NCS^- \longrightarrow RNCS$
10-46	$RX + X'^- \longrightarrow RX'$
10-47	$R{-}OSO_2OR' + X^- \longrightarrow RX$
10-48	$ROH + 2PCl_5 \longrightarrow RCl$
10-49	$ROR' + 2HI \longrightarrow RI + RT$
10-50	
10-51	$R{-}O{-}COR' + LiI \longrightarrow RI + R'COO^-$

TABLE 10.4 (*Continued*)

10-57	$RX + 2HIR_2CuLi \longrightarrow RI$
10-65	
10-67	$RX + H\bar{C}(CO_2R'_2) \longrightarrow RCH(CO_2R')_2$
10-68	$RX + R''CH{-}COR' \longrightarrow RCR''{-}COR'$
10-70	$RX + R'CHCOO^- \longrightarrow RR'CHCOO^-$
10-71	
10-74	$RX + R'C{\equiv}C^- \longrightarrow RC{\equiv}CR'$
10-75	$RX + CN^- \longrightarrow RCN$

[a] R = primary, often secondary, alkyl. [b] This is a schematic list only. Some of these reactions may also take place by other mechanisms and the scope may vary greatly. See the discussion of each reaction for details.

S_N1 reaction. Thus solvolysis of benzyl tosylate in methanol gives benzyl methyl ether (the nucleophile is the solvent methanol). If the more powerful nucleophile Br^- is added, the rate is unchanged, but the product is now benzyl bromide.

It is noted that the so-called *cation affinity* is used to measure to ability of a cation to interact with an electron-donating species. While this is not formally used to describe S_N1 reactions, it is important for catalytic activity due to different ligands.[369]

For S_N2 reactions in solution there are four main principles that govern the effect of the nucleophile on the rate. The nucleophilicity order is not invariant, but depends on substrate, solvent, leaving group, and so on.

1. A nucleophile with a negative charge is always a more powerful nucleophile than its conjugate acid (assuming the latter is also a nucleophile). Thus ^-OH is more powerful than H_2O, $^-NH_2$ more powerful than NH_3, and so on.
2. In comparing nucleophiles whose attacking atom is in the same row of the periodic table, nucleophilicity is approximately the same as the order of basicity,[370] although *basicity is thermodynamically controlled and nucleophilicity is kinetically controlled*. So an approximate order of nucleophilicity is $^-NH_2 > RO^- > {}^-OH > R_2NH > ArO^- > NH_3 >$ pyridine $> F^- > H_2O > ClO_4{}^-$, and another is $R_3C^- > R_2N^- > RO^- > F^-$ (see Table 8.1). This type of correlation works best when the structures of the nucleophiles being compared are similar, as with a set of substituted phenoxides. Within such a series, linear relationships can often be established between nucleophilic rates and p*K* values.[371]
3. Going down the periodic table, nucleophilicity increases, although basicity decreases. Thus the usual order of halide nucleophilicity is $I^- > Br^- > Cl^- > F^-$ (as will been seen below, this order is solvent dependent). Similarly, any sulfur

[369] See Wei, Y.; Sastry, G.N.; Zipse, H. *J. Am. Chem. Soc.* ***2008***, *130*, 3473.
[370] Uggerud, E. *Chem. Eur. J.* ***2006***, *12*, 1127.
[371] See Bordwell, F.G.; Hughes, D.L. *J. Am. Chem. Soc.* ***1984***, *106*, 3234.

nucleophile is more powerful than its oxygen analog, and the same is true for phosphorus versus nitrogen. The main reason for this distinction between basicity and nucleophilic power is that the smaller negatively charged nucleophiles are more solvated by the usual polar protic solvents; that is, because the negative charge of Cl^- is more concentrated than the charge of I^-, the former is more tightly surrounded by a shell of solvent molecules that constitute a barrier between it and the substrate. This is most important for protic polar solvents in which the solvent may be hydrogen bonded to small nucleophiles. Evidence for this is that many nucleophilic substitutions with small negatively charged nucleophiles are much more rapid in aprotic polar solvents than in protic ones[372] and that, in DMF (an aprotic solvent) the order of nucleophilicity was $Cl^- > Br^- > I^-$.[373] Another experiment was the use of $Bu_4N^+ X^-$ and LiX as nucleophiles in acetone, where X^- was a halide ion. The halide ion in the former salt is much less associated than in LiX. The relative rates with LiX were Cl^-, 1; Br^-, 5.7; I^-, 6.2, which is in the normal order, while with $Bu_4N^+ X^-$, where X^- is much freer, the relative rates were Cl^-, 68; Br^-, 18; I^-, 3.7.[374] In a further experiment, halide ions were allowed to react with the molten salt $(n\text{-}C_5H_{11})_4N^+ X^-$ at 180 °C in the absence of a solvent.[375] Under these conditions, where the ions are unsolvated and unassociated, the relative rates were Cl^-, 620; Br^-, 7.7; I^-, 1. In the gas phase (no solvent), an approximate order of nucleophilicity was found to be $^-OH > F^- \approx MeO^- > MeS^- \gg Cl^- > {}^-CN > Br^-$,[376] providing further evidence that solvation[377] is responsible for the effect in solution.

However, solvation is not the entire answer since, even for *uncharged* nucleophiles, nucleophilicity increases going down a column in the periodic table. These nucleophiles are not so greatly solvated and changes in solvent do not greatly affect their nucleophilicity.[378] To explain these cases, the principle of hard and soft acids and bases (Sec. 8.E) may be used.[379] The proton is a hard acid, but an alkyl substrate (which may be considered to act as a Lewis acid toward the nucleophile considered as a base) is a good deal softer. According to the principle given in Sec. 8.F, an alkyl group is expected to prefer softer nucleophiles than the proton. Thus the larger, more polarizable (softer) nucleophiles have a greater (relative) attraction toward an alkyl carbon than toward a proton.

4. The freer the nucleophile, the greater the rate.[380] One instance of this has already been discussed.[374] Another is that the rate of attack by $(EtOOC)_2CBu^- Na^+$ in benzene was increased by the addition of substances (e.g., 1,2-dimethoxyethane,

[372] Parker, A.J. *J. Chem. Soc.* ***1961***, 1328 has a list of about 20 such reactions.

[373] Weaver, W.M.; Hutchison, J.D. *J. Am. Chem. Soc.* ***1964***, *86*, 261; See also, Bordwell, F.G.; Hughes, D.L. *J. Org. Chem.* ***1981***, *46*, 3570. For a contrary result in liquid sulfur dioxide, see Lichtin, N.N.; Puar, M.S.; Wasserman, B. *J. Am. Chem. Soc.* ***1967***, *89*, 6677.

[374] Winstein, S.; Savedoff, L.G.; Smith, S.G.; Stevens, I.D.R.; Gall, J.S. *Tetrahedron Lett.* ***1960***, *9*, 24.

[375] Gordon, J.E.; Varughese, P. *Chem. Commun.* ***1971***, 1160. See also, Ford, W.T.; Hauri, R.J.; Smith, S.G. *J. Am. Chem. Soc.* ***1974***, *96*, 4316.

[376] Olmstead, W.N.; Brauman, J.I. *J. Am. Chem. Soc.* ***1977***, *99*, 4219. See also, Tanaka, K.; Mackay, G.I.; Payzant, J.D.; Bohme, D.K. *Can. J. Chem.* ***1976***, *54*, 1643.

[377] See Kormos, B.L.; Cramer, C.J. *J. Org. Chem.* ***2003***, *68*, 6375.

[378] Parker, A.J. *J. Chem. Soc.* ***1961***, 4398.

[379] Pearson, R.G. *Surv. Prog. Chem.* ***1969***, *5*, 1 (pp. 21–38).

[380] See Guibe, F.; Bram, G. *Bull. Soc. Chim. Fr.* ***1975***, 933.

adipamide) that specifically solvated the Na^+ and thus left the anion freer.[381] In a nonpolar solvent, such as benzene, salts, such as $(EtOOC)_2CBu^- Na^+$, usually exist as ion-pair aggregations of large molecular weights.[382] Similarly, it was shown that the half-life of the reaction between $C_6H_5COCHEt^-$ and ethyl bromide depended on the positive ion: K^+, 4.5×10^{-3}; Na^+, 3.9×10^{-5}; Li^+, 3.1×10^{-7}.[383] Presumably, the potassium ion leaves the negative ion freest to attack most rapidly. Further evidence is that in the gas phase,[384] where nucleophilic ions are completely free, without solvent or counterion, reactions take place orders of magnitude faster than the same reactions in solution.[385] It has proven possible to measure the rates of reaction of ^-OH with methyl bromide in the gas phase, with ^-OH either unsolvated or solvated with one, two, or three molecules of water.[386] The rates were, with the number of water molecules in parentheses: (0) 1.0×10^{-9}; (1) 6.3×10^{-10}; (2) 2×10^{-12}; (3) 2×10^{-13} cm^3 $molecule^{-1}$ s^{-1}, evidence that solvation of the nucleophile decreases the rate. The rate of this reaction in aqueous solution is 2.3×10^{-25} cm^3 $molecule^{-1}$ s^{-1}. Similar results were found for other nucleophiles and other solvents.[387] In solution too, studies have been made of the effect of solvation of the nucleophile by a specific number of water molecules. Indeed, hydrogen bonding lowers the intrinsic nucleophilicity.[388] When the salt $(n\text{-}C_6H_{13})_4N^+ F^-$ reacted with *n*-octyl methanesulfonate, the relative rate fell from 822 for no water molecules to 96 for 1.5 water molecules to 1 for 6 water molecules.[389]

In Chapter 3 cryptands were seen to specifically solvate the alkali metal portion of salts such as KF, KOAc, and so on. Synthetic advantage can be taken of this fact to allow anions to be freer, thus increasing the rates of nucleophilic substitutions and other reactions (Sec. 10.G.v).

However, the four rules given above do not always hold. One reason is that steric influences often play a part. For example, the *tert*-butoxide ion Me_3CO^- is a stronger base than ^-OH or ^-OEt, but a much poorer nucleophile because its large bulk hinders it from closely approaching a substrate.

The following overall nucleophilicity order for S_N2 mechanisms (in protic solvents) was given by Edwards and Pearson:[390] $RS^- > ArS^- > I^- > {}^-CN > {}^-OH > N_3{}^- > Br^- > ArO^- > Cl^- >$ pyridine $> AcO^- > H_2O$. A quantitative relationship[391] (the *Swain-Scott*

[381] Zaugg, H.E.; Leonard, J.E. *J. Org. Chem.* ***1972***, *37*, 2253. See also, Solov'yanov, A.A.; Ahmed, E.A.A.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1987***, *23*, 1243; Jackman, L.M.; Lange, B.C. *J. Am. Chem. Soc.* ***1981***, *103*, 4494.

[382] See, for example, Williard, P.G.; Carpenter, G.B. *J. Am. Chem. Soc.* ***1986***, *108*, 462.

[383] Zook, H.D.; Gumby, W.L. *J. Am. Chem. Soc.* ***1960***, *82*, 1386. See also, Cacciapaglia, R.; Mandolini, L. *J. Org. Chem.* ***1988***, *53*, 2579.

[384] See Barlow, S.E.; van Doren, J.M.; Bierbaum, V.M. *J. Am. Chem. Soc.* ***1988***, *110*, 7240; Merkel, A.; Havlas, Z.; Zahradník, R. *J. Am. Chem. Soc.* ***1988***, *110*, 8355.

[385] Olmstead, W.N.; Brauman, J.I. *J. Am. Chem. Soc.* ***1977***, *99*, 4219.

[386] Bohme, D.K.; Raksit, A.B. *J. Am. Chem. Soc.* ***1984***, *106*, 3447. See also, Hierl, P.M.; Ahrens, A.F.; Henchman, M.; Viggiano, A.A.; Paulson, J.F.; Clary, D.C. *J. Am. Chem. Soc.* ***1986***, *108*, 3142.

[387] Bohme, D.K.; Raksit, A.B. *Can. J. Chem.* ***1985***, *63*, 3007.

[388] Chen, X.; Brauman, J.I. *J. Am. Chem. Soc.* ***2008***, *130*, 15038.

[389] Landini, D.; Maia, A.; Rampoldi, A. *J. Org. Chem.* ***1989***, *54*, 328.

[390] Edwards, J.O.; Pearson, R.G. *J. Am. Chem. Soc.* ***1962***, *84*, 16.

[391] Swain, C.G.; Scott, C.B. *J. Am. Chem. Soc.* ***1953***, *75*, 141.

TABLE 10.5 Nucleophilicities of some common reagents[394]

Nucleophile	*n*
SH	5.1
CN^-	5.1
I^-	5.0
$PhNH_2$	4.5
^-OH	4.2
N_3^-	4.0
Pyridine	3.6
Br^-	3.5
PhO^-	3.5
AcO^-	2.7
Cl^-	2.7
F^-	2.0
NO_3^-	1.0
H_2O	0.0

Reprinted with permission from Wells, P.R. *Chem. Rev.* ***1963***, *63*, 171. Copyright 1963 American Chemical Society.

equation, which can be derived from *Marcus theory*[392]) has been worked out similar to the linear free-energy equations considered in Chapter 9.[393] The equation is

$$\log\ k/k_0 = s \bullet n$$

where n is the nucleophilicity of a given group, s is the sensitivity of a substrate to nucleophilic attack, and k_0 is the rate for H_2O, which is taken as the standard and for which n is assigned a value of zero. The parameter s is defined as 1.0 for bromomethane. Table 10.5[394] contains values of n for some common nucleophiles. The order is similar to that of Edwards and Pearson.

It is now evident that there is *no* absolute order of either nucleophilicity[395] or leaving-group ability, even in the gas phase where solvation is not a factor, because they have an effect on each other. When the nucleophile and leaving group are both hard or both soft, the reaction rates are relatively high, but when one is hard and the other soft, rates are reduced.[384] Although this effect is smaller than the effects in points one and four above, it still prevents an absolute scale of either nucleophilicity or leaving-group ability.[396] There

[392] Albery, W.J.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* ***1978***, *16*, 87 (pp. 113–115).

[393] Also see Ritchie, C.D. *Pure Appl. Chem.* ***1978***, *50*, 1281; Duboc, C. in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry, Recent Advances*, Plenum, NY, ***1978***, pp. 313–355; Ibne-Rasa, K.M. *J. Chem. Educ.* ***1967***, *44*, 89; Kawazoe, Y.; Ninomiya, S.; Kohda, K.; Kimoto, H. *Tetrahedron Lett.* ***1986***, *27*, 2897; Kevill, D.N.; Fujimoto, E.K. *J. Chem. Res. (S)* ***1988***, 408.

[394] From Wells, P.R. *Chem. Rev.* ***1963***, *63*, 171 (p. 212). See also, Koskikallio, J. *Acta Chem. Scand.* ***1969***, *23*, 1477, 1490.

[395] See Pellerite, M.J.; Brauman, J.I. *J. Am. Chem. Soc.* ***1983***, *105*, 2672.

[396] For reference scales for the characterization of cationic electrophiles and neutral nucleophiles see Mayr, H.; Bug, T.; Gotta, M.F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A.R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* ***2001***, *123*, 9500.

has been controversy as to whether the selectivity of a reaction should increase with decreasing reactivity of a series of nucleophiles, or whether the opposite holds. There is evidence for both views.[397]

For substitution at a carbonyl carbon, the nucleophilicity order is not the same as it is at a saturated carbon, but follows the basicity order more closely. The reason is presumably that the carbonyl carbon has a partial positive charge. That is, a carbonyl carbon is a much harder acid than a saturated carbon. The following nucleophilicity order for these substrates has been determined:[398] $Me_2C{=}NO^- > EtO^- > MeO^- > {}^-OH > {}^-OAr > N_3^- > F^- > H_2O > Br^- \sim I^-$. Soft bases are ineffective at a carbonyl carbon.[399] In a reaction carried out in the gas phase with alkoxide nucleophiles OR^- solvated by only one molecule of an alcohol R'OH, it was found that both RO^- and $R'O^-$ attacked the formate substrate (HCO_2R'') about equally, although in the unsolvated case, the more basic alkoxide is the better nucleophile.[400] The product ion R^2O^- was also solvated by one molecule of ROH or R'OH.

If an atom containing one or more unshared pairs is adjacent to the attacking atom on the nucleophile, the nucleophilicity is enhanced.[401] Examples of such nucleophiles are HO_2^-, $Me_2C{-}NO^-$, NH_2NH_2, and so on. This is called the *alpha effect* (α effect),[402] and a broader definition is a positive deviation exhibited by an α nucleophile from a Brønsted-type nucleophilicity plot,[403] where the reference (or normal) nucleophile is one that possesses the same basicity as the α nucleophile but does not deviate from the Brønsted-type plot. Several reviews of the α effect have been published previously.[88,404] Several possible explanations have been offered.[405] One is that the ground state of the nucleophile is destabilized by repulsion between the adjacent pairs of electrons;[406] another is that the transition state is stabilized by the extra pair of electrons;[407] a third is that the adjacent electron pair reduces solvation of the nucleophile.[408] Evidence supporting the third explanation is that there was no α effect in the reaction of HO_2^- with methyl formate in the gas phase,[409] although HO_2^- shows a strong alpha effect in solution. The α effect has been demonstrated to be remarkably dependent on the nature of the solvent.[410] The α effect is substantial for substitution at a carbonyl or other unsaturated carbon, at some inorganic atoms,[411] and for reactions of a

[397] For discussions, see Dietze, P.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 5880.
[398] Jencks, W.P.; Gilchrist, M. *J. Am. Chem. Soc.* ***1968***, *90*, 2622.
[399] For theoretical treatments of nucleophilicity at a carbonyl carbon, see Buncel, E.; Shaik, S.S.; Um, I.; Wolfe, S. *J. Am. Chem. Soc.* ***1988***, *110*, 1275, and references cited therein.
[400] Baer, S.; Stoutland, P.O.; Brauman, J.I. *J. Am. Chem. Soc.* ***1989***, *111*, 4097.
[401] Definition in the Glossary of Terms used in Physical Organic Chemistry, *Pure & Appl. Chem.* ***1979***, *51*, 1731.
[402] See Ren, Y.; Yamataka, H. *J. Org. Chem.* ***2007***, *72*, 5660; *Org. Lett.* ***2006***, *8*, 119; *Chem. Eur. J.* ***2007***, *13*, 677.
[403] Hoz, S.; Buncel, E. *Israel J. Chem.* ***1985***, *26*, 313.
[404] Grekov, A.P.; Veselov, V.Ya. *Russ. Chem. Rev.* ***1978***, *47*, 631; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, ***1969***; pp 107–111.
[405] See Ho, S.; Buncel, E. *Isr. J. Chem.* ***1985***, *26*, 313.
[406] Buncel, E.; Hoz, S. *Tetrahedron Lett.* ***1983***, *24*, 4777. For evidence that this is not the sole cause, see Oae, S.; Kadoma, Y. *Can. J. Chem.* ***1986***, *64*, 1184.
[407] See Hoz, S. *J. Org. Chem.* ***1982***, *47*, 3545; Laloi-Diard, M.; Verchere, J.; Gosselin, P.; Terrier, F. *Tetrahedron Lett.* ***1984***, *25*, 1267.
[408] Also see Hudson, R.F.; Hansell, D.P.; Wolfe, S.; Mitchell, D.J. *J. Chem. Soc., Chem. Commun.* ***1985***, 1406. See Herschlag, D.; Jencks, W.P. *J. Am. Chem. Soc.* ***1990***, *112*, 1951.
[409] Terrier, F.; Degorre, F.; Kiffer, D.; Laloi, M. *Bull. Soc. Chim. Fr.* ***1988***, 415. For arguments against, see Moss, R.A.; Swarup, S.; Ganguli, S. *J. Chem. Soc., Chem. Commun.* ***1987***, 860.
[410] Buncel, E.; Um, I.-H. *Tetrahedron* ***2004***, *60*, 7801.
[411] For example, see Kice, J.L.; Legan, E. *J. Am. Chem. Soc.* ***1973***, *95*, 3912.

nucleophile with a carbocation,[412] but is generally smaller or absent entirely for substitution at a saturated carbon.[413]

Attempts have been made to establish a general scale of nucleophilicity,[414] and the nucleophilic reactivity of other moieties have been determined, including alcohols and alkoxides,[415] carbanions,[416] amines,[417] pyridines,[418] pyrroles,[419] indoles,[420] imides and amides,[421] amino acids and peptides,[422] and sulfur ylids.[423] The correlation of nucleophilicity and basicity has been discussed for alkyl amines.[424] The nucleophilicity of metal-bound superoxide ligands has been discussed.[425] The nucleophilicity of 2-imdiazolines and other *N*-heterocyclic compounds has been discussed.[426] The nucleophilic reactivity of ethyl arylacetate anions has been discussed.[427] The nucleophilic reactivity of hydrazine and amines has been examined.[428]

10.G.iii. The Effect of the Leaving Group

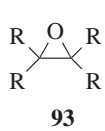
The leaving group at a saturated carbon comes off more easily the more stable it is as a free entity. This is usually inverse to its basicity, and the best leaving groups are the weakest bases. Thus iodide is the best leaving group among the halides and fluoride the poorest. Since XH is always a weaker base than X^-, nucleophilic substitution is always easier at a substrate RXH^+ than at RX. An example of this effect is that OH and OR are not leaving groups from ordinary alcohols and ethers but can come off when the groups are protonated, that is, converted to ROH_2^+ or $RORH^+$.[429] Reactions in which the leaving group does not come off until it has been protonated have been called S_N1cA or S_N2cA, depending on whether after protonation the reaction is an S_N1 or S_N2 process (these designations are often shortened to A1 and A2). The cA stands for conjugate acid, since the substitution takes

[412] Dixon, J.E.; Bruice, T.C. *J. Am. Chem. Soc.* ***1971***, *93*, 3248, 6592.
[413] McIsaac Jr., J.E.; Subbaraman, L.R.; Subbaraman, J.; Mulhausen, H.A.; Behrman, E.J. *J. Org. Chem.* ***1972***, *37*, 1037. See, however, Buncel, E.; Wilson, H.; Chuaqui, C. *J. Am. Chem. Soc.* ***1982***, *104*, 4896; *Int. J. Chem. Kinet.* ***1982***, *14*, 823.
[414] Phan, T.B.; Breugst, M.; Mayr, H. *Angew. Chem. Int. Ed.* ***2006***, *45*, 3869.
[415] Phan, T.B.; Mayr, H. *Can. J. Chem.* ***2005***, *83*, 1554.
[416] Phan, T.B.; Mayr, H. *Eur. J. Org. Chem.* ***2006***, 2530.
[417] Brotzel, F.; Chu, Y.C.; Mayr, H. *J. Org. Chem.* ***2007***, *72*, 3679; Korzhenevskaya, N.G. *Russ. J. Org. Chem.* ***2008***, *44*, 1255.
[418] Brotzel, F.; Kempf, B.; Singer, T.; Zipse, H.; Mayr, H. *Chem. Eur. J.* ***2007***, *13*, 336.
[419] Nigst, T.A.; Westermaier, M.; Ofial, A.R.; Mayr, H. *Eur. J. Org. Chem.* ***2008***, 2369.
[420] Lakhdar, S.; Westermaier, M.; Terrier, F.; Goumont, R.; Boubaker, T.; Ofial, A.R.; Mayr, H. *J. Org. Chem.* ***2006***, *71*, 9088.
[421] Breugst, M.; Tokuyasu, T.; Mayr, H. *J. Org. Chem.* ***2010***, *75*, 5250.
[422] Brotzel, F.; Mayr, H. *Org. Biomol. Chem.* ***2007***, *5*, 3814.
[423] Appel, R.; Mayr, H. *Chem. Eur. J.* ***2010***, *16*, 8610.
[424] Hall, H.K.; Bates, R.B. *Tetrahedron Lett.* ***2012***, *53*, 1830.
[425] Ure, A.D.; McDonald, A.R. *Synlett* ***2015***, *26*, 2060.
[426] Maji, B.; Baidya, M.; Ammer, J.; Kobayashi, S.; Mayer, P.; Ofial, A.R.; Mayr, H. *Eur. J. Org. Chem.* ***2013***, 3369.
[427] Corral-Bautista, F.; Mayr, H. *Eur. J. Org. Chem.* ***2013***, 4255.
[428] Nigst, T.A.; Antipova, A.; Mayr, H. *J. Org. Chem.* ***2012***, *77*, 8142.
[429] See Staude, E.; Patat, F. in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 22–46. See Anderson, P.; Petit, A.; Ho, J.; Mitoraj, M.P.; Coote, M.L.; Danovich, D.; Shaik, S.; Braïda, B.; Ess, D.H. *J. Org. Chem.* ***2014***, *79*, 9998. For a discussion of SN1-type reactions of alcohols, see Emer, E.; Sinisi, R.; Capdevila, M.G.; Petruzziello, D.; De Vincentiis, F.; Cozzi, P.G. *Eur. J. Org. Chem.* ***2011***, 647.

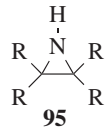
place on the conjugate acid of the substrate. The IUPAC designations for these mechanisms are, respectively, $A_h + D_N + A_N$ and $A_h + A_N D_N$; that is, the same designations as S_N1 and S_N2, with A_h to show the preliminary step. When another electrophile assumes the role of the proton, the symbol A_e is used instead. The ions ROH_2^+ and $RORH^+$ can be observed as stable entities at low temperatures in superacid solutions.[430] At higher temperatures they cleave to give carbocations.

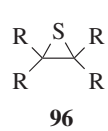
It is obvious that the best nucleophiles (e.g., NH_2^-, ^-OH) cannot take part in S_N1cA or S_N2cA processes, because they would be converted to their conjugate acids under the acidic conditions necessary to protonate the leaving groups.[431] Because S_N1 reactions do not require powerful nucleophiles but do require good leaving groups, most of them take place under acidic conditions. In contrast, S_N2 reactions, which do require powerful nucleophiles (which are generally strong bases), most often take place under basic or neutral conditions.

Another circumstance that increases leaving-group power is ring strain. Ordinary ethers do not cleave at all and protonated ethers only under strenuous conditions, but epoxides[432] (**93**) are cleaved quite easily and protonated epoxides (**94**) even more easily. Aziridines (**95**)[433] and episulfides (**96**) are also easily cleaved (Sec. 10.G.viii).[434]

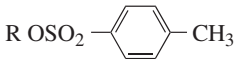

93

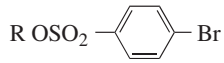

94

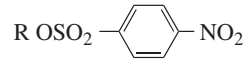

95


96

Although halides are common leaving groups in nucleophilic substitution for synthetic purposes, it is often more convenient to use alcohols. Since OH does not leave from ordinary alcohols, it must be converted to a group that does leave. One way is protonation, mentioned above. Another is conversion to a reactive ester, most commonly a sulfonic ester. The sulfonic ester groups *tosylate*, *brosylate*, *nosylate*, and *mesylate* are better leaving groups than halides and are frequently used.[435]


ROTs
p-Toluenesulfonates
Tosylates


ROBs
p-Bromobenzenesulfonates
Brosylates


RONs
p-Nitrobenzenesulfonates
Nosylates


ROMs
Methanesulfonates
Mesylates

Other leaving groups are still better, and compounds containing these groups make powerful alkylating agents. Among them are oxonium ions (ROR_2^+),[436] and the fluorinated

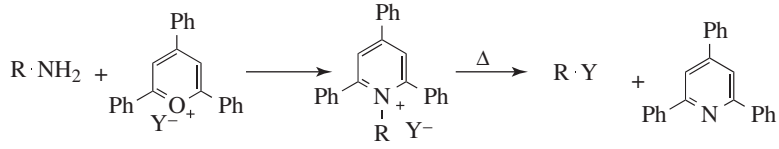
[430] Olah, J.A.; Olah, G.A. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 743–747.
[431] See Okada, S.; Abe, Y.; Taniguchi, S.; Yamabe, S. *J. Chem. Soc., Chem. Commun.* ***1989***, 610.
[432] See Smith, J.G. *Synthesis* ***1984***, 629; Bartók, M.; Láng, K.L.in Patai, S. *The Chemistry of Functional Groups*, *Supplement E*, Wiley, NY, ***1980***, pp. 609–681.
[433] See Hu, X.E. *Tetrahedron* ***2004***, *60*, 2701.
[434] See Di Vona, M.L.; Illuminati, G.; Lillocci, C. *J. Chem. Soc., Perkin Trans. 2* ***1985***, 1943; Bury, A.; Earl, H.A.; Stirling, C.J.M. *J. Chem. Soc., Chem. Commun.* ***1985***, 393.
[435] Bentley, T.W.; Christl, M.; Kemmer, R.; Llewellyn, G.; Oakley, J.E. *J. Chem. Soc., Perkin Trans. 2* ***1994***, 2531.
[436] Perst, H. *Oxonium Ions in Organic Chemistry*, Verlag Chemie, Deerfield Beach, FL, ***1971***, pp. 100–127; Perst, H. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 1961–2047; Granik, V.G.; Pyatin, B.M.; Glushkov, R.G. *Russ. Chem. Rev.* ***1971***, *40*, 747; See Curphey, T.J. *Org. Synth.* ***VI***, 1021.

compounds *triflates*[437] and *nonaflates*.[437] *Tresylates* are ~400 times less reactive than triflates, but still ~100 times more reactive than tosylates.[438]

$R—OSO_2CF_3$	$R—OSO_2C_4F_9$	$R—OSO_2CCH_2F_3$
ROTf Trifluoromethanesulfonates Triflates	Nonafluorobutanesulfonates Nonaflates	2,2,2-Trifluoroethanesulfonates Tresylates

Halonium ions ($RClR^+$, $RBrR^+$, RIR^+), which can be prepared in superacid solutions (Sec. 5.A.ii) and isolated as solid SbF_6^- salts, are also extremely reactive in nucleophilic substitution.[439] Of the above types of compound, the most important in organic synthesis are tosylates, mesylates, oxonium ions, and triflates. The others have been used mostly for mechanistic purposes.

The leaving-group ability of NH_2, NHR, and NR_2 are extremely poor,[440] but the leaving-group ability of NH_2 can be greatly improved by converting a primary amine RNH_2 to the ditosylate $RNTs_2$. The NTs_2 group has been successfully replaced by a number of nucleophiles.[441] Another way of converting NH_2 into a good leaving group has been extensively developed by Katritzky and co-workers.[442] In this method the amine is converted to a pyridinium compound (**98**) by treatment with a pyrylium salt (frequently a 2,4,6-triphenylpyrylium salt, **97**).[443] When the salt is heated, the counterion acts as a nucleophile. In some cases a nonnucleophilic ion, such as BF_4^-, is used as the counterion for the conversion **97** → **98**, and then Y^- is added to **98**.



Among the nucleophiles that have been used successfully in this reaction are I^-, Br^-, Cl^-, F^-, ^-OAc, N_3^-, NHR_2, and H^-. Ordinary NR_2 groups are good leaving groups when the substrate is a *Mannich base* (these are compounds of the form $RCOCH_2CH_2NR_2$; see reaction **16-19**).[444] The elimination–addition mechanism applies in this case.

Probably the best leaving group is N_2 from the species RN_2^+, which can be generated in several ways,[445] of which the two most important are the treatment of primary amines with nitrous acid (see **13-19**):

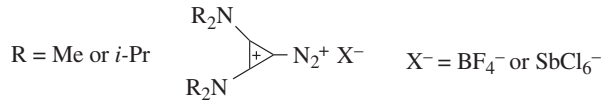
$$RNH_2 + HONO \longrightarrow RN_2^+$$

[437] See Stang, P.J.; Hanack, M.; Subramanian, L.R. *Synthesis* ***1982***, 85; Howells, R.D.; McCown, J.D. *Chem. Rev.* ***1977***, *77*, 69 (pp. 85–87).
[438] Crossland, R.K.; Wells, W.E.; Shiner Jr., V.J. *J. Am. Chem. Soc.* ***1971***, *93*, 4217.
[439] Olah, G.A.; Mo, Y.K. *J. Am. Chem. Soc.* ***1974***, *96*, 3560.
[440] See Baumgarten, R.J.; Curtis, V.A. in Patai, S. *The Chemistry of Functional Groups*, *Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 929–997.
[441] See Curtis, V.A.; Knutson, F.J.; Baumgarten, R.J. *Tetrahedron Lett.* ***1981***, *22*, 199.
[442] See Katritzky, A.R.; Sakizadeh, K.; Musumarra, G. *Heterocycles* ***1985***, *23*, 1765; Katritzky, A.R.; Musumarra, G. *Chem. Soc. Rev.* ***1984***, *13*, 47.
[443] See Katritzky, A.R.; Brycki, B. *J. Am. Chem. Soc.* ***1986***, *108*, 7295, and other papers in this series.
[444] For a review of *Mannich bases*, see Tramontini, M. *Synthesis* ***1973***, 703.
[445] Kirmse, W. *Angew. Chem. Int. Ed.* ***1976***, *15*, 251; Collins, C.J. *Acc. Chem. Res.* ***1971***, *4*, 315.

and the protonation of diazo compounds.[446]

$$R_2C{=}\overset{+}{N}{=}N^- + H^+ \longrightarrow R_2CHN_2^+$$

No matter how produced, RN_2^+ are usually too unstable to be isolable,[447] reacting presumably by the S_N1 or S_N2 mechanism.[448a] The simplest aliphatic diazonium ion $CH_2N_2^+$ has been prepared at − 120 °C in superacid solution, where it lived long enough for an NMR spectrum to be taken.[448b] Actually, the exact mechanisms are in doubt because the rate laws, stereochemistry, and products have proved difficult to interpret.[449] If there are free carbocations they should give the same ratio of substitution to elimination to rearrangements, and so on, as carbocations generated in other S_N1 reactions, but they often do not. "Hot" carbocations (unsolvated and/or chemically activated) that can hold their configuration have been postulated,[450] as have ion pairs, in which $^-$OH (or $^-$OAc, and so on, depending on how the diazonium ion is generated) is the counterion.[451] One class of aliphatic diazonium salts, of which several members have been isolated as stable salts in solution, lived long enough for an NMR spectrum to be taken.[452] Actually, the exact mechanisms are known for cyclopropeniumyldiazonium salts:[453]



Diazonium ions generated from ordinary aliphatic primary amines are usually useless for preparative purposes since they lead to a mixture of products, giving not only substitution by any nucleophile present, but also elimination and rearrangements if the substrate permits. For example, diazotization of *n*-butylamine gave 25% butan-1-ol, 5.2% 1-chlorobutane, 13.2% butan-2-ol, 36.5% butenes (consisting of 71% but-1-ene, 20% *trans*-but-2-ene, and 9% *cis*-but-2-ene), and traces of butyl nitrites.[454]

In the S_N1cA and S_N2cA mechanisms (see above) there is a preliminary step, the addition of a proton, before the normal S_N1 or S_N2 process occurs. There are also reactions in which the substrate *loses* a proton in a preliminary step. In these reactions, there is a carbene intermediate.

[446] See Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***; Hegarty, A.F. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 2, Wiley, NY, 1978, pp. 511–591 (pp. 571–575); More O'Ferrall, R.A. *Adv. Phys. Org. Chem.* ***1967***, *5*, 331; Studzinskii, O.P.; Korobitsyna, I.K. *Russ. Chem. Rev.* ***1970***, *39*, 834.

[447] For aromatic diazoium salts, see Weiss, R.; Wagner, K.; Priesner, C.; Macheleid, J. *J. Am. Chem. Soc.* ***1985***, *107*, 4491; Laali, K.; Olah, G.A. *Rev. Chem. Intermed.* ***1985***, *6*, 237; Bott, K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement C*, pt. 1, Wiley, NY, ***1983***, pp. 671–697.

[448] (a) See Mohrig, J.R.; Keegstra, K.; Maverick, A.; Roberts, R.; Wells, S. *J. Chem. Soc., Chem. Commun.* ***1974***, 780. (b) Berner, D.; McGarrity, J.F. *J. Am. Chem. Soc.* ***1979***, *101*, 3135.

[449] See Manuilov, A.V.; Barkhash, V.A. *Russ. Chem. Rev.* ***1990***, *59*, 179; Saunders Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 280–317.

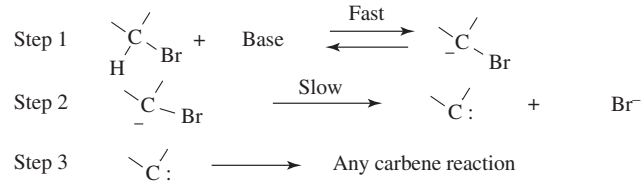
[450] See Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, including the articles by Keating, J.T.; Skell, P.S. pp. 573–653.

[451] Connor, J.K.; Maskill, H. *Bull. Soc. Chim. Fr.* ***1988***, 342.

[452] Berner, D.; McGarrity, J.F. *J. Am. Chem. Soc.* ***1979***, *101*, 3135.

[453] Weiss, R.; Wagner, K.; Priesner, C.; Macheleid, J. *J. Am. Chem. Soc.* ***1985***, *107*, 4491.

[454] Streitwieser Jr., A.; Schaeffer, W.D. *J. Am. Chem. Soc.* ***1957***, *79*, 2888.



Once formed by this process, the carbene may undergo any of the normal carbene reactions (Sec. 5.D.ii). When the net result is substitution, this mechanism has been called the S_N1cB (for conjugate base) mechanism.[455] Although the slow step is an S_N1 step, the reaction is second order; first order in substrate and first order in base.

Table 10.6 lists some leaving groups in approximate order of ability to leave. The order of leaving-group ability is about the same for S_N1 and S_N2 reactions.

TABLE 10.6 Common leaving groups listed in approximate order of decreasing ability to leave[a]

Substrate RX	At saturated carbon	At carbonyl carbon
RN_2^+	x	
$ROR'_2{}^+$		
$ROSO_2C_4F_9$		
$ROSO_2CF_3$	x	
$ROSO_2F$		
ROTs, etc.[b]	x	
RI	x	
RBr	x	
ROH_2^+	x (conjugate acid of alcohol)	
RCl	x	x (acyl halides)
$RORH^+$	x (conjugate acid of ether)	
$RONO_2$, etc.[b]		
$RSR'_2{}^+$[456]		
$RNR'_2{}^+$	x	
RF		
ROCOR'[457]	x	x (anhydrides)
RNH_3^+		
ROAr[458]		x (aryl esters)
ROH		x (carboxylic acids)
ROR		x (alkyl esters)
RH		
RNH_2		x (amides)
RAr		
RR		

[a]Groups that are common leaving groups at saturated and carbonyl carbons are indicated; [b] ROTs, and so on, includes esters of sulfuric and sulfonic acids in general, for example, $ROSO_2OH$, $ROSO_2OR$, $ROSO_2R$, etc. $RONO_2$, and so on, includes inorganic ester leaving groups, such as $ROPO(OH)_2$ and $ROB(OH)_2$.

[455] Pearson, R.G.; Edgington, D.N. *J. Am. Chem. Soc.* ***1962***, *84*, 4607.

[456] See Knipe, A.C. in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, pt. 1, Wiley, NY, ***1981***, pp. 313–385. See also, Badet, B.; Julia, M.; Lefebvre, C. *Bull. Soc. Chim. Fr.* ***1984***, II-431.

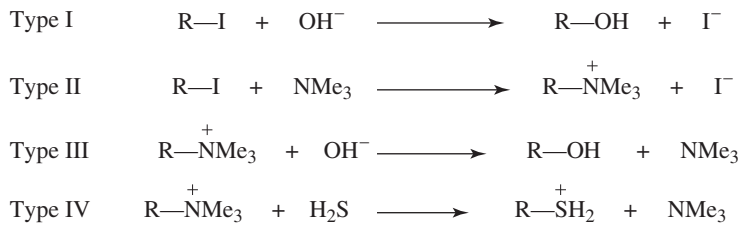
[457] See McMurry, J.E. *Org. React.* ***1976***, *24*, 187.

[458] For the effect of nitro substitution, see Sinnott, M.L.; Whiting, M.C. *J. Chem. Soc. B* ***1971***, 965. See also, Page, I.D.; Pritt, J.R.; Whiting, M.C. *J. Chem. Soc., Perkin Trans. 2* ***1972***, 906.

10.G.iv. The Effect of the Reaction Medium[459]

The effect of solvent polarity[460] on the rate of S_N1 reactions depends on whether the substrate is neutral or positively charged.[461] For neutral substrates, which constitute the majority of cases, the more polar the solvent, the faster the reaction, since there is a greater charge in the transition state than in the starting compound[462] and the energy of an ionic transition state is reduced by polar solvents. However, when the substrate is positively charged, the charge is more spread out in the transition state than in the starting ion, and a greater solvent polarity slows the reaction. Even for solvents with about the same polarity, there is a difference between protic and aprotic solvents.[463] The S_N1 reactions of un-ionized substrates are more rapid in protic solvents, which can form hydrogen bonds with the leaving group. Examples of protic solvents are water,[464] alcohols, and carboxylic acids, while some polar aprotic solvents are DMF, dimethyl sulfoxide (DMSO),[465] acetonitrile, acetone, sulfur dioxide, and hexamethylphosphoramide [$(Me_2N)_3PO$] (HMPA).[466] An algorithm has been developed to accurately calculate dielectric screening effects in solvents.[467] S_N2 reactions have been done in ionic liquids (Sec. 9.D.iii)[468] and in supercritical carbon dioxide (Sec. 9.D.ii).[469] In addition, S_N1 reactions have been done in supercritical CO_2.[470]

For S_N2 reactions, the effect of the solvent[471] depends on which of the four charge types the reaction belongs to. These types were first discussed at the opening of this chapter.



- In types I and IV, an initial charge is dispersed in the transition state, so the reaction is hindered by polar solvents.
- In type III, initial charges are *decreased* in the transition state, so that the reaction is even more hindered by polar solvents.

[459] See Reichardt, C.; Welton, T. *Solvents and Solvent Effects in Organic Chemistry*, 4th ed., Wiley-VCH, NY, ***2011***; Buncel, E.; Stairs, R.; *Solvent Efects in Chemistry*, 2nd ed., Wiley, Hoboken NJ, ***2016***.
[460] Mu, L.; Drago, R.S.; Richardson, D.E. *J. Chem. Soc., Perkin Trans 2*, ***1998***, 159.
[461] Bentley, T.W.; Llewellyn, G.; Ryu, Z.H. *J. Org. Chem.* ***1998***, *63*, 4654.
[462] This analysis is due to Ingold, C.K. *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1970***, pp. 457–463.
[463] See Ponomareva, E.A.; Dvorko, G.F.; Kulik, N.I.; Evtushenko, N.Yu. *Doklad. Chem.* ***1983***, *272*, 291.
[464] See Bug, T.; Mayr, H. *J. Am. Chem. Soc.* ***2003***, *125*, 12980.
[465] See Buncel, E.; Wilson, H. *Adv. Phys. Org. Chem.* ***1977***, *14*, 133; Martin, D.; Weise, A.; Niclas, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 318.
[466] See Normant, H. *Russ. Chem. Rev.* ***1970***, *39*, 457; *Angew. Chem. Int. Ed.* ***1967***, *6*, 1046.
[467] Klamt, A.; Schüürmann, G. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 799.
[468] Kim, D.W.; Song, C.E.; Chi, D.Y. *J. Org. Chem.* ***2003***, *68*, 4281; Chiappe, C.; Pieraccini, D.; Saullo, P. *J. Org. Chem.* ***2003***, *68*, 6710.
[469] DeSimone, J.; Selva, M.; Tundo, P. *J. Org. Chem.* ***2001***, *66*, 4047.
[470] Qiao, Y.X.; Theyssen, N.; Eifert, T.; Liauw, M.A.; Franciò, G.; Schenk, K.; Leitner, W.; Reetz, M.T. *Chem. Eur. J.* ***2017***, *23*, 3898.
[471] See Craig, S.L.; Brauman, J.I. *J. Am. Chem. Soc.* ***1999***, *121*, 6690.

- Only type II, where the reactants are uncharged but the transition state has built up a charge, is aided by polar solvents.[462]

Westaway has proposed a "solvation rule" for S_N2 reactions, which states that changing the solvent will not change the structure of the transition state for type I reactions, but will change it for type II reactions.[472] For S_N2 reactions also, the difference between protic and aprotic solvents must be considered.[473] For reactions of types I and III the transition state is more solvated in polar aprotic solvents than in protic ones,[474] while (as seen in Sec. 10.G.ii) the original charged nucleophile is less solvated in aprotic solvents[475] (the second factor is generally much greater than the first[476]). So the change from, say, methanol to DMSO should greatly increase the rate. As an example, the relative rates at 25 °C for the reaction between MeI and Cl^- were in MeOH, 1[372]; in $HCONH_2$ (still protic although a weaker acid), 12.5; in HCONHMe, 45.3; and $HCONMe_2$, 1.2×10^6.

The change in rate in going from a protic to an aprotic solvent is also related to the *size* of the attacking anion. Small ions are solvated best in protic solvents, since hydrogen bonding is most important for them, while large anions are solvated best in aprotic solvents (protic solvents have highly developed structures held together by hydrogen bonds; aprotic solvents have much looser structures, and it is easier for a large anion to be fitted in). So the rate of attack by small anions is most greatly increased by the change from a protic to an aprotic solvent. This may have preparative significance. The review in Ref. 457 has lists of several dozen reactions of charge types I and III in which yields are improved and reaction times reduced in polar aprotic solvents. Reaction types II and IV are much less susceptible to the difference between protic and aprotic solvents.

Since for most reactions S_N1 rates go up and S_N2 rates go down in solvents of increasing polarity, it is quite possible for the same reaction to go by the S_N1 mechanism in one solvent and the S_N2 in another. Table 10.7[477] is a list of solvents in order of ionizing power; a solvent high on the list is a good solvent for S_N1 reactions. Trifluoroacetic acid, which was not studied by Smith, Fainberg, and Winstein, has greater ionizing power[478] than any solvent listed in Table 10.7. Because it also has very low nucleophilicity, it is an excellent solvent for S_N1 solvolyses. Other good solvents for this purpose are 2,2,2-trifluoroethanol CF_3CH_2OH and 3,3,3-trifluoro-2-(trifluoromethyl)propan-1-ol $(F_3C)_2CHOH$.[479]

Previously, the influence of the polarity of the solvent on the rates of S_N1 and S_N2 reactions was discussed. The ionic strength of the medium has similar effects. In general, the addition of an external salt affects the rates of S_N1 and S_N2 reactions in the same way as an increase in solvent polarity, although this is not quantitative; different salts have different effects.[480] However, there are exceptions: although the rates of S_N1 reactions are usually increased by the addition of salts (this is called the *salt effect)*, addition of the leaving-group ion often decreases the rate (the common-ion effect, Sec. 10.A.ii). There is also the special

[472] Westaway, K.C.; Lai, Z. *Can. J. Chem.* ***1989***, *67*, 345.

[473] For reviews of the effects of protic and aprotic solvents, see Parker, A.J. *Chem. Rev.* ***1969***, *69*, 1; Madaule-Aubry, F. *Bull. Soc. Chim. Fr.* ***1966***, 1456.

[474] See Magnera, T.F.; Caldwell, G.; Sunner, J.; Ikuta, S.; Kebarle, P. *J. Am. Chem. Soc.* ***1984***, *106*, 6140.

[475] See, for example, Fuchs, R.; Cole, L.L. *J. Am. Chem. Soc.* ***1973***, *95*, 3194.

[476] See, however, Haberfield, P.; Clayman, L.; Cooper, J.S. *J. Am. Chem. Soc.* ***1969***, *91*, 787.

[477] Smith, S.G.; Fainberg, A.H.; Winstein, S. *J. Am. Chem. Soc.* ***1961***, *83*, 618.

[478] Capon, B.; McManus, S. *Neighboring Group Participation*, Vol. 1, Plenum, NY, ***1976***; Haywood-Farmer, J. *Chem. Rev.* ***1974***, *74*, 315.

[479] Schadt, F.L.; Schleyer, P.v.R.; Bentley, T.W. *Tetrahedron Lett.* ***1974***, 2335.

[480] See Bunton, C.A.; Robinson, L. *J. Am. Chem. Soc.* ***1968***, *90*, 5965.

TABLE 10.7 Relative rates of ionization of *p*-methoxyneophyl toluenesulfonate in various solvents[477]

Solvent	Relative rate
HCOOH	153
H_2O	39
80% EtOH–H_2O	1.85
AcOH	1.00
MeOH	0.947
EtOH	0.370
Me_2SO	0.108
Octanoic acid	0.043
MeCN	0.036
$HCONMe_2$	0.029
Ac_2O	0.020
Pyridine	0.013
Acetone	0.0051
EtOAc	6.7×10^{-4}
THF	5.0×10^{-4}
Et_2O	3×10^{-5}
$CHCl_3$	Lower still
Benzene	Lower still
Alkanes	Lower still

Reprinted with permission from Smith, S.G.; Fainberg, A.H.; Winstein, S. *J. Am. Chem. Soc.* ***1961***, *83*, 618. Copyright 1961 American Chemical Society.

salt effect of $LiClO_4$, mentioned in Sec. 10.A.iii, category 2. In addition to these effects, S_N1 rates are also greatly accelerated when there are ions present that specifically help in pulling off the leaving group.[481] Especially important are Ag^+, Hg^{2+}, and Hg_2^{2+}, but H^+ helps to pull off F (hydrogen bonding).[482] Even primary halides have been reported to undergo S_N1 reactions when assisted by metal ions.[483] This does not mean, however, that reactions in the presence of metallic ions invariably proceed by the S_N1 mechanism. It has been shown that alkyl halides can react with $AgNO_2$ and $AgNO_3$ by the S_N1 or S_N2 mechanism, depending on the reaction conditions.[484]

The effect of solvent has been treated quantitatively (for S_N1 mechanisms, in which the solvent pulls off the leaving group) by a linear free-energy relationship,[485]

$$\log\ k/k_0 = m \bullet Y$$

where m is characteristic of the substrate (defined as 1.00 for *tert*-BuCl) and is usually near unity, Y is characteristic of the solvent and measures its "ionizing power," and k_0 is the rate in a standard solvent, 80% aqueous ethanol at 25 °C. This is known as the *Grunwald-Winstein*

[481] See Kevill, D.N. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement D*, pt. 2, Wiley, NY, ***1983***, pp. 933–984.

[482] See Rudakov, E.S.; Kozhevnikov, I.V.; Zamashchikov, V.V. *Russ. Chem. Rev.* ***1974***, *43*, 305. For an example of assistance in removal of F by H+, see Coverdale, A.K.; Kohnstam, G. *J. Chem. Soc.* ***1960***, 3906.

[483] Zamashchikov, V.V.; Rudakov, E.S.; Bezbozhnaya, T.V.; Matveev, A.A. *J. Org. Chem. USSR* ***1984***, *20*, 424. See, however, Kevill, D.N.; Fujimoto, E.K. *J. Chem. Soc., Chem. Commun.* ***1983***, 1149.

[484] Kornblum, N.; Jones, W.J.; Hardies, D.E. *J. Am. Chem. Soc.* ***1966***, *88*, 1704; Kornblum, N.; Hardies, D.E. *J. Am. Chem. Soc.* ***1966***, *88*, 1707.

[485] Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* ***1948***, *70*, 846.

equation, and its utility is at best limited. The *Y* values can of course be measured for solvent *mixtures* too, and this is one of the principal advantages of the treatment, since it is not easy otherwise to assign a polarity arbitrarily to a given mixture of solvents.[486] The treatment is most satisfactory for different proportions of a given solvent pair. For wider comparisons the treatment is not so good quantitatively, although the *Y* values do give a reasonably good idea of solvolyzing power.[487] Table 10.8[488] contains a list of some *Y* values.

Ideally, *Y* should measure only the ionizing power of the solvent, and should not reflect any back-side attack by a solvent molecule in helping the nucleofuge to leave (nucleophilic assistance; k_s, Sec. 10.C.i, category 3). Actually, there is evidence that many solvents do lend some nucleophilic assistance,[489] even with tertiary substrates.[490] It was proposed that a better measure of solvent "ionizing power" would be a relationship based on 2-adamantyl substrates, rather than *tert*-BuCl, since the structure of this system completely prevents back-side nucleophilic assistance (Sec. 10.G.i). Such a scale, called Y_{OTs}, was developed, with *m* defined as 1.00 for 2-adamantyl tosylate.[491] Some values of Y_{OTs} are given in Table 10.8. These values, which are actually based on both 1- and 2-adamantyl tosylates (both are equally impervious to nucleophilic assistance and show almost identical responses to solvent ionizing power[492]) are called Y_{OTs} because they apply only to tosylates. It has been found that solvent "ionizing power" depends on the leaving group, so separate scales[493] have been set up for OTf,[494] Cl,[456] Br,[495] I,[496] and other nucleofuges,[497] all based on the corresponding adamantyl compounds. A new Y scale has been established based on benzylic bromides.[498] In part, this was done because benzylic tosylates did not give a linear correlation with the 2-adamantyl Y_{OTs} parameter.[499] This

[486] See Reichardt, C.; Welton, T. *Solvents and Solvent Effects in Organic Chemistry*, 4th ed., Wiley-VCH, NY, ***2011***; Langhals, H. *Angew. Chem. Int. Ed.* ***1982***, *21*, 724.

[487] For a criticism of the *Y* scale, see Abraham, M.H.; Doherty, R.M.; Kamlet, M.J.; Harris, J.M.; Taft, R.W. *J. Chem. Soc., Perkin Trans. 2* ***1987***, 1097.

[488] *Y* values are from Fainberg, A.H.; Winstein, S. *J. Am. Chem. Soc.* ***1956***, *78*, 2770, except for the value for CF_3CH_2OH, which is from Shiner Jr., V.J.; Dowd, W.; Fisher, R.D.; Hartshorn, S.R.; Kessick, M.A.; Milakofsky, L.; Rapp, M.W. *J. Am. Chem. Soc.* ***1969***, *91*, 4838. Y_{OTs} values are from Bentley, T.W.; Llewellyn, G. *Prog. Phys. Org. Chem.* ***1990***, *17*, pp. 143–144. *Z* values are from Kosower, E.M.; Wu, G.; Sorensen, T.S. *J. Am. Chem. Soc.* ***1961***, *83*, 3147. See also, Larsen, J.W.; Edwards, A.G.; Dobi, P. *J. Am. Chem. Soc.* ***1980***, *102*, 6780. $E_T(30)$ values are from Reichardt, C. *Chem. Rev.* ***1994***, *94*, 2319; Machado, V.G.; Stock, R.I.; Reichardt, C. *Chem. Rev.* ***2014***, *114*, 10429; Ceron-Carrasco, J.P.; Jacquermin, D.; Lawrence, C.; Planchat, A.; Reichardt, C.; Sraidi, K. *J. Phys. Org. Chem.* ***2014***, *27*, 512. See also, Reichardt, C.; Welton, T. *Solvents and Solvent Effects in Organic Chemistry*, 4th ed., Wiley-VCH, NY, ***2011***, Table 7-3, pp. 455–461.

[489] A scale of solvent nucleophilicity (as opposed to ionizing power), called the N_T scale, has been developed: Kevill, D.N.; Anderson, S.W. *J. Org. Chem.* ***1991***, *56*, 1845.

[490] See Kevill, D.N.; Anderson, S.W. *J. Am. Chem. Soc.* ***1986***, *108*, 1579; McManus, S.P.; Neamati-Mazreah, N.; Karaman, R.; Harris, J.M. *J. Org. Chem.* ***1986***, *51*, 4876; Abraham, M.H.; Doherty, R.M.; Kamlet, M.J.; Harris, J.M.; Taft, R.W. *J. Chem. Soc., Perkin Trans. 2* ***1987***, 913.

[491] Schadt, F.L.; Bentley, T.W.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1976***, *98*, 7667.

[492] Bentley, T.W.; Carter, G.E. *J. Org. Chem.* ***1983***, *48*, 579.

[493] For a review of these scales, see Bentley, T.W.; Llewellyn, G. *Prog. Phys. Org. Chem.* ***1990***, *17*, 121.

[494] Kevill, D.N.; Anderson, S.W. *J. Org. Chem.* ***1985***, *50*, 3330. See also, Creary, X.; McDonald, S.R. *J. Org. Chem.* ***1985***, *50*, 474.

[495] Bentley, T.W.; Carter, G.E. *J. Am. Chem. Soc.* ***1982***, *104*, 5741. See also, Liu, K.; Sheu, H. *J. Org. Chem.* ***1991***, *56*, 3021.

[496] Bentley, T.W.; Carter, G.E.; Roberts, K. *J. Org. Chem.* ***1984***, *49*, 5183.

[497] See Kevill, D.N.; Hawkinson, D.C. *J. Org. Chem.* ***1990***, *55*, 5394 and references cited therein.

[498] Liu, K.-T.; Chin, C.-P.; Lin, Y.-S.; Tsao, M.-L. *J. Chem. Res. (S)* ***1997***, 18.

[499] Fujio, M.; Susuki, T.; Goto, M.; Tsuji, Y.; Yatsugi, K.; Saeki, Y.; Kim, S.H.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***1994***, *67*, 2233.

TABLE 10.8 The Y, Y_{OTs}, Z, and $E_T(30)$ values for some solvents[488]

Solvent	Y	Y_{OTs}	Z	$E_T(30)$
CF_3CO_2H		4.57		
H_2O	3.5	4.1	94.6	63.1
$(CF_3)_2CHOH$		3.82		65.3
HCO_2H	2.1	3.04		
H_2O–EtOH (1:1)	1.7	1.29	90	55.6
CF_3CH_2OH	1.0	1.77		59.8
$HCONH_2$	0.6		83.3	56.6
80% EtOH	0.0	0.0	84.8	53.7
MeOH	−1.1	−0.92	83.6	55.4
AcOH	−1.6	−0.9	79.2	51.7
EtOH	−2.0	−1.96	79.6	51.9
90% dioxane	−2.0	−2.41	76.7	46.7
i-PrOH	−2.7	−2.83	76.3	48.4
95% acetone	−2.8	−2.95	72.9	48.3
t-BuOH	−3.3	−3.74	71.3	43.9
MeCN		−3.21	71.3	45.6
Me_2SO			71.1	45.1
$HCONMe_2$		−4.14	68.5	43.8
Acetone			65.7	42.2
HMPA				40.9
CH_2Cl_2				40.7
Pyridine			64.0	40.5
$CHCl_3$			63.2	39.1
PhCl				37.5
THF				37.4
Dioxane				36.0
Et_2O				34.5
C_6H_6			54	34.3
PhMe				33.9
CCl_4				32.4
n-Octane				31.1
n-Hexane				31.0
Cyclohexane				30.9

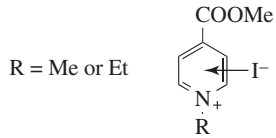
is substrate dependent, since solvolysis of 2,2,-dimethyl-1-phenylpropan-1-ol tosylate showed no nucleophilic solvent participation.[500]

In order to include a wider range of solvents than those in which any of the Y values can be conveniently measured, other attempts have been made at correlating solvent polarities.[501] Kosower found that the position of the charge-transfer peak (Sec. 3.C.i) in the UV spectrum of the complex (**99**) between iodide ion and 1-methyl- or

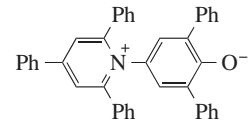
[500] Tsuji, Y.; Fujio, M.; Tsuno, Y. *Tetrahedron Lett.* ***1992***, *33*, 349.

[501] See Abraham, M.H.; Grellier, P.L.; Abboud, J.M.; Doherty, R.M.; Taft, R.W. *Can. J. Chem.* ***1988***, *66*, 2673; Shorter, J. *Correlation Analysis of Organic Reactivity*, Wiley, NY, ***1982***, pp. 127–172; See also, Chastrette, M.; Rajzmann, M.; Chanon, M.; Purcell, K.F. *J. Am. Chem. Soc.* ***1985***, *107*, 1.

1-ethyl-4-carbomethoxypyridinium ion was dependent on the polarity of the solvent.[502] From these peaks, which are very easy to measure, Kosower calculated transition energies that he called *Z* values. These values are thus measures of solvent polarity analogous to *Y* values. Another scale is based on the position of electronic spectra peaks of the pyridinium-*N*-phenolbetaine (**100**) in various solvents.[503] Solvent polarity values on this scale are called $E_T(30)$[504] values.



99



100

The $E_T(30)$ values are related to *Z* values by the expression[505]

$$Z = 1.27\ E_T\,(30) + 13.0$$

Table 10.8 shows that *Z* and $E_T(30)$ values are generally in the same order as *Y* values. Other scales, the π* scale,[506] the π^*_{azo} scale,[507] and the Py scale,[508] are also based on spectral data.[509]

Carbon dioxide can be liquefied under high pressure (supercritical CO_2). Several reactions have been done using supercritical CO_2 as the medium (Sec. 9.D.ii), but special apparatus is required. This medium offers many advantages,[510] and some disadvantages, but is an interesting new area of research.

The effect of solvent on nucleophilicity has already been discussed (Sec. 10.G.ii).

10.G.v. Phase-Transfer Catalysis

A difficulty that occasionally arises when carrying out nucleophilic substitution reactions is that the reactants do not mix. For a reaction to take place the reacting molecules must collide. In nucleophilic substitutions the substrate is usually insoluble in water and other polar solvents, while the nucleophile is often an anion, which is soluble in water but not in the substrate or other organic solvents. Consequently, when the two reactants are brought together, their concentrations in the same phase are too low for convenient reaction rates. One way to overcome this difficulty is to use a solvent that will dissolve both species. As seen in Sec. 10.G.iv, a dipolar aprotic solvent may serve this purpose. Another way, which

[502] Kosower, E.M.; Wu, G.; Sorensen, T.S. *J. Am. Chem. Soc.* ***1961***, *83*, 3147. See also, Larsen, J.W.; Edwards, A.G.; Dobi, P. *J. Am. Chem. Soc.* ***1980***, *102*, 6780.

[503] Dimroth, K.; Reichardt, C. *Liebigs Ann. Chem.* ***1969***, *727*, 93. See also, Haak, J.R.; Engberts, J.B.F.N. *Recl. Trav. Chim. Pays-Bas* ***1986***, *105*, 307.

[504] The symbol E_T comes from *energy*, *transition*. The (30) is used because the zwitterion **100** bore this number in Dimroth, K.; Reichardt, C. *Liebigs Ann. Chem.* ***1969***, *727*, 93. Values based on other ions have also been reported: See, for example, Reichardt, C.; Harbusch-Görnert, E.; Schäfer, G. *Liebigs Ann. Chem.* ***1988***, 839.

[505] Marcus, Y. *Chem. Rev.* ***1993***, *22*, 409.

[506] Doherty, R.M.; Abraham, M.H.; Harris, J.M.; Taft, R.W.; Kamlet, M.J. *J. Org. Chem.* ***1986***, *51*, 4872. See also, Bekárek, V. *J. Chem. Soc., Perkin Trans. 2* ***1986***, 1425; Abe, T. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 2328.

[507] Buncel, E.; Rajagopal, S. *J. Org. Chem.* ***1989***, *54*, 798.

[508] Dong, D.C.; Winnik, M.A. *Can. J. Chem.* ***1984***, *62*, 2560.

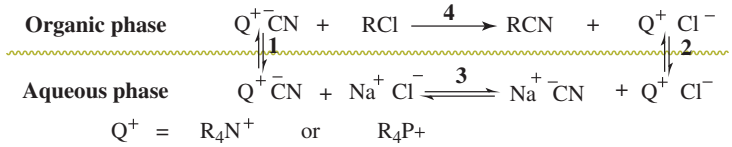
[509] For a review of such scales, see Buncel, E.; Rajagopal, S. *Acc. Chem. Res.* ***1990***, *23*, 226.

[510] Kaupp, G. *Angew. Chem. Int. Ed.* ***1994***, *33*, 1452.

is used very often, is *phase-transfer catalysis*.[511] Asymmetric phase-transfer reactions are known.[512]

In this method, a catalyst is used to carry the nucleophile from the aqueous into the organic phase.[513] As an example, simply heating and stirring a two-phase mixture of 1-chlorooctane for several days with aqueous NaCN gives essentially no yield of 1-cyanooctane. But if a small amount of an appropriate quaternary ammonium salt is added, the product is quantitatively formed in ~2 hours.[514] There are two principal types of phase-transfer catalyst; although the action of the two types is somewhat different, the effects are the same. Both get the anion into the organic phase and allow it to be relatively free to react with the substrate.

1. *Quaternary ammonium or phosphonium salts*. In the above-mentioned case of NaCN, the uncatalyzed reaction does not take place because the $^-$CN ions cannot cross the interface between the two phases, except in very low concentration. The reason is that the Na^+ ions are solvated by the water, and this solvation energy would not be present in the organic phase. The $^-$CN ions cannot cross without the Na^+ ions because that would destroy the electrical neutrality of each phase. In contrast to Na^+ ions, quaternary ammonium ions (R_4N^+)[515] and quaternary phosphonium ions (R_4P^+) with sufficiently large R groups are poorly solvated in water and prefer organic solvents. If a small amount of such a salt is added, three equilibria are set up:



The Na^+ ions remain in the aqueous phase; they cannot cross. The Q^+ ions do cross the interface and carry an anion with them. At the beginning of the reaction the chief anion present is $^-$CN. This gets carried into the organic phase (equilibrium 1) where it reacts with RCl to produce RCN and Cl^-. The Cl^- then gets carried into the aqueous phase (equilibrium 2). Equilibrium 3, taking place entirely in the aqueous phase, allows Q^+ $^-$CN to be regenerated. All the equilibria are normally reached much faster than the actual conversion of RCl to RCN, so the latter is the rate-determining step.

In some cases, the Q^+ ions have such a low solubility in water that virtually all remain in the organic phase.[516] In such cases the exchange of ions (equilibrium 3)

[511] Dehmlow, E.V.; Dehmlow, S.S. *Phase Transfer Catalysis*, 2nd ed., Verlag Chemie, Deerfield Beach, FL, ***1983***; Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***; Makosza, M. *Pure Appl. Chem.* ***2000***, *72*, 1399; Montanari, F.; Landini, D.; Rolla, F. *Top. Curr. Chem.* ***1982***, *101*, 147; Alper, H. *Adv. Organomet. Chem.* ***1981***, *19*, 183; Sjöberg, K. *Aldrichimica Acta* ***1980***, *13*, 55.

[512] For reviews, see Shirakawa, S.; Maruoka, K. *Tetrahedron Lett.* ***2014***, *55*, 3833; Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* ***2013***, *52*, 4312. Also see Denmark, S.E.; Gould, N.D.; Wolf, L.M. *J. Org. Chem.* ***2011***, *76*, 4260, 4337. Herchl, R.; Waser, M. *Tetrahedron* ***2014***, *70*, 1935.

[513] For the use of *N*-heterocyclic alkenes as phase-transfer catalysts, see Blümel, M.; Crocker, R.D.; Harper, J.B.; Enders, D.; Nguyen, T.V. *Chem. Commun.* ***2016***, *52*, 7958.

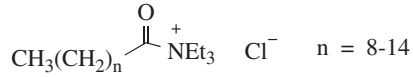
[514] Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***, p. 2.

[515] See Lissel, M.; Feldman, D.; Nir, M.; Rabinovitz, M. *Tetrahedron Lett.* ***1989***, *30*, 1683.

[516] Landini, D.; Maia, A.; Montanari, F. *J. Am. Chem. Soc.* ***1978***, *100*, 2796.

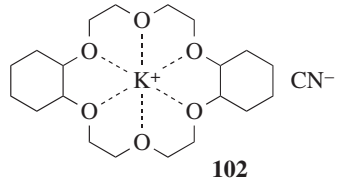
takes place across the interface. Still another mechanism (*the interfacial mechanism*) can operate where $^-$OH extracts a proton from an organic substrate.[517] In this mechanism, the $^-$OH ions remain in the aqueous phase and the substrate remains in the organic phase; the deprotonation takes place at the interface.[518]

Thermal stability of the quaternary ammonium salt is a problem, limiting the use of some catalysts. The trialkylacyl ammonium halide **101** is thermally stable, however, even at high reaction temperatures.[519] The use of molten quaternary ammonium salts as ionic reaction media for substitution reactions has also been reported.[520]

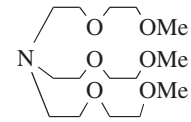


101

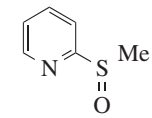
2. *Crown ethers and other cryptands*.[521] As seen in Sec. 3.C.ii, certain cryptands are able to surround certain cations. In effect, a salt such as KCN is converted by dicyclohexano-18-crown-6 into a new salt (**102**) whose anion is the same, but whose cation is now a much larger species with the positive charge spread over a large volume and hence much less concentrated. This larger cation is much less solubilized by water than K^+ and is much more attracted to organic solvents. Although KCN is generally insoluble in organic solvents, the cryptate salt is soluble in many of them. In these cases we do not need an aqueous phase at all but simply add the salt to the organic phase. Suitable cryptands have been used to increase the rates of reactions where F^-, Br^-, I^-, $^-$OAc, and $^-$CN are nucleophiles.[522] Certain compounds that are not cryptands can act in a similar manner. One example is the podand tris(3,6-dioxaheptyl)amine (**103**), also called TDA-1.[523] Another, not related to the crown ethers, is the pyridyl sulfoxide **104**.[524] Cyclohexapeptoids have been prepared and used as phase-transfer catalysts.[525]



102



103



104

Both of the above-mentioned catalyst types get the anions into the organic phase, but there is another factor as well. There is evidence that sodium and potassium salts of many anions, even if they could be dissolved in organic solvents, would undergo reactions very

[517] For a review, see Rabinovitz, M.; Cohen, Y.; Halpern, M. *Angew. Chem. Int. Ed.* ***1986***, *25*, 960.

[518] See Makosza, M. *Pure Appl. Chem.* ***1975***, *43*, 439. See also, Dehmlow, E.V.; Thieser, R.; Sasson, Y.; Pross, E. *Tetrahedron* ***1985***, *41*, 2927; Mason, D.; Magdassi, S.; Sasson, Y. *J. Org. Chem.* ***1990***, *55*, 2714.

[519] Bhalerao, U.T.; Mathur, S.N.; Rao, S.N. *Synth. Commun.* ***1992***, *22*, 1645.

[520] Badri, M.; Brunet, J.-J.; Perron R. *Tetrahedron Lett.* ***1992***, *33*, 4435.

[521] See Liotta, C. in Patai, S. *The Chemistry of Functional Groups*, *Supplement E*, Wiley, NY, ***1980***, pp. 157–174.

[522] See Liotta, C.; Harris, H.P.; McDermott, M.; Gonzalez, T.; Smith, K. *Tetrahedron Lett.* ***1974***, 2417; Sam, D.J.; Simmons, H.E. *J. Am. Chem. Soc.* ***1974***, *96*, 2252; Durst, H.D. *Tetrahedron Lett.* ***1974***, 2421.

[523] Soula, G. *J. Org. Chem.* ***1985***, *50*, 3717.

[524] Furukawa, N.; Ogawa, S.; Kawai, T.; Oae, S. *J. Chem. Soc., Perkin Trans. 1* ***1984***, 1833. See also, Fujihara, H.; Imaoka, K.; Furukawa, N.; Oae, S. *J. Chem. Soc., Perkin Trans. 1* ***1986***, 333.

[525] Sala, G.D.; Nardone, B.; De Riccardis, F.; Izzo, I. *Org. Biomol. Chem.* ***2013***, *11*, 726.

slowly (dipolar aprotic solvents are exceptions) because in these solvents the anions exist as ion pairs with Na^+ or K^+ and are not free to react with the substrate (Sec. 10.G.ii, category 4). Fortunately, ion pairing is usually much less with the quaternary ions and with the positive cryptate ions, so the anions in these cases are quite free to attack. Such anions are sometimes referred to as "naked" anions.

Not all quaternary salts and cryptands work equally well in all situations. Some experimentation is often required to find the optimum catalyst.

Although phase-transfer catalysis has been most often used for nucleophilic substitutions, it is not confined to these reactions. Any reaction that needs an insoluble anion dissolved in an organic solvent can be accelerated by an appropriate phase-transfer catalyst. Some examples will be seen in later chapters. In fact, in principle, the method is not even limited to anions, and a small amount of work has been done in transferring cations,[526] radicals, and molecules.[527] The reverse type of phase-transfer catalysis has also been reported: transport into the aqueous phase of a reactant that is soluble in organic solvents.[528] Microwave-activated phase-transfer catalysis has been reported.[529]

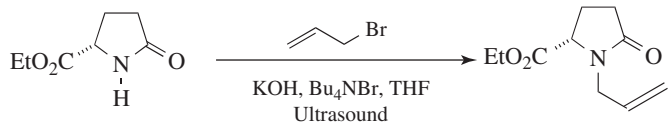
The catalysts mentioned above are soluble. Certain cross-linked polystyrene resins, as well as alumina[530] and silica gel, have been used as insoluble phase-transfer catalysts. These, called *triphase catalysts*,[531] have the advantage of simplified product work-up and easy and quantitative catalyst recovery, since the catalyst can easily be separated from the product by filtration.

10.G.vi. Influencing Reactivity by External Means

In many cases, reactions are slow. This is sometimes due to poor mixing or the aggregation state of one or more reactants. A powerful technique used to increase reaction rates is *ultrasound* (Sec. 7.B). In this technique, the reaction mixture is subjected to high-energy sound waves, most often 20 KHz, but sometimes higher (a frequency of 20 KHz is about the upper limit of human hearing). When these waves are passed through a mixture, small bubbles form (*cavitation*). Collapse of these bubbles produces powerful shock waves that greatly increase the temperatures and pressures within these tiny regions, resulting in an increased reaction rate.[532] In an instance where a metal, as a reactant or catalyst, is in contact with a liquid phase, a further effect is that the surface of the metal is cleaned and/or eroded by the ultrasound, allowing the liquid-phase molecules to come into closer contact with the metal atoms. Among the advantages of ultrasound is that it may increase yields, reduce side reactions, and permit the use of lower temperatures and/or pressures. The reaction of pyrrolidinone **105** with allyl bromide, under phase-transfer conditions, gave < 10% of the *N*-allyl product, **106**. When the reaction was done under identical conditions, but with exposure to ultrasound (in an ultrasonic bath), the yield of **106** was 78%.[533] It has been

[526] Iwamoto, H.; Yoshimura, M.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 796.
[527] See, for example, Dehmlow, E.V.; Slopianka, M. *Chem. Ber.* ***1979***, *112*, 2765.
[528] Fife, W.K.; Xin, Y. *J. Am. Chem. Soc.* ***1987***, *109*, 1278.
[529] Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J.-L.; Petit, A. *Tetrahedron* ***1999***, *55*, 10851.
[530] Quici, S.; Regen, S.L. *J. Org. Chem.* ***1979***, *44*, 3436.
[531] See Regen, S.L. *Nouv. J. Chim.* ***1982***, *6*, 629; *Angew. Chem. Int. Ed.* ***1979***, *18*, 421. See also, Pugia, M.J.; Czech, B.P.; Czech, B.P.; Bartsch, R.A. *J. Org. Chem.* ***1986***, *51*, 2945.
[532] See Mingos, D.M.P.; Baghurst, D.R. *Chem. Soc. Rev.* ***1991***, *20*, 1; Giguere, R.J. *Org. Synth. Theory Appl.* ***1989***, *1*, 103.
[533] Keusenkothen, P.F.; Smith, M.B. *Tetrahedron Lett.* ***1989***, *30*, 3369.

postulated that ultrasound has its best results with reactions that proceed, at least partially, through free-radical intermediates.[534]



105 **106**

As noted in Sec. 7.C, microwave irradiation is used extensively in these reactions. Reaction times are greatly accelerated in many reactions, and reactions that took hours to be complete in refluxing solvents are done in minutes. Benzyl alcohol was converted to benzyl bromide, for example, using microwave irradiation (650 W) in only 9 min on a doped K-10 Montmorillonite clay.[535] Microwave-assisted reactions are a growing and very useful technique.

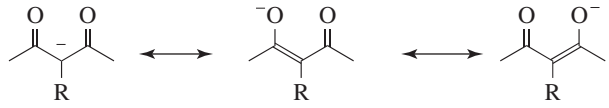
The rate of many reactions can be increased by application of high pressure, as discussed in Sec. 9.E.[536] In solution, the rate of a reaction can be expressed in terms of the activation volume, $\Delta V^{\ddagger}$.[537] Increasing pressure decreases the value of $\Delta V^{\ddagger}$ and $\Delta V^{\ddagger}$ is negative as the reaction rate is accelerated. This equation is not strictly obeyed above 10 kbar. If the transition state of a reaction involves bond formation, concentration of charge, or ionization, a negative volume of activation often results. Many high pressure reactions are done neat, but if a solvent is used, the influence of pressure on that solvent is important. In most reactions, pressure is applied (5–20 kbar) at room temperature and then the temperature is increased until reaction takes place.

10.G.vii. Ambident (Bidentant) Nucleophiles: Regioselectivity

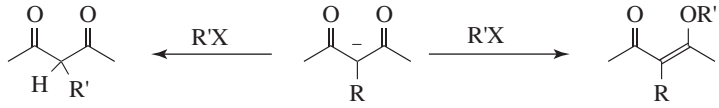
Some nucleophiles have a pair of electrons on each of two or more atoms, or canonical forms can be drawn in which two or more atoms bear an unshared pair. In these cases, the nucleophile may attack in two or more different ways to give different products. Such reagents are called *ambident nucleophiles*.[538] In most cases, a nucleophile with two potentially attacking atoms can attack with either of them, depending on conditions, and mixtures are often obtained, although this is not always the case. For example, the nucleophile NCO^- usually gives only isocyanates RNCO and not the isomeric cyanates ROCN.[539] When a reaction can potentially give rise to two or more structural isomers (e.g., ROCN or RNCO), but actually produces only one, the reaction is said to be *regioselective*.[540] See also the definitions of stereoselective (Sec. 4.N) and enantioselective (Sec. 4.H, category 2). Some important ambident nucleophiles are listed here.

[534] See Einhorn, C.; Einhorn, J.; Dickens, M.J.; Luche, J. *Tetrahedron Lett.* ***1990***, *31*, 4129.
[535] Kad, G.-L.; Singh, V.; Kuar, K.P.; Singh, J. *Tetrahedron Lett.* ***1997***, *38*, 1079.
[536] Matsumoto, K.; Morris, A.R. *Organic Synthesis at High Pressure*, Wiley, NY, ***1991***; Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* ***1985***, 1, 999.
[537] Isaacs, N.S. *Liquid Phase High Pressure Chemistry*, Wiley, Chichester, ***1981***; Asano, T.; le Noble, W.J. *Chem. Rev.* ***1978***, *78*, 407.
[538] See Reutov, O.A.; Beletskaya, I.P.; Kurts, A.L. *Ambident Anions*, Plenum, NY, ***1983***. For a review, see Black, T.H. *Org. Prep. Proced. Int.* ***1989***, *21*, 179.
[539] See Holm, A.; Wentrup, C. *Acta Chem. Scand.* ***1966***, *20*, 2123.
[540] This term was introduced by Hassner, A. *J. Org. Chem.* ***1968***, *33*, 2684.

1. *Ions of the type —CO—⁻CR—CO—*. These ions, which are derived by removal of a proton from malonic esters, β-keto esters, β-diketones, and so on, are resonance hybrids:



Attack is therefore possible at a saturated carbon via the carbon atoms (*C*-alkylation) or the oxygen atoms (*O*-alkylation):

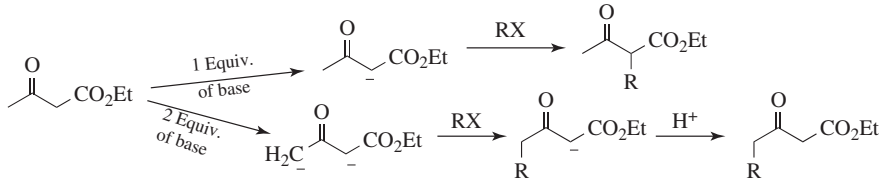


With unsymmetrical ions, three products are possible, since either oxygen can attack. With a carbonyl substrate the ion can analogously undergo *C*-acylation or *O*-acylation.

2. *Compounds of the Type CH_3CH—CH_2—CO—*. These compounds can give up two protons, if treated with 2 molar equivalents of a strong enough base, to give dicarbanions:

$$CH_3—CO—CH_2—CO— \xrightarrow{\text{2 Equivalents of base}} \underset{\textbf{107}}{\bar{C}H_2—CO—\bar{C}H—CO—}$$

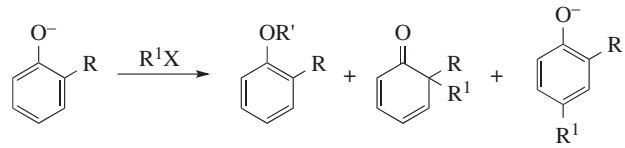
Such ions are ambident nucleophiles, since they have two possible attacking carbon atoms, aside from the possibility of attack by oxygen. In such cases, the attack is virtually always by the more basic carbon.[541] Since the hydrogen of a carbon bonded to two carbonyl groups is more acidic than that of a carbon bonded to just one (see Chapter 8), the CH group of **107** is less basic than the CH_2 group, so the latter attacks the substrate. This gives rise to a useful general principle: whenever the goal is to remove a proton at a given position for use as a nucleophile, but there is a stronger acidic group in the molecule, it may be possible to take off both protons; if it is, then attack is always by the desired position since it is the ion of the weaker acid. On the other hand, if the goal is to attack with the more acidic position, all that is necessary is to remove just one proton.[542] For example, ethyl acetoacetate can be alkylated at either the methyl or the methylene group (**10-67**).



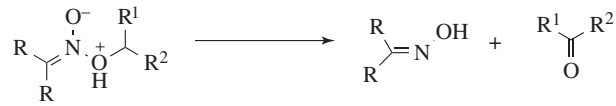
[541] For an exception, see Trimitsis, G.B.; Hinkley, J.M.; TenBrink, R.; Faburada, A.L.; Anderson, R.; Poli, M.; Christian, B.; Gustafson, G.; Erdman, J.; Rop, D. *J. Org. Chem.* ***1983***, *48*, 2957.

[542] See Hauser, C.R.; Harris, C.M. *J. Am. Chem. Soc.* ***1958***, *80*, 6360. For reviews, see Thompson, C.M.; Green, D.L.C. *Tetrahedron* ***1991***, *47*, 4223; Harris, T.M.; Harris, C.M. *Org. React.* ***1969***, *17*, 155.

3. *The ^-CN ion*. This nucleophile can give nitriles RCN (**10-76**) or isocyanides RN≡C.
4. *The nitrite ion*. This ion can give nitrite esters R—O—N=O (**10-22**) or nitro compounds RNO_2 (**10-77**), which are not esters.
5. *Phenoxide ions.* These ions are analogous to enolate anions and can undergo *C*-alkylation or *O*-alkylation:



6. *Removal of a proton from an aliphatic nitro compound.* This reaction gives a carbanion ($R_2C^-—NO_2$) that can be alkylated at oxygen or carbon.[543] *O*-Alkylation gives a nitronic ester, and such compounds are generally unstable to heat and break down to give an oxime and an aldehyde or ketone.



There are many other ambident nucleophiles.

It would be useful to have general rules as to which atom of an ambident nucleophile will attack a given substrate under a given set of conditions.[544] Unfortunately, the situation is complicated by the large number of variables. It might be expected that the more electronegative atom would always attack, but this is often not the case. Where the products are determined by thermodynamic control (Sec. 6.F), the principal product is usually the one in which the atom of higher basicity has attacked (i.e., C > N > O > S).[545] However, in most reactions, the products are kinetically controlled and matters are much less simple. Nevertheless, the following generalizations can be made, while recognizing that there are many exceptions and unexplained results. As in the discussion of nucleophilicity in general (Sec. 10.G.ii), there are two major factors: (i) the polarizability (hard–soft character) of the nucleophile and (ii) solvation effects.

1. The principle of hard and soft acids and bases states that hard acids prefer hard bases and soft acids prefer soft bases (Sec. 8.E.i). In an S_N1 mechanism the nucleophile attacks a carbocation, which is a hard acid. In an S_N2 mechanism, the nucleophile attacks the carbon atom of a molecule, which is a softer acid. The more electronegative atom of an ambident nucleophile is a harder base than the less electronegative atom. Therefore, as the character of a given reaction changes from S_N1 to S_N2-like, an ambident nucleophile becomes more likely to attack with its less electronegative atom.[546] Thus, changing from S_N1 to S_N2 conditions should favor C attack by

[543] See Erashko, V.I.; Shevelev, S.A.; Fainzil'berg, A.A. *Russ. Chem. Rev.* ***1966***, *35*, 719.

[544] See Jackman, L.M.; Lange, B.C. *Tetrahedron* ***1977***, *33*, 2737; Reutov, O.A.; Kurts, A.L. *Russ. Chem. Rev.* ***1977***, *46*, 1040; Gompper, R.; Wagner, H. *Angew. Chem. Int. Ed.* ***1976***, *15*, 321.

[545] See Bégué, J.; Charpentier-Morize, M.; Née, G. *J. Chem. Soc., Chem. Commun.* ***1989***, 83.

[546] This principle, sometimes called *Kornblum's rule*, was first stated by Kornblum, N.; Smiley, R.A.; Blackwood, R.K.; Iffland, D.C. *J. Am. Chem. Soc.* ***1955***, *77*, 6269.

$^{-}$CN, N attack by NO_2^-, C attack by enolate or phenoxide ions, etc. As an example, primary alkyl halides are attacked (in protic solvents) by the carbon atom of the anion of $CH_3COCH_2CO_2Et$, while α-chloro ethers, which react by the S_N1 mechanism, are attacked by the oxygen atom. However, this does not mean that attack is by the less electronegative atom in all S_N2 reactions and by the more electronegative atom in all S_N1 reactions. The position of attack also depends on the nature of the nucleophile, the solvent, the leaving group, and other conditions. The rule merely states that increasing the S_N2 character of the transition state makes attack by the less electronegative atom more likely.

2. All negatively charged nucleophiles must of course have a positive counterion. If this ion is Ag^+ (or some other ion that specifically helps in removing the leaving group, Sec. 10.G.iv), rather than the more usual Na^+ or K^+, then the transition state is more S_N1-like. Therefore, the use of Ag^+ promotes attack at the more electronegative atom. For example, alkyl halides treated with NaCN generally give mostly RCN, but the use of AgCN increases the yield of isocyanides RNC.[547]
3. In many cases, the solvent influences the position of attack. The freer the nucleophile, the more likely it is to attack with its more electronegative atom, but the more this atom is encumbered by either solvent molecules or positive counterions, the more likely is attack by the less electronegative atom. In protic solvents, the more electronegative atom is better solvated by hydrogen bonds than the less electronegative atom. In polar aprotic solvents, neither atom of the nucleophile is greatly solvated, but these solvents are very effective in solvating cations. Thus in a polar aprotic solvent the more electronegative end of the nucleophile is freer from entanglement by both the solvent and the cation, so that a change from a protic to a polar aprotic solvent often increases the extent of attack by the more electronegative atom. An example is attack by sodium β-naphthoxide on benzyl bromide, which resulted in 95% *O*-alkylation in dimethyl sulfoxide and 85% *C*-alkylation in 2,2,2-trifluoroethanol.[548] Changing the cation from Li^+ to Na^+ to K^+ (in nonpolar solvents) also favors *O*-alkylation over *C*-alkylation[549] for similar reasons (K^+ leaves the nucleophile much freer than Li^+), as does the use of crown ethers, which are good at solvating cations (Sec. 3.C.ii).[550] Alkylation of the enolate anion of cyclohexanone in the gas phase, where the nucleophile is completely free, showed only *O*-alkylation and no *C*-alkylation.[551]
4. In extreme cases, steric effects can govern the regioselectivity.[552]

10.G.viii. Ambident Substrates

Some substrates (e.g., 1,3-dichlorobutane) can be attacked at two or more positions, and these may be called *ambident substrates*. In the example given, there happen to be two

[547] Carretero, J.C.; García-Ruano, J.L. *Tetrahedron Lett.* ***1985***, *26*, 3381.

[548] Kornblum, N.; Berrigan, P.J.; le Noble, W.J. *J. Chem. Soc.* ***1963***, *85*, 1141; Kornblum, N.; Seltzer, R.; Haberfield, P. *J. Am. Chem. Soc.* ***1963***, *85*, 1148. See Schick, H.; Schwarz, H.; Finger, A.; Schwarz, S. *Tetrahedron* ***1982***, *38*, 1279.

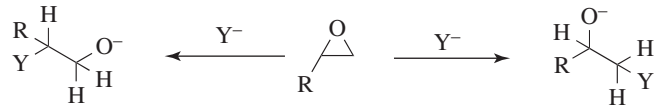
[549] Kurts, A.L.; Beletskaya, I.P.; Masias, A.; Reutov, O.A. *Tetrahedron Lett.* ***1968***, 3679. See, however, Sarthou, P.; Bram, G.; Guibe, F. *Can. J. Chem.* ***1980***, *58*, 786.

[550] Smith, S.G.; Hanson, M.P. *J. Org. Chem.* ***1971***, *36*, 1931; Akabori, S.; Tuji, H. *Bull. Chem. Soc. Jpn.* ***1978***, *51*, 1197. See also, le Noble, W.J.; Palit, S.K. *Tetrahedron Lett.* ***1972***, 493.

[551] Jones, M.E.; Kass, S.R.; Filley, J.; Barkley, R.M.; Ellison, G.B. *J. Am. Chem. Soc.* ***1985***, *107*, 109.

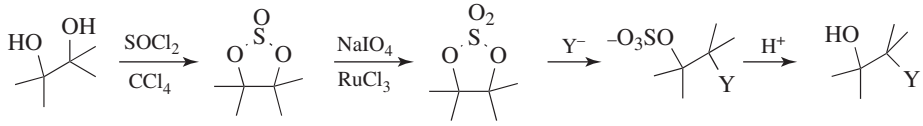
[552] See, for example, O'Neill, P.; Hegarty, A.F. *J. Org. Chem.* ***1987***, *52*, 2113.

leaving groups in the molecule. Apart from dichlorobutane, and in general, there are two kinds of substrates that are inherently ambident (unless symmetrical). One of these, the allylic type, has already been discussed (Sec. 10.E). The other is the epoxy (or the similar aziridine[553] or episulfide) substrate.[554] Selectivity for one or the other position is usually called *regioselectivity*.



Substitution of the free epoxide, which generally occurs under basic or neutral conditions, usually involves an S_N2 mechanism. Since primary substrates undergo S_N2 attack more readily than secondary, unsymmetrical epoxides are attacked in neutral or basic solution at the less highly substituted carbon, and are attacked stereospecifically, with inversion at that carbon. Under acidic conditions, it is the protonated epoxide that undergoes the reaction. Under these conditions the mechanism can be either S_N1 or S_N2. In S_N1 mechanisms, which favor tertiary carbons, attack may be expected be at the more highly substituted carbon, and this is indeed the case. However, even when protonated epoxides react by what is expected to be an S_N2 mechanism, attack is usually at the more highly substituted position.[555] This result probably indicates significant carbocation character at the carbon (ion pairing for example). Thus, it is often possible to change the direction of ring opening by changing the conditions from basic to acidic or vice versa. In the ring opening of 2,3-epoxy alcohols, the presence of Ti(O-*i*-Pr)$_4$ increases both the rate and the regioselectivity, favoring attack at C-3 rather than C-2.[556] When an epoxide ring is fused to a cyclohexane ring, S_N2 ring opening invariably gives diaxial rather than diequatorial ring opening.[557]

Cyclic sulfates (**108**), prepared from 1,2-diols, react in the same manner as epoxides, but usually more rapidly.[558]



108

[553] Chechik, V.O.; Bobylev, V.A. *Acta Chem. Scand. B*, ***1994***, *48*, 837.

[554] Rao, A.S.; Paknikar, S.K.; Kirtane, J.G. *Tetrahedron* ***1983***, *39*, 2323; Behrens, C.H.; Sharpless, K.B. *Aldrichimica Acta* ***1983***, *16*, 67; Enikolopiyan, N.S. *Pure Appl. Chem.* ***1976***, *48*, 317; Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, ***1969***, pp. 206–273.

[555] Biggs, J.; Chapman, N.B.; Finch, A.F.; Wray, V. *J. Chem. Soc. B* ***1971***, 55.

[556] Caron M.; Sharpless, K.B. *J. Org. Chem.* ***1985***, *50*, 1557. See also, Chong, J.M.; Sharpless, K.B. *J. Org. Chem.* ***1985***, *50*, 1560; Behrens, C.H.; Sharpless, K.B. *J. Org. Chem.* ***1985***, *50*, 5696.

[557] Murphy, D.K.; Alumbaugh, R.L.; Rickborn, B. *J. Am. Chem. Soc.* ***1969***, *91*, 2649. For a method of overriding this preference, see McKittrick, B.A.; Ganem, B. *J. Org. Chem.* ***1985***, *50*, 5897.

[558] Gao, Y.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1988***, *110*, 7538; Kim, B.M.; Sharpless, K.B. *Tetrahedron Lett.* ***1989***, *30*, 655.

10.H. REACTIONS

The reactions in this chapter are classified according to the attacking atom of the nucleophile in the order O, S, N, halogen, H, C. For a given nucleophile, reactions are classified by the substrate and leaving group. For the most part, only alkyl substrates are considered, since acyl substrates are considered in Chapter 16. Nucleophilic substitutions at a sulfur atom are treated at the end.

Not all the reactions in this chapter are actually nucleophilic substitutions. In some cases, the mechanisms are not known with enough certainty even to decide whether a nucleophile, an electrophile, or a free radical is attacking. In other cases, conversion of one compound to another can occur by two or even all three of these possibilities, depending on the reagent and the reaction conditions. However, one or more of the nucleophilic mechanisms previously discussed do hold for the overwhelming majority of the reactions in this chapter. For the alkylations, the S_N2 is by far the most common mechanism, as long as R is primary or secondary alkyl. For the acylations, the tetrahedral mechanism is the most common.

10.H.i. Oxygen Nucleophiles

A. Attack by OH at an Alkyl Carbon

10-1 Hydrolysis of Alkyl Halides

$$\begin{aligned} RX + H_2O &\longrightarrow ROH_2^+ \xrightarrow{-H^+} ROH + H^+ \\ RX + OH^- &\longrightarrow ROH \end{aligned}$$

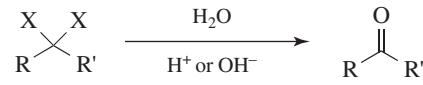
Alkyl halides can be converted to alcohols. Hydroxide ion is usually required, although particularly active substrates such as allylic or benzylic alcohols can be hydrolyzed by water. Ordinary halides can be hydrolyzed by water,[559] if the solvent is HMPA or *N*-methyl-2-pyrrolidinone,[560] or if the reaction is done in an ionic solvent.[561] If the hydrolysis (solvolysis) reaction proceeds via ionization, by an S_N1-type mechanism, this reaction can be performed on tertiary substrates without significant interference from elimination side reactions.

Vinylic halides are unreactive (Sec. 10.F), but they can be hydrolyzed to ketones at room temperature with mercuric trifluoroacetate, or with mercuric acetate in either trifluoroacetic acid or acetic acid containing BF_3 etherate.[562] Primary bromides and iodides give alcohols when treated with bis(tributyltin)oxide, $Bu_3Sn{-}O{-}SnBu_3$, in the presence of silver salts.[563]

OS **II**, 408; **III**, 434; **IV**, 128; **VI**, 142, 1037.

[559] See, however, Kurz, J.L.; Lee, J.; Love, M.E.; Rhodes, S. *J. Am. Chem. Soc.* ***1986***, *108*, 2960.
[560] Hutchins, R.O.; Taffer, I.M. *J. Org. Chem.* ***1983***, *48*, 1360.
[561] Kim, D.W.; Hong, D.J.; Seo, J.W.; Kim, H.S.; Kim, H.K.; Song, C.E.; Chi, D.Y. *J. Org. Chem.* ***2004***, *69*, 3186.
[562] Martin, S.F.; Chou, T. *Tetrahedron Lett.* ***1978***, 1943; Yoshioka, H.; Takasaki, K.; Kobayashi, M.; Matsumoto, T. *Tetrahedron Lett.* ***1979***, 3489.
[563] Gingras, M.; Chan, T.H. *Tetrahedron Lett.* ***1989***, *30*, 279.

10-2 Hydrolysis of *gem*-Dihalides



gem-Dihalides can be hydrolyzed using either acid or basic catalysis to give aldehydes or ketones.[564] Formally, the reaction may be regarded as giving R—C(OH)XR′, which is unstable and loses HX to give the carbonyl compound. For aldehydes derived from $RCHX_2$, strong bases cannot be used, because the product undergoes the *aldol reaction* (**16-34**) or the *Cannizzaro reaction* (**19-85**). A mixture of calcium carbonate and sodium acetate is effective,[565] and heating to 100 °C in DMSO gives good yields.[566] A simple method heats a *gem*-dibromide with pyridine, and subsequent treatment with water gives the aldehyde.[567] Heating 1,1-dihaloalkenes ($C{=}CX_2$) with zinc and water leads to the corresponding methyl ketone.[568]

OS **I**, 95; **II**, 89, 133, 244, 549; **III**, 538, 788; **IV**, 110, 423, 807. Also see, OS **III**, 737.

10-3 Hydrolysis of 1,1,1-Trihalides

$$RCX_3 + H_2O \longrightarrow RCO_2H$$

This reaction is similar to **10-2**. The utility of the method is limited by the lack of availability of trihalides, although these compounds can be prepared by addition of CCl_4 and similar compounds to double bonds (**15-34**) and by the free-radical halogenation of methyl groups on aromatic rings (**14-1**). When the reaction is carried out in the presence of an alcohol, a carboxylic ester can be obtained directly.[569] 1,1-Dichloroalkenes can also be hydrolyzed to carboxylic acids, by treatment with aqueous H_2SO_4. In general 1,1,1-trifluorides do not undergo this reaction,[570] but exceptions are known.[571]

Hydrolysis with base is faster for chloroform than for dichloromethane or carbon tetrachloride and gives not only formic acid but also carbon monoxide.[572] However, Hine[573] has shown that the mechanism of chloroform hydrolysis is quite different, although superficially the three reactions appear similar. For chloroform, the first step is the loss of a proton to give CCl_3^- which then loses Cl^- to give dichlorocarbene:CCl_2, which is hydrolyzed to formic acid or carbon monoxide. This reaction is an example of an S_N1cB mechanism (Sec. 10.G.iii, category 1). Both CHB_3 and CHI_3 react by the normal mechanisms. Carbon tetrachloride cannot give up a proton and dichloromethane is not acidic enough.

OS **III**, 270; **V**, 93. Also see, OS **I**, 327.

[564] Salomaa, P. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 177–210.
[565] Mataka, S.; Liu, G.-B.; Sawada, T.; Tori-i, A.; Tashiro, M. *J. Chem. Res. (S)* ***1995***, 410.
[566] Li, W.; Li, J.; DeVincentis, D.; Masour, T.S. *Tetrahedron Lett.* ***2004***, *45*, 1071.
[567] Augustine, J.K.; Naik, Y.A.; Mandal, A.B.; Chowdappa, N.; Praveen, V.B. *Tetrahedron* ***2008***, *64*, 688.
[568] Wang, L.; Li, P.; Yan, J.; Wu, Z. *Tetrahedron Lett.* ***2003***, *44*, 4685.
[569] See, for example, Le Fave, G.M.; Scheurer, P.G. *J. Am. Chem. Soc.* ***1950***, *72*, 2464.
[570] Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, ***1976***, pp. 273–274.
[571] See, for example, Kobayashi, Y.; Kumadaki, I. *Acc. Chem. Res.* ***1978***, *11*, 197.
[572] See Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 129–141.
[573] Hine, J. *J. Am. Chem. Soc.* ***1950***, *72*, 2438. See le Noble, W.J. *J. Am. Chem. Soc.* ***1965***, *87*, 2434.

10-4 Hydrolysis of Alkyl Esters of Inorganic Acids

$$\mathrm{R{-}X} \longrightarrow \mathrm{R{-}OH}$$

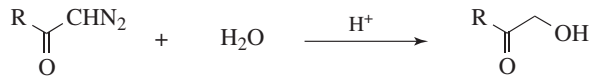
$\mathrm{X} = \mathrm{OSO_2R'}, \mathrm{OSO_2OH}, \mathrm{OSO_2OR}, \mathrm{OSO_2R'}, \mathrm{OSOR'}$
$= \mathrm{ONO_2}, \mathrm{ONO}, \mathrm{OPO(OH)_2}, \mathrm{OPO(OR')_2}, \mathrm{OB(OH)_2}$ and others

Esters of inorganic acids, including those given above and others, can be hydrolyzed to alcohols. The reactions are most successful when the ester is that of a strong acid, but it can be done for esters of weaker acids by the use of hydroxide ion (a more powerful nucleophile) or acidic conditions (which make the leaving group come off more easily). Allylic halides are converted to allylic alcohols by reaction with water, in the presence of a Ru complex.[574] Heating benzylic amines with KOH as a catalyst gave benzylic alcohol products.[575] A Brønsted acid facilitated an intramolecular substitution of the OH group in stereogenic alcohols.[576] Alkyl fluorides have been converted to alcohols or thiols using YbI_3 as a catalyst.[577] When vinylic substrates (C═C—X) are hydrolyzed, the products are enols, which tautomerize to aldehydes or ketones (Sec. 2.N).

It is possible for the same inorganic ester to be cleaved at either position, depending on the conditions. Thus benzhydryl *p*-toluenesulfinate ($Ph_2CHOSOC_6H_4CH_3$) was found to undergo C—O cleavage in $HClO_4$ solutions and S—O cleavage in alkaline media.[578] In general, the weaker the corresponding acid, the less likely is C—O cleavage. Thus, sulfonic acid esters $ROSO_2R'$ generally give C—O cleavage,[579] while nitrous acid esters RONO usually give N—O cleavage.[580] Esters of sulfonic acids that are frequently hydrolyzed are mentioned in Sec. 10.G.iii. For hydrolysis of sulfonic acid esters, see **16-94**.

OS **VI**, 852. See also, **VIII**, 50.

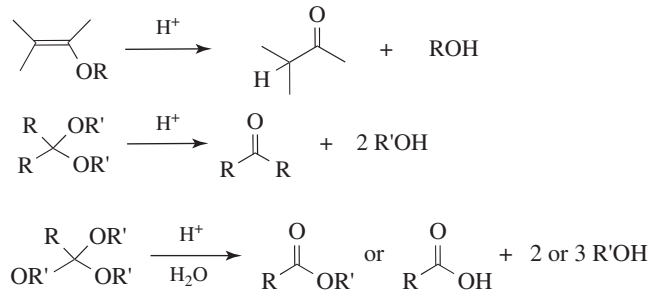
10-5 Hydrolysis of Diazoketones



Diazoketones are relatively easy to prepare (see **12-10**). When treated with acid, they add a proton to give α-keto diazonium salts, which are hydrolyzed to the alcohols by the S_N1 or S_N2 mechanism.[581] Relatively good yields of α-hydroxy ketones can be prepared in this way, since the diazonium ion is somewhat stabilized by the presence of the carbonyl group, which discourages N_2 from leaving because that would result in an unstable α-carbonyl carbocation.

[574] Kanbayashi, N.; Onitsuka, K. *Angew. Chem. Int. Ed.* ***2011***, *50*, 5197.
[575] Kanbara, Y.; Abe, T.; Fushimi, N.; Ikeno, T. *Synlett* ***2012***, *23*, 706.
[576] Bunrit, A.; Dahlstrand, C.; Srifa, P.; Olsson, S.K.; Huang, G.; Biswas, S.; Himo, F.; Samec, J.S.M. *Synlett* ***2016***, *27*, 173.
[577] Träff, A.M.; Janjetovic, M.; Ta, L.; Hilmersson, G. *Angew. Chem. Int. Ed.* ***2013***, *52*, 12073.
[578] Batts, B.D. *J. Chem. Soc. B* ***1966***, 551.
[579] Barnard, P.W.C.; Robertson, R.E. *Can. J. Chem.* ***1961***, *39*, 881. See also, Drabicky, M.J.; Myhre, P.C.; Reich, C.J.; Schmittou, E.R. *J. Org. Chem.* ***1976***, *41*, 1472.
[580] SeeWilliams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 162–163.
[581] Thomas, C.W.; Leveson, L.L. *Int. J. Chem. Kinet.* ***1983***, *15*, 25. See Smith III, A.B; Dieter, R.K. *Tetrahedron* ***1981***, *37*, 2407.

10-6 Hydrolysis of Acetals, Enol Ethers, and Similar Compounds[582]



The alkoxyl group OR is not a leaving group in these reactions, so these compounds must be converted to the conjugate acids before they can be hydrolyzed. Although 100% sulfuric acid and other concentrated strong acids readily cleave simple ethers,[583] many of those acids are oxidizing acids, so HBr and HI are typically used preparatively (**10-48**). Note that acetals, ketals, and ortho esters[584] are easily cleaved by dilute acids, because carbocations of type $R_2(RO)C^+$ are greatly stabilized by resonance (Sec. 5.A.ii). These reactions proceed by the S_N1 mechanism,[585] as shown for acetals.[586]

This mechanism (which is an S_N1cA or A1 mechanism) is the reverse of that for acetal formation by reaction of an aldehyde and an alcohol (**16-5**). Among the facts supporting the mechanism are:[587] (i) the reaction proceeds with *specific* H_3O^+ catalysis (Sec. 8.D); (ii) it is faster in D_2O; (iii) optically active ROH are not racemized; (iv) even with *tert*-butyl alcohol the R—O bond does not cleave, as shown by ^{18}O labeling;[588] (v) in the case of acetophenone ketals, the intermediate corresponding to **109** [$ArCMe(OR)_2$] could be trapped with sulfite ions (SO_3^{2-});[589] (vi) trapping of this ion did not affect the hydrolysis rate,[558] so the rate-determining step must come earlier; (vii) in the case of 1,1-dialkoxyalkanes, intermediates corresponding to **109** were isolated as stable ions in superacid solution at −75 °C, where their spectra could be studied;[590] (viii) hydrolysis rates greatly increase in the order $CH_2(OR')_2 < RCH(OR')_2 < R_2C(OR')_2 < RC(OR')_3$, as would be expected for a carbocation intermediate.[591] Formation of **109** is usually the rate-determining step, but

[582] Bergstrom, R.G. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, ***1980***, pp. 881–902; Cordes, E.H.; Bull, H.G. *Chem. Rev.* ***1974***, *74*, 581; Pindur, U.; Müller, J.; Flo, C.; Witzel, H. *Chem. Soc. Rev.* ***1987***, *16*, 75 (ortho esters); Rekasheva, A.F. *Russ. Chem. Rev.* ***1968***, *37*, 1009 (enol ethers).

[583] Jaques, D.; Leisten, J.A. *J. Chem. Soc.* ***1964***, 2683. See also, Olah, G.A.; O'Brien, D.H. *J. Am. Chem. Soc.* ***1967***, *89*, 1725.

[584] See Pavlova, L.A.; Davidovich, Yu.A.; Rogozhin, S.V. *Russ. Chem. Rev.* ***1986***, *55*, 1026.

[585] See Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1990***, *19*, 55.

[586] Kreevoy, M.M.; Taft, R.W. *J. Am. Chem. Soc.* ***1955***, *77*, 3146, 5590.

[587] See Cordes, E.H. *Prog. Phys. Org. Chem.* ***1967***, *4*, 1.

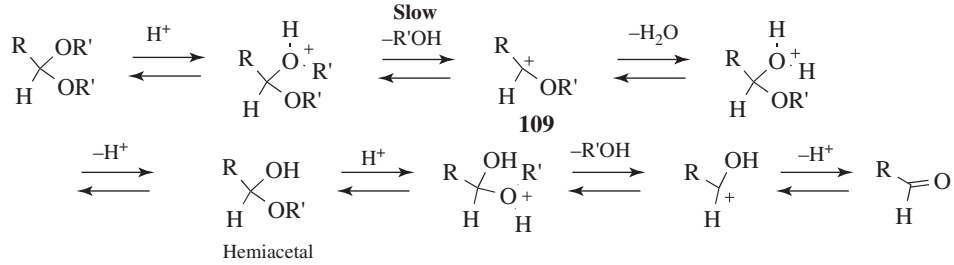
[588] Cawley, J.J.; Westheimer, F.H. *Chem. Ind. (London)* ***1960***, 656.

[589] Young, P.R.; Jencks, W.P. *J. Am. Chem. Soc.* ***1977***, *99*, 8238. See also, Jencks, W.P. *Acc. Chem. Res.* ***1980***, *13*, 161; Young, P.R.; Bogseth, R.C.; Rietz, E.G. *J. Am. Chem. Soc.* ***1980***, *102*, 6268. However, see Amyes, T.L.; Jencks, W.P. *J. Am. Chem. Soc.* ***1988***, *110*, 3677.

[590] See White, A.M.; Olah, G.A. *J. Am. Chem. Soc.* ***1969***, *91*, 2943; Akhmatdinov, R.T.; Kantor, E.A.; Imashev, U.B.; Yasman, Ya.B.; Rakhmankulov, D.L. *J. Org. Chem. USSR* ***1981***, *17*, 626.

[591] See Belarmino, A.T.N.; Froehner, S.; Zanette, D.; Farah, J.P.S.; Bunton, C.A.; Romsted, L.S. *J. Org. Chem.* ***2003***, *68*, 706.

there is evidence that at least in some cases this step is fast, and the rate-determining step is loss of R'OH from the protonated hemiacetal.[592] Rate-determining addition of water to **109** has also been reported.[593]



While the A1 mechanism shown above operates in most acetal hydrolyses, it has been shown that at least two other mechanisms can take place with suitable substrates.[594] In one of these mechanisms the second and third of the above steps are concerted, so that the mechanism is S_N2cA (or A2). An example is the hydrolysis of 1,1-diethoxyethane, using isotope effect studies, which showed that water protonated the OEt group and that ethanol was the leaving group.[595]

In the second mechanism, the first and second steps are concerted. In the case of hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran, *general* acid catalysis was demonstrated,[596] demonstrating that the substrate is protonated in the rate-determining step (Sec. 8.D). Reactions in which a substrate is protonated in the rate-determining step are called $A\text{-}S_E2$ reactions.[597] However, if protonation of the substrate were all that happens in the slow step, then the proton in the transition state would be expected to lie closer to the weaker base (Sec. 8.D). Because the substrate is a much weaker base than water, the proton should be largely transferred. Since the Brønsted coefficient was found to be 0.5, the proton was actually transferred only about halfway. This behavior can be explained if the basicity of the substrate is increased by partial breaking of the C—O bond. The conclusion drawn is that steps 1 and 2 are concerted. The hydrolysis of ortho esters in most cases is also subject to general acid catalysis.[598]

The hydrolysis of acetals and ortho esters is governed by the stereoelectronic control factor discussed in Sec. 16.A.i, category 4,[599] although the effect can generally be seen only in systems where conformational mobility is limited, especially in cyclic systems. There is evidence for synplanar stereoselection in the acid hydrolysis of acetals.[600] The

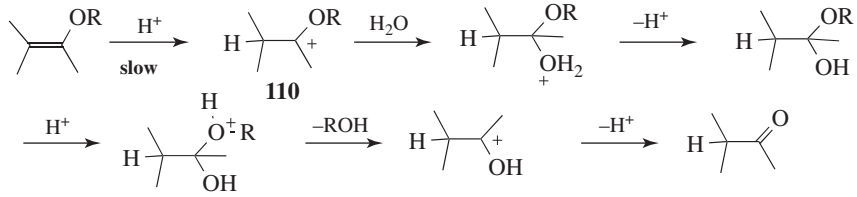
[592] McClelland, R.A.; Sørensen, P.E. *Acta Chem. Scand.* ***1990***, *44*, 1082.
[593] Fife, T.H.; Natarajan, R. *J. Am. Chem. Soc.* ***1986***, *108*, 2425, 8050.
[594] See Fife, T.H. *Acc. Chem. Res.* ***1972***, *5*, 264; Wann, S.R.; Kreevoy, M.M. *J. Org. Chem.* ***1981***, *46*, 419.
[595] Kresge, A.J.; Weeks, D.P. *J. Am. Chem. Soc.* ***1984***, *106*, 7140. See also, Amyes, T.L.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 7888, 7900.
[596] Jensen, J.L.; Herold, L.R.; Lenz, P.A.; Trusty, S.; Sergi, V.; Bell, K.; Rogers, P. *J. Am. Chem. Soc.* ***1979***, *101*, 4672.
[597] See Williams Jr., J.M.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* ***1968***, *6*, 63.
[598] Chiang, Y.; Kresge, A.J.; Lahti, M.O.; Weeks, D.P. *J. Am. Chem. Soc.* ***1983***, *105*, 6852 and references cited therein; Fife, T.H.; Przystas, T.J. *J. Chem. Soc., Perkin Trans. 2* ***1987***, 143.
[599] See, for example, Kirby, A.J. *Acc. Chem. Res.* ***1984***, *17*, 305; Bouab, O.; Lamaty, G.; Moreau, C. *Can. J. Chem.* ***1985***, *63*, 816. See, however, Ratcliffe, A.J.; Mootoo, D.R.; Andrews, C.W.; Fraser-Reid, B. *J. Am. Chem. Soc.* ***1989***, *111*, 7661.
[600] Li, S.; Kirby, A.J.; Deslongchamps, P. *Tetrahedron Lett.* ***1993***, *34*, 7757.

mechanism of Lewis acid-mediated cleavage of chiral acetals is also known.[601] Both cyclic and acyclic acetals and ketals can be converted to aldehydes or ketones by treatment with Lewis acids such as In,[602] Ce,[603] or Bi[604] compounds. Pyridine–HF has also been used for this conversion.[605]

Although acetals, ketals, and ortho esters are easily hydrolyzed by acids, they are extremely resistant to hydrolysis by bases. An aldehyde or ketone can therefore be protected from attack by a base by conversion to the acetal or ketal (**16-5**), and then can be cleaved with acid. Thioacetals, thioketals, *gem*-diamines, and other compounds that contain any two of the groups OR, OCOR, NR_2, NHCOR, SR, and halogen on the same carbon can also be hydrolyzed to aldehydes or ketones, in most cases, by acid treatment. Thioacetals $RCH(SR')_2$ and thioketals $R_2C(SR')_2$ are, however, generally resistant to acid hydrolysis.[606]

Because conversion to these sulfur compounds (**16-10**) serves as an important method for protection of aldehydes and ketones, many methods have been devised to cleave them to the parent carbonyl compounds. Among reagents used for this purpose are $HgCl_2$,[607] $CH_3(CH_2)_{15}N(CH_3)_3Br_3$,[608] mcpba, and the *Dess-Martin periodinane*[609] (see **19-3**). Mixed acetals and ketals (RO—C—SR) can be hydrolyzed with most of the reagents mentioned above, including *N*-NBS in aqueous acetone[610] and glyoxylic acid on Amberlyst 15 with microwave irradiation.[611]

Enol ethers (vinyl ethers) are readily hydrolyzed by acids; the rate-determining step is protonation of the substrate.[612] However, protonation does not take place at the oxygen, but at the β carbon,[613] because that gives rise to the stable carbocation **110**.[614] Subsequently, the mechanism is similar to the A1 mechanism given above for the hydrolysis of acetals.



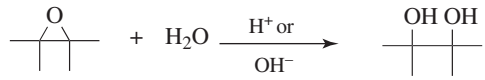
Among the facts supporting this mechanism (which is an A-S_E2 mechanism because the substrate is protonated in the rate-determining step) are: (i) ^{18}O labeling shows that

[601] Sammakia, T.; Smith, R.S. *J. Org. Chem.* ***1992***, *57*, 2997.
[602] Gregg, B.T.; Golden, K.C.; Quinn, J.F. *J. Org. Chem.* ***2007***, *72*, 5890.
[603] Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.M.; Quesnel, Y.; Markó, I.E. *Tetrahedron Lett.* ***1999***, *40*, 1799.
[604] Carringan, M.D.; Sarapa, D.; Smith, R.C.; Wieland, L.C.; Mohan, R.S. *J. Org. Chem.* ***2002***, *67*, 1027.
[605] Watanabe, Y.; Kiyosawa, Y.; Tatsukawa, A.; Hayashi, M. *Tetrahedron Lett.* ***2001***, *42*, 4641.
[606] Ali, M.; Satchell, D.P.N.; Le, V.T. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 917.
[607] Satchell, D.P.N.; Satchell, R.S. *J. Chem. Soc., Perkin Trans. 2* ***1987***, 513.
[608] Mondal, E.; Bose, G.; Khan, A.T. *Synlett* ***2001***, 785.
[609] Langille, N.F.; Dakin, L.A.; Panek, J.S. *Org. Lett.* ***2003***, *5*, 575. See also, Stork, G.; Zhao, K. *Tetrahedron Lett.* ***1989***, *30*, 287.
[610] Karimi, B.; Seradj, H.; Tabaei, M.H. *Synlett* ***2000***, 1798.
[611] Chavan, S.P.; Soni, P.; Kamat, S.K. *Synlett* ***2001***, 1251.
[612] Jones, J.; Kresge, A.J. *Can. J. Chem.* ***1993***, *71*, 38.
[613] See Burt, R.A.; Chiang, Y.; Kresge, A.J.; Szilagyi, S. *Can. J. Chem.* ***1984***, *62*, 74.
[614] See Chwang, W.K.; Kresge, A.J.; Wiseman, J.R. *J. Am. Chem. Soc.* ***1979***, *101*, 6972.

in ROCH=CH_2 it is the vinyl–oxygen bond and not the RO bond that cleaves;[615] (ii) the reaction is subject to general acid catalysis;[616] and (iii) there is a solvent isotope effect when D_2O is used.[616] A method has been developed to determine primary kinetic isotope effects relating to proton transfer in the hydrolysis of enol ethers.[617] Enantioselective protonation is possible in some cases. Cyclic silyl enol ethers are converted to chiral α-substituted ketones, for example, with high enantioselectivity using a chiral Brønsted acid.[618]

OS **I**, 67, 205; **II**, 302, 305, 323; **III**, 37, 127, 465, 470, 536, 541, 641, 701, 731, 800; **IV**, 302, 499, 660, 816, 903; **V**, 91, 292, 294, 703, 716, 937, 967, 1088; **VI**, 64, 109, 312, 316, 361, 448, 496, 683, 869, 893, 905, 996; **VII**, 12, 162, 241, 249, 251, 263, 271, 287, 381, 495; **VIII**, 19, 155, 241, 353, 373.

10-7 Hydrolysis of Epoxides and Oxetanes



The hydrolysis of epoxides is a convenient method for the preparation of *vic*-diols, catalyzed by acids or bases. A basic reagent will attack the polarized carbon of the epoxide unit to open the ring, whereas an acid-catalyzed reaction leads to a protonated epoxide (an oxonium ion),[619] which is opened by nucleophilic attack at an adjacent carbon. There is evidence that ring-opening cascades promoted by water are stepwise, and become faster after the first reaction.[620] Among acid catalysts, perchloric acid leads to minimal side reactions,[621] and 10% Bu_4NHSO_4 in water is effective;[622] however, water reacts directly with epoxides at 60 °C.[623] Dimethyl sulfoxide is a superior solvent for the alkaline hydrolysis of epoxides.[624] Graphene oxide has been used as an acid catalyst for the ring opening of epoxides.[625]

Cobalt salen catalysts [salen = bis(salicylidene)ethylenediamine], in the presence of water, open epoxides with high stereoselectivity.[626] The enzyme *epoxide hydrolase* opens epoxides with high enantioselectivity.[627] Hydrolytic and aminolytic kinetic resolution of terminal bis(epoxide)s has been reported.[628]

[615] Kiprianova, L.A.; Rekasheva, A.F. *Dokl. Akad. Nauk SSSR*, ***1962***, *142*, 589.
[616] Kresge, A.J.; Yin, Y. *Can. J. Chem.* ***1987***, *65*, 1753.
[617] Tsang, W.-Y.; Richard, J.P. *J. Am. Chem. Soc.* ***2007***, *129*, 10330.
[618] Cheon, C.H.; Yamamoto, H. *J. Am. Chem. Soc* ***2008***, *130*, 9246.
[619] For a density-functional analysis, see Zhao, Y.; Truhlar, D.G. *J. Org. Chem.* ***2007***, *72*, 295.
[620] Morten; C.J.; Byers, J.A.; Jamison, T.F. *J. Am. Chem. Soc.* ***2011***, *133*, 1902.
[621] Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 1, Wiley, NY, ***1967***, p. 796.
[622] Fan, R.-H.; Hou, X.-L. *Org. Biomol. Chem.* ***2003***, *1*, 1565. For a reaction with NaHSO4, see Cavdar, H.; Saracoglu, N. *Tetrahedron* ***2009***, *65*, 985.
[623] Wang, Z.; Cui, Y.-T.; Xu, Z.-B.; Qu, J. *J. Org. Chem.* ***2008***, *73*, 2270.
[624] Berti, G.; Macchia, B.; Macchia, F. *Tetrahedron Lett.* ***1965***, 3421.
[625] Dhakshinamoorthy, A.; Alvaro, M.; Concepción, P.; Fornés, V.; Garcia, H. *Chem. Commun.* ***2012***, *48*, 5443.
[626] Ready, J.M.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2001***, *123*, 2687.
[627] See Zhao, L.; Han, B.; Huang, Z.; Miller, M.; Huang, H.; Malashock, D.S.; Zhu, Z.; Milan, A.; Robertson, D.E.; Weiner, D.P.; Burk, M.J. *J. Am. Chem. Soc.* ***2004***, *126*, 11156.
[628] Bredihhina, J.; Villo, P.; Andersons, K.; Toom, L.; Vares, L. *J. Org. Chem.* ***2013***, *78*, 2379.

Oxetanes are not as strained as oxiranes, or as useful in organic synthesis. Nonetheless, hydrolysis reactions of oxetanes are known.[629] Chiral phosphoric acid-catalyzed desymmetrization of oxetanes is known.[630]

OS **V**, 414.

B. Attack by OR at an Alkyl Carbon

10-8 Alkoxylation: The Williamson Reaction

$$RX + OR'^{-} \longrightarrow ROR'$$

The *Williamson reaction* (*Williamson ether synthesis*), discovered in 1850, is still the best general method for the preparation of unsymmetrical or symmetrical ethers.[631] The reaction can also be carried out with aromatic R′.[632] The normal method involves treatment of a primary or secondary alkyl halide with alkoxide or aroxide ion prepared from an alcohol[633] or phenol by reaction with a suitable base. Most Williamson reactions proceed by the S_N2 mechanism, but there is evidence (Sec. 10.C) that *in some cases* the SET mechanism can take place, especially with alkyl iodides.

The solvent is usually an aprotic solvent such as THF, ether, etc., rather than an alcohol solvent, which typically promotes elimination reactions in the presence of alkoxides (see Chapter 17). The reaction can be carried out in a dry medium,[634] neat,[635] in solvents using microwave irradiation,[636] in ionic liquids,[637] using phase-transfer catalysis (Sec. 10.G.v),[638] and with micellar catalysis.[639] Aryl ethers have been prepared using *Mitsunobu conditions* (see **10-17**).[640]

Benzyl ethers were formed from benzyl halides and phenol in choline chloride-based deep eutectic solvent.[641] The benzylation of alcohols has been accomplished using tertiary amines as a base.[642] Unsymmetrical ethers, catalyzed by sodium bisulfite, have been prepared by dehydration of benzylic alcohols with aliphatic alcohols in the absence of solvent.[643] Aryl trifluoromethyl ethers have been prepared by *O*-carboxydifluoromethylation

[629] Han, W.B.; Wu, Y. *Org. Lett.* ***2014***, *16*, 5706.
[630] Champagne, P.A.; Houk, K.N. *J. Am. Chem. Soc.* ***2016***, *138*, 12356.
[631] See Feuer, H.; Hooz, J. in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 446–450, 460–468.
[632] For a list of reagents used to convert alcohols and phenols to ethers, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 890–893.
[633] Räder, A.F.B.; Tiefenbacher, K. *Angew. Chem. Int. Ed.* ***2014***, *53*, 1206.
[634] Bogdal, D.; Pielichowski, J.; Jaskot, K. *Org. Prep. Proceed. Int.* ***1998***, *30*, 427.
[635] Yuncheng, Y.; Yulin, J.; Jun, P.; Xiaohui, Z.; Conggui, Y. *Gazz. Chim. Ital.* ***1993***, *123*, 519.
[636] Paul, S.; Gupta, M. *Tetrahedron Lett.* ***2004***, *45*, 8825.
[637] Xu, Z.Y.; Xu, D.Q.; Liu, B.Y. *Org. Prep. Proceed. Int.* ***2004***, *36*, 156; Altimari, J.M.; Delaney, J.P.; Servinis, L.; Squire, J.S.; Thornton, M.T.; Khosa, S.K.; Long, B.M.; Johnstone, M.D.; Fleming, C.L.; Pfeffer, F.M.; Hickey, S.M.; Wride, M.P.; Ashton, T.D.; Fox, B.L.; Byrne, N.; Henderson, L.C. *Tetrahedron Lett.* ***2012***, *53*, 2035.
[638] Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Springer, NY, ***1978***, pp. 128–138; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 73–84. See de la Zerda, J.; Barak, G.; Sasson, Y. *Tetrahedron* ***1989***, *45*, 1533.
[639] Jursic, B. *Tetrahedron* ***1988***, *44*, 6677.
[640] Lepore, S.D.; He, Y. *J. Org. Chem.* ***2003***, *68*, 8261.
[641] Singh, A.S.; Shendage, S.S.; Nagarkar, J.M. *Tetrahedron Lett.* ***2014***, *55*, 7243.
[642] Gathirwa, J.W.; Maki, T. *Tetrahedron* ***2012***, *68*, 370.
[643] Yu, J.-L.; Wang, H.; Zou, K.-F.; Zhang, J.-R.; Gao, X.; Zhang, D.-W.; Li, Z.-T. *Tetrahedron* ***2013***, *69*, 310.

followed by decarboxylative fluorination.[644] Alkyl halides can be coupled with phenols and alcohols in a PEG1000-DAIL[$CdCl_3$]–toluene temperature-dependent biphasic system.[645]

Under S_N2 conditions the reaction is *not* successful for tertiary alkyl halides (elimination predominates), and low yields may be obtained with secondary halides. Ethers with one tertiary group *can* be prepared by treatment of an alkyl halide or sulfate ester (**10-10**) with a tertiary alkoxide $R'O^-$. Di-*tert*-alkyl ethers in general have proved difficult to make, but they can be prepared in low-to-moderate yields by treatment of a tertiary halide with Ag_2CO_3 or Ag_2O.[646] Active halides, such as Ar_3CX, may react directly with the alcohol[647] and hindered alcohols may react as well[648] via a S_N1 mechanism. *tert*-Butyl halides can be converted to aryl *tert*-butyl ethers by treatment with phenols and an amine such as pyridine.[649]

There is significant research in the area of transition metal-catalyzed etherification reactions.[650] The transition metal-catalyzed formation of ethers with substrates that do not contain an activated C—H unit has been reviewed.[651] Catalysts including Rh,[652] Ir,[653] Au,[654] and In-Si[655] have been used in ether-forming reactions. The Pd-catalyzed displacement of allylic acetates with aliphatic alcohols has been shown to give the corresponding alkyl allyl ether.[656] The reaction of allylic alcohols with an In catalyst and a suitable nucleophile gave the allylic substitution product.[657] Secondary alcohols have been converted to the corresponding methyl ether by reaction with methanol in the presence of an Fe catalyst.[658] Symmetrical benzylic ethers have been prepared by reaction of benzylic alcohols with Mg/I_2 followed by triflic anhydride.[659] The trifluoromethylthiolation of alkyl alcohols has been developed using $AgSCF_3$ and *n*-Bu_4NI.[660] Diaryl ethers are prepared in the presence of Cu_2O/Cu-CNTs as a heterogeneous catalyst.[661] A Ru catalyst has been used as a precatalyst in the allylic etherification of phenol with cinnamyl chlorides.[662] The use of Pd/Sn bimetallic catalysts for the monoallylation of 1,2-diols has been reported.[663]

[644] Zhou, M.; Ni, C.; He, Z.; Hu, J. *Org. Lett.* ***2016***, *18*, 3754.
[645] Hu, Y.L.; Ma, X.Y.; Lu, M. *Can. J. Chem.* ***2011***, *89*, 471.
[646] Masada, H.; Sakajiri, T. *Bull. Chem. Soc. Jpn.* ***1978***, *51*, 866.
[647] See Salomaa, P.; Kankaanperä, A.; Pihlaja, K. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 454–466; Biordi, J.; Moelwyn-Hughes, E.A. *J. Chem. Soc.* ***1962***, 4291.
[648] Aspinall, H.C.; Greeves, N.; Lee, W.-M.; McIver, E.G.; Smith, P.M. *Tetrahedron Lett.* ***1997***, *38*, 4679.
[649] Camps, F.; Coll, J.; Moretó, J.M. *Synthesis* ***1982***, 186.
[650] Krishnan, K.K.; Ujwaldev, S.M.; Sindhu, K.S.; Anilkumar, G. *Tetrahedron* ***2016***, *72*, 7393. For a Au-catalyzed reaction, see Vinson, A.R.S.; Davis, V.K.; Arunasalam, A.; Jesse, K.A.; Hamilton, R.E.; Shattuck, M.A.; Hu, A.C.; Iafe, R.G.; Wenzel, A.G. *Synlett* ***2015***, *26*, 765.
[651] Liu, B.; Shi, B.-F. *Tetrahedron Lett.* ***2015***, *56*, 15.
[652] Evans, P.A.; Leahy, D.K. *J. Am. Chem. Soc.* ***2002***, *124*, 7882.
[653] Ueno, S.; Hartwig, J.F. *Angew. Chem. Int. Ed.* ***2008***, *47*, 1928.
[654] Young, P.C.; Schopf, N.A.; Lee, A.-L. *Chem. Commun.* ***2013***, *49*, 4262.
[655] Saito, T.; Yasuda, M.; Baba, A. *Synlett* ***2005***, 1737.
[656] See Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2004***, *69*, 3474.
[657] Webster, S.; Schaefer, L.; Barker, G.; Lee, A.-L. *Synlett* ***2015***, *26*, 2673.
[658] Namboodiri, V.V.; Varma, R.S. *Tetrahedron Lett.* ***2002***, *43*, 4593.
[659] Nishiyama, T.; Kameyama, H.; Maekawa, H.; Watanuki, K. *Can. J. Chem.* ***1999***, *77*, 258.
[660] Liu, J.-B.; Xu, X.-H.; Chen, Z.-H.; Qing, F.-L. *Angew. Chem. Int. Ed.* ***2015***, *54*, 897. See Wu, H.; Xiao, Z.; Wu, J.; Guo, Y.; Xiao, J.-C.; Liu, C.; Chen, Q.-Y. *Angew. Chem. Int. Ed.* ***2015***, *54*, 4070.
[661] Zhang, Y.-P.; Jiao, Y.-C.; Yang, Y.-S.; Li, C.-L. *Tetrahedron Lett.* ***2013***, *54*, 6494.
[662] Siddappa, R.K.G.; Chang, C.-W.; Chein, R.-J. *Tetrahedron Lett.* ***2014***, *55*, 1031.
[663] Kuriyama, M.; Takeichi, T.; Ito, M.; Yamasaki, N.; Yamamura, R.; Demizu, Y.; Onomura, O. *Chem. Eur. J.* ***2012***, *18*, 2477. See Jha, S.C.; Joshi, N.N. *J. Org. Chem.* ***2002***, *67*, 3897.

Diaryl ethers have been prepared from unsymmetrical diaryliodonium tosylates and phenols, with high regioselectivity.[664] A diastereoconvergent nucleophilic substitution of bromocyclopropanes has been reported using oxygen- and sulfur-based nucleophiles.[665] An Ir(P,alkene) complex has been used to catalyze the enantioselective allylic etherification of allylic alcohols.[666] Chiral *tert*-butanesulfinylphosphine ligands are effective for the Pd-catalyzed asymmetric allylic etherification of 1,3-diphenylpropenyl acetate with alcohols.[667] A chiral phosphine was used in the Pd-catalyzed asymmetric allylic etherification of alcohols and silanols with excellent enantioselectivity.[668]

Intramolecular reactions to produce cyclic ethers can proceed via S_N2 reactions. The water-promoted, intramolecular etherification of allylic alcohols with tethered alcohol moieties proceeds via a S_N2'-like process.[669] Cyclic ethers were prepared by the intramolecular cyclization of diols using trimethylphosphate and NaH.[670] Brønsted acids catalyze an intramolecular S_N2-type alkylation of alcohols with ethers.[671]

$$RO^- + CH_3OCH_2Cl \longrightarrow ROCH_2OCH_3$$

The Williamson ether synthesis has been used for the protection of hydroxy group.[672] *p*-Methoxybenzyl-*N*-phenyl-2,2,2-trifluoroacetimidate reacted with alcohols in the presence of $Bi(OTf)_3$ to give *p*-methoxybenzyl ethers.[673] Primary or secondary esters reacted with KO*t*-Bu in the presence of allylic or benzylic halides to give the corresponding ether.[674] The reaction of alkoxide (alcohol salts) with chloromethyl methyl ether gives the protecting group known as MOM (methoxymethyl), and such compounds are called MOM ethers. The resulting acetals are stable to bases and are easily cleaved with mild acid treatment (**10-7**). The 2-methoxyethoxymethyl group (the MEM group) is formed in a similar manner. Both MOM and MEM groups can be cleaved with dialkyl- and diarylboron halides such as Me_2BBr.[675]

Another common method for the protection of alcohols is conversion to the silyl ether ($R{-}O{-}SiR'_3$).[676] The alcohol is generally treated with a base such a trimethylamine or imidazole, and then with a chlorotrialkylsilane (R_3SiCl), or the analogous bromide.[639] There

[664] Kakinuma, Y.; Moriyama, K.; Togo, H. *Synthesis* ***2013***, *45*, 183.

[665] Banning, J.E.; Prosser, A.R.; Alnasleh, B.K.; Smarker, J.; Rubina, M.; Rubin, M. *J. Org. Chem.* ***2011***, *76*, 3968. See Zhu, X.; Xie, X.; Li, P.; Guo, J.; Wang, L. *Org. Lett.* ***2016***, *18*, 1546.

[666] Roggen, M.; Carreira, E.M. *Angew. Chem. Int. Ed.* ***2011***, *50*, 5568.

[667] Xing, J.; Cao, P.; Liao, J. *Tetrahedron: Asymmetry* ***2012***, *23*, 527.

[668] Ye, F.; Zheng, Z.-J.; Li, L.; Yang, K.-F.; Xia, C.-G.; Xu, L.-W. *Chem. Eur. J.* ***2013***, *19*, 15452.

[669] Zhang, F.-Z.; Tian, Y.; Li, G.-X.; Qu, J. *J. Org. Chem.* ***2015***, *80*, 1107.

[670] Asai, S.; Kato, M.; Monguchi, Y.; Sajiki, H.; Sawama, Y. *Chem. Commun.* ***2017***, *53*, 4787.

[671] Čorić, I.; Kim, H.-K.; Vlaar, T.; Patil, M.; Thiel, W.; List, B. *Angew. Chem. Int. Ed.* ***2013***, *52*, 3490.

[672] See Greene, T.W. *Protective Groups in Organic Synthesis*, Wiley, New York, ***1980***; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis*, 2nd ed., Wiley, New York, ***1991***; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, New York, ***1999***; Wuts, P.G.M.; Greene, T.W. *Greene's Protective Groups in Organic Synthesis*, 4th ed., Wiley, New Jersey, ***2006***; Wuts, P.G.M. *Greene's Protective Groups in Organic Synthesis*, 5th ed., Wiley, New Jersey, ***2014***.

[673] Barroca-Aubry, N.; Benchekroun, M.; Gomes, F.; Bonnaffé, D. *Tetrahedron Lett.* ***2013***, *54*, 5118.

[674] Xu, H.-D.; Xu, K.; Zheng, Q.; He, W.-J.; Shen, M.-H.; Hu, W.-H. *Tetrahedron Lett.* ***2014***, *55*, 6836.

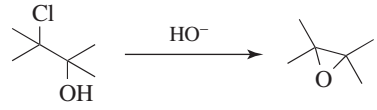
[675] Guindon, Y.; Yoakim, C.; Morton, H.E. *J. Org. Chem.* ***1984***, *49*, 3912. For other methods, see Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.* ***1984***, *25*, 2515; Rigby, J.H.; Wilson, J.Z. *Tetrahedron Lett.* ***1984***, *25*, 1429.

[676] Crouch, R.D. *Synth. Commun.* ***2013***, *43*, 2265.

are many variations of this basic procedure. An $InBr_3$ catalyst has been used.[677] There are also many ways to remove the silyl group to regenerate the alcohol, although fluoride ion, including tetrabutylammonium fluoride in THF, is probably the most common method.[639]

OS **I**, 75, 205, 258, 296, 435; **II**, 260; **III**, 127, 140, 209, 418, 432, 544; **IV**, 427, 457, 558, 590, 836; **V**, 251, 258, 266, 403, 424, 684; **VI**, 301, 361, 395, 683; **VII**, 34, 386, 435; **VIII**, 26, 161, 155, 373; *80*, 227.

10-9 Epoxide Formation (Internal Williamson Ether Synthesis)



Reaction of a chlorohydrin or bromohydrin with base removes the proton from the OH, and the resulting alkoxide subsequently attacks in an internal S_N2 reaction.[678] The course of the reaction can be influenced by neighboring group effects.[679] Epoxidation of alkenes has also been accomplished using HOF–MeCN in a continuous flow system (Sec. 7.D).[680] Enantioselective epoxide-forming reactions are known, using chiral additives such as dihydrocinchonidines.[681]

Larger cyclic ethers can be prepared, including five- and six-membered rings (tetrahydrofurans and tetrahydropyrans, respectively).[682] Additional treatment with base yields the glycol (**10-7**). Thiiranes can be prepared by the reaction of α-chloro ketones with $(EtO)_2P(=O)—SH$ and $NaBH_4–Al_2O_3$ with microwave irradiation.[683]

1,2-Diols can be converted to epoxides by treatment with DMF dimethyl acetal, $(MeO)_2CHNMe_2$,[684] with diethyl azodicarboxylate ($Et_2OCN{=}NCO_2Et$) and Ph_3P,[685] with a dialkoxytriphenylphosphorane,[686] or with $TsCl^-Na^+OHPhCH_2NEt_2^+\ Cl^-$.[687]

OS **I**, 185, 233; **II**, 256; **III**, 835; **VI**, 560; **VII**, 164, 356; **VIII**, 434.

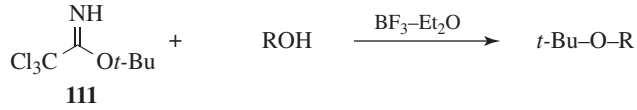
10-10 Alkylation with Inorganic Esters

$$R—OSO_2OR^2 + R'O^- \longrightarrow ROR$$

The reaction of alkyl sulfates with alkoxide ions is quite similar to **10-8** in mechanism and scope. Other inorganic esters can also be used. Methyl ethers of alcohols and

[677] Sridhar, M.; Raveendra, J.; Ramanaiah, B.C.; Narsaiah, C. *Tetrahedron Lett.* ***2011***, *52*, 5980.
[678] See Knipe, A.C. *J. Chem. Soc., Perkin Trans. 2* ***1973***, 589; Berti, G. *Top. Stereochem.* ***1973***, *7*, 93 (p. 187).
[679] Lang, F.; Kassab, D.J.; Ganem, B. *Tetrahedron Lett.* ***1998***, *39*, 5903.
[680] McPake, C.B.; Murray, C.B.; Sandford, G. *Tetrahedron Lett.* ***2009***, *50*, 1674.
[681] Lygo, B.; Gardiner, S.D.; McLeod, M.C.; To, D.C.M. *Org. Biomol. Chem.* ***2007***, *5*, 2283.
[682] See Kim, K.M.; Jeon, D.J.; Ryu, E.K. *Synthesis* ***1998***, 835. Also see Marek, I.; Lefrancois, J.-M.; Normant, J.-F. *Tetrahedron Lett.* ***1992***, *33*, 1747.
[683] Yadav, L.D.S.; Kapoor, R. *Synthesis* ***2002***, 2344.
[684] Neumann, H. *Chimia*, ***1969***, *23*, 267.
[685] Guthrie, R.D.; Jenkins, I.D.; Yamasaki, R.; Skelton, B.W.; White, A.H. *J. Chem. Soc., Perkin Trans. 1* ***1981***, 2328 and references cited therein. For a review of diethyl azodicarboxylate-Ph3P, see Mitsunobu, O. *Synthesis* ***1981***, 1.
[686] Kelly, J.W.; Evans Jr., S.A. *J. Org. Chem.* ***1986***, *51*, 5490. See also, Hendrickson, J.B.; Hussoin, M.S. *Synlett*, ***1990***, 423.
[687] Szeja, W. *Synthesis* ***1985***, 983.

phenols are commonly formed by treatment of alkoxides or aroxides with methyl sulfate. The alcohol or phenol can be methylated directly with dimethyl sulfate under various conditions.[688] The reaction of aliphatic alcohols and potassium organotrifluoroborate salts also gives ethers.[689] *tert*-Butyl ethers can be prepared by treating the compound *tert*-butyl-2,2,2-trichloroacetimidate (**111**) with an alcohol or phenol in the presence of boron trifluoride etherate.[690] *tert*-Butyl ethers can be cleaved by acid-catalyzed hydrolysis.[691]



OS **I**, 58, 537; **II**, 387, 619; **III**, 127, 564, 800; **IV**, 588; **VI**, 737, 859, **VII**, 41. See OS **V**, 431.

10-11 Alkylation with Diazo Compounds

$$CH_2N_2 + ROH \xrightarrow{HBF_4} CH_3OR$$
$$R_2CN_2 + ArOH \longrightarrow R_2CHOAr$$

Alcohols react with diazo compounds to form ethers, but diazomethane and diazo ketones are most readily available, giving methyl ethers or α-keto ethers,[692] respectively. With diazomethane[693] the method is expensive and requires great caution, but the conditions are mild and high yields are obtained. Diazomethane is used chiefly to methylate alcohols and phenols that are expensive or available in small amounts. Hydroxy compounds react better as their acidity increases; ordinary alcohols do not react at all unless a catalyst, such as HBF_4,[694] is present. The more acidic phenols react very well in the absence of a catalyst. The reaction of oximes, and ketones that have substantial enolic contributions, give *O*-alkylation to form *O*-alkyl oximes and enol ethers, respectively. The mechanism[695] is as in **10-5**. Note that *O*-aryloximes are prepared from oximes and aryl halides, mediated by CuI.[696]

Diazoalkanes can also be converted to ethers by thermal or photochemical cleavage in the presence of an alcohol via a carbene or carbenoid.[697] Enantioselective insertion into phenolic O—H bonds leads to highly substituted ethers.[698] Similar intermediates are

[688] Cao, Y.-Q.; Pei, B.-G. *Synth. Commun.* ***2000***, *30*, 1759.
[689] Quach, T.D.; Batey, R.A. *Org. Lett.* ***2003***, *5*, 1381.
[690] See Rai, A.N.; Basu, A. *Tetrahedron Lett.* ***2003***, *44*, 2267.
[691] Lajunen, M.; Ianskanen-Lehti, K. *Acta Chem. Scand. B*, ***1994***, *48*, 861.
[692] Pansare, S.V.; Jain, R.P.; Bhattacharyya, A. *Tetrahedron Lett.* ***1999***, *40*, 5255.
[693] For a review, see Pizey, J.S. *Synthetic Reagents*, Vol. 2; Wiley, NY, ***1974***, pp. 65–142.
[694] Neeman, M.; Caserio, M.C.; Roberts, J.D.; Johnson, W.S. *Tetrahedron* ***1959***, *6*, 36.
[695] Kreevoy, M.M.; Thomas, S.J. *J. Org. Chem.* ***1977***, *42*, 3979. See also, McGarrity, J.F.; Smyth, T. *J. Am. Chem. Soc.* ***1980***, *102*, 7303.
[696] De, P.; Pandurangan, K.; Maitra, U.; Wailes, S. *Org. Lett.* ***2007***, *9*, 2767.
[697] Noels, A.F.; Demonceau, A.; Petiniot, N.; Hubert, A.J.; Teyssié, P. *Tetrahedron* ***1982***, *38*, 2733.
[698] Chen, C.; Zhu, S.-F.; Liu, B.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* ***2007***, *129*, 12616.

involved when diazoalkanes react with alcohols in the presence of *t*-BuOCl to give acetals.[699]

OS **V**, 245. Also see, OS **V**, 1099.

10-12 Dehydration of Alcohols to Give Ethers

$$2\ \mathrm{ROH} \xrightarrow{\mathrm{H_2SO_4}} \mathrm{ROR} + \mathrm{H_2O}$$

The dehydration of alcohols can form symmetrical ethers[700] and the species from which the leaving group departs is ROH_2^+ or $ROSO_2OH$. The leaving group is obtained directly by treatment of alcohols with sulfuric acid and may go, by an S_N1 or S_N2 pathway, directly to the ether if attacked by another molecule of alcohol or by the nucleophile HSO_4^-, in which case $ROSO_2OH$ is formed. In the latter case, attack by an alcohol molecule will give ROR. Elimination is always a side reaction and, in the case of tertiary alkyl substrates, completely predominates. Lewis acids can be used with alcohols in some cases.[701]

Mixed (unsymmetrical) ethers can be prepared if one group is tertiary alkyl and the other primary or secondary, since the latter group is not likely to compete with the tertiary group in the formation of the carbocation, while a tertiary alcohol is a very poor nucleophile.[702] *If one group is not tertiary, the reaction of a mixture of two different alcohols leads to all three possible ethers.* Unsymmetrical ethers have been formed by treatment of two different alcohols with $BiBr_3$.[703] Unsymmetrical ethers have been prepared under *Mitsunobu conditions* (**10-17**) with a polymer-supported phosphine and diethyl azadicarboxylate (DEAD).[704] Symmetrical ethers are formed by heating benzylic alcohols with the polymer poly(3,4-ethylenedioxythiophene) in toluene or heptane (a two-phase system), with no other additives.[705]

Diols can be converted to cyclic ethers;[706] the reaction is most successful for five-membered rings, and five-, six-, and seven-membered rings have been prepared.[707] Thus, hexane-1,6-diol gives mostly 2-ethyltetrahydrofuran. The reaction of 1,4- and 1,5-diols with 2,3-diphenylcyclopropene and methanesulfonic anhydride led to a cyclopropenium intermediate that cyclized via an internal S_N2 reaction to give tetrahydrofurans and tetrahydropyrans.[708] Addition of PPh_3 to a NBS solution of 1,4-diols at − 78 °C and then warming to ambient temperature gave tetrahydrofurans but an excess of Ph_3P/NBS gave the dibromobutane.[709]

OS **I**, 280; **II**, 126; **IV**, 25, 72, 266, 350, 393, 534; **V**, 539, 1024; **VI**, 887; **VIII**, 116. Also see OS **V**, 721.

[699] Baganz, H.; May, H. *Angew. Chem. Int. Ed.* ***1966***, *5*, 420.
[700] See Feuer, H.; Hooz, J. in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp.457–460, 468–470.
[701] See Ooi, T.; Ichikawa, H.; Itagaki, Y.; Maruoka, K. *Heterocycles* ***2000***, *52*, 575.
[702] See, for example, Jenner, G. *Tetrahedron Lett.* ***1988***, *29*, 2445.
[703] Boyer, B.; Keramane, E.-M.; Roque, J.-P.; Pavia, A.A. *Tetrahedron Lett.* ***2000***, *41*, 2891.
[704] Lizarzaburu, M.E.; Shuttleworth, S. *Tetrahedron Lett.* ***2002***, *43*, 2157.
[705] D'Angelo, J.G.; Sawyer, R.; Kumar, A.; Onorato, A.; McCluskey, C.; Delude, C.; Vollenweider, L.; Reyes, N.; French, R.; Warner, S.; Chou, J.; Stenzel, J.; Sotzing, G.A.; Smith, M.B. *J. Polymer Sci. Part A* ***2007***, *45*, 2328.
[706] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 893–894.
[707] See Olah, G.A.; Fung, A.P.; Malhotra, R. *Synthesis* ***1981***, 474.
[708] Kelly, B.D.; Lambert, T.H. *Org. Lett.* ***2011***, *13*, 740.
[709] Zhao, S.; Wu, Y.; Sun, Q.; Cheng, T.-M.; Li, R.-T. *Synthesis* ***2015***, *47*, 1154.

10-13 Transetherification

$$ROR' + R''OH \longrightarrow ROR'' + R'OH$$

The exchange of one alkoxy group for another is rare for *ethers* without a reactive R group such as diphenylmethyl,[710] or by treatment of alkyl aryl ethers with alkoxide ions:[711]

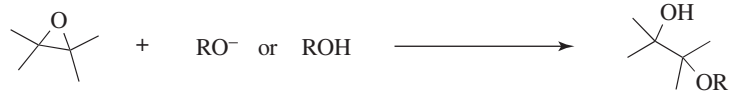
$$ROAr + R'O^- \rightarrow ROR' + ArO^-$$

Diethyl acetals were converted to the corresponding dioxolane by an internal transetherification catalyzed by $BF_3{\bullet}OEt_2$.[712]

Acetals and ortho esters undergo transetherification readily.[713] Loss of the leaving group from an acetal gives a particularly stable oxocarbenium ion. It is also possible to convert a dimethyl ketal directly to a dithiane by reaction with butane-1,4-dithiol on clay.[714] These are equilibrium reactions, and most often the equilibrium is shifted by removing the lower-boiling alcohol by distillation. Enol ethers can be prepared by treating an alcohol with an enol ester or a different enol ether, with mercuric acetate as a catalyst.[715] *N*,*N*-Diethylaminoethylthiol reacts with aryl ethers to give the phenol derivative and the corresponding sulfide in what is effectively a transetherification.[716]

OS **VI**, 298, 491, 584, 606, 869; **VII**, 334; **VIII**, 155, 173. Also see OS **V**, 1080, 1096.

10-14 Reaction of Epoxides With Alcohols or Thiols



This reaction can use an acid (including a Lewis acid[717]), a base, or an alumina[718] catalyst, and may occur by either an S_N1 or S_N2 mechanism. Catalysts such as graphite oxide,[719] amine-terephthaldehyde resin *p*-toluenesulfonate,[720] $Cu(BF_4)_2{\bullet}nH_2O$,[721] $Al(OTf)_3$,[722] or

[710] Pratt, E.F.; Draper, J.D. *J. Am. Chem. Soc.* ***1949***, *71*, 2846. See Salehi, P.; Irandoost, M.; Seddighi, B.; Behbahani, F.K.; Tahmasebi, D.P. *Synth. Commun.* ***2000***, *30*, 1743.

[711] Zoltewicz, J.A.; Sale, A.A. *J. Org. Chem.* ***1970***, *35*, 3462.

[712] Itoh, A.; Hirose, Y.; Kashiwagi, H.; Masaki, Y. *Heterocycles* ***1994***, *38*, 2165.

[713] See Salomaa, P.; Kankaanperä, A.; Pihlaja, K. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 458–463; DeWolfe, R.H. *Carboxylic Ortho Acid Derivatives*, Academic Press, NY, ***1970***, pp. 18–29, 146–148.

[714] Jnaneshwara, G.K.; Barahate, N.B.; Sudalai, A.; Deshpande, V.H.; Wakharkar, R.D.; Gajare, A.S.; Shingare, M.S.; Sukumar, R. *J. Chem. Soc., Perkin Trans. 1* ***1998***, 965.

[715] Gareev, G.A. *J. Org. Chem. USSR* ***1982***, *18*, 36.

[716] Magano, J.; Chen, M.H.; Clark, J.D.; Nussbaumer, T. *J. Org. Chem.* ***2006***, *71*, 7103.

[717] Iranpoor, N.; Tarrian, T.; Movahedi, Z. *Synthesis* ***1996***, 1473. Also see, Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Synlett*, ***1992***, 673.

[718] See Posner, G.H.; Rogers, D.Z. *J. Am. Chem. Soc.* ***1977***, *99*, 8208, 8214.

[719] Aghayan, M.M.; Alizadeh, M.; Tavana, M.M.; Boukherroub, R. *Tetrahedron Lett.* ***2014***, *55*, 6694.

[720] Tanemura, K.; Suzuki, T. *Synth. Commun.* ***2016***, *46*, 1781.

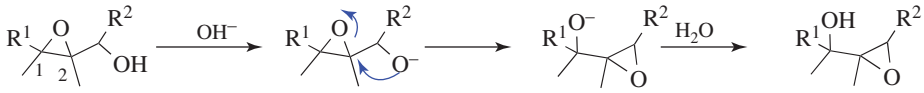
[721] Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J.M. *Org. Lett.* ***2002***, *4*, 2817. See Capes, A.S.; Crossman, A.T.; Webster, L.A.; Ferguson, M.A.J.; Gilbert, I.H. *Tetrahedron Lett.* ***2011***, *52*, 7091.

[722] Williams, D.B.G.; Lawton, M. *Org. Biomol. Chem.* ***2005***, *3*, 3269.

$Fe(Cp)_2BF_4$[723] have been used. β-Cyclodextrin has been used to promote the reaction with phenoxides in aqueous media.[724] Many of the β-hydroxy ethers produced in this way are valuable solvents, for example, diethylene glycol, and Cellosolve (2-ethoxyethanol). Reaction with thiols leads to hydroxy thioethers.[725]

Opening an epoxide by an alkoxide moiety can be done intramolecularly, and a new cyclic ether is generated. Ethers of various ring sizes can be produced, depending upon the length of the tether between the alkoxide unit and the epoxide. A specialized version has the alkoxide moiety on the carbon adjacent to the epoxide, leading to the *Payne rearrangement* where a 2,3-epoxy alcohol is converted to an isomeric one by treatment with aqueous base:[726]

Payne rearrangement



The reaction results in inverted configuration at C-2. Of course, the product can also revert to the starting material by the same pathway, so a mixture of epoxy alcohols is generally obtained.

The Pd-catalyzed alkoxycarbonylative 1,5-substitution of conjugated enyne oxiranes, catalyzed by a Pd complex, gives (*E*)-configured 7-hydroxy-2,3,5-trienoates.[727] Phenols open allylic epoxides in the presence of C2-symmetric Pd catalysts.[728] The asymmetric nucleophilic ring-opening reaction of *meso* epoxides, catalyzed the presence of a BINOL-based phosphoric acid derivative, has been descried.[729] In the presence of a catalytic amount of TBAF, ketene silyl acetals react with epoxides and subsequent ring closure gives a lactone.[730] Boronic acid-derived catalysts lead to acyl and sulfonyl chloride ring opening of 2,3-epoxy alcohols to give *O*-acylated or *O*-sulfonylated chlorohydrin diols.[731] Aryl, heteroaryl, and vinyl esters react regioselectively with epoxides, in the presence of $Mn_2(CO)_{10}$, and BPh_3 catalysts, to give the corresponding alcohol that closes to give the lactone, an isobenzylfuranone in the case of aryl derivatives.[732] Cyclic carbonates are formed by the reaction of epoxides with CO_2, catalyzed by $InBr_3$–PPh_3, solvent-free and at ambient temperature.[733] Epoxides react with *S*-alkylisothiouronium salts in urea–choline chloride as a deep eutectic solvent to prepare β-hydroxy sulfides in an odorless reaction.[734] Treatment of 2,3-epoxy esters and alcohols with 30% BF_3•OEt_2 gives the corresponding 4-alkoxy-3-hydroxy ester.[735]

[723] Yadav, G.D.; Singh, S. *Tetrahedron Lett.* ***2014***, *55*, 3979.
[724] Surendra, K.; Krishnaveni, N.; Nageswar, Y.V.D.; Rao, K.R. *J. Org. Chem.* ***2003***, *68*, 4994.
[725] Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *J. Org. Chem.* ***2003***, *68*, 8248; Amantini, D.; Friguelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *Synlett* ***2003***, 2292.
[726] Behrens, C.H.; Ko, S.Y.; Sharpless, K.B.; Walker, F.J. *J. Org. Chem.* ***1985***, *50*, 5687. See Yamazaki, T.; Ichige, T.; Kitazume, T. *Org. Lett.* ***2004***, *6*, 4073.
[727] Kuş, M.; Artok, L.; Aygün, M. *J. Org. Chem.* ***2015***, *80*, 5494.
[728] Vaccarello, D.N.; Moschitto, M.J.; Lewis, C.A. *J. Org. Chem.* ***2015***, *80*, 6262.
[729] Wang, Z.; Law, W.K.; Sun, J. *Org. Lett.* ***2013***, *15*, 5964.
[730] Bonollo, S.; Ahmady, A.Z.; Petrucci, C.; Marrocchi, A.; Pizzo, F.; Vaccaro, L. *Org. Lett.* ***2014***, *16*, 5721.
[731] Tanveer, K.; Jarrah, K.; Taylor, M.S. *Org. Lett.* ***2015***, *17*, 3482.
[732] Sueki, S.; Wang, Z.; Kuninobu, Y. *Org. Lett.* ***2016***, *18*, 304.
[733] Shibata, I.; Mitani, I.; Imakuni, A.; Baba, A. *Tetrahedron Lett.* ***2011***, *52*, 721.
[734] Azizi, N.; Yadollahy, Z.; Rahimzadeh-oskooee, A. *Synlett* ***2014***, *25*, 1085.
[735] Izquierdo, J.; Rodríguez, S.; González, F.V. *Org. Lett.* ***2011***, *13*, 3856.

The reaction of alcohols with aziridines leads to β-amino ethers,[736] and reaction with thiols gives β-amino thioethers.[737] Aziridines also react with aromatic and aliphatic thiols in liquid sulfur dioxide, which serves as both a Lewis acid as well as a solvent.[738] It has been shown that ring opening of aziridines by phenols is promoted by tributylphosphine.[739] Metal catalysts such as $Cu(OTf)_2$ mediate the ring opening of *N*-tosylaziridines by alcohols.[740] In addition, *N*-tosyl aziridines are opened by acetic acid in the presence of $In(OTf)_3$ to give *N*-tosylamino acetates.[741] In the presence of Amberlyst 15, *N*-Boc aziridines (Boc = *tert*-butoxycarbonyl, $-CO_2t$-Bu) react with LiBr to give the corresponding bromo amide.[742] Catalytic enantioselective ring opening of *N*-acyl aziridines with TMSCN and a Gd catalyst leads to amino nitriles.[743] *aza-Payne rearrangements* are known, based on reactions of aziridines rather than epoxides (see above).[744]

10-15 Alkylation With Onium Salts

$$R_3O^+ + R'OH \longrightarrow ROR' + R_2O$$

Oxonium ions are excellent alkylating agents, and ethers can be conveniently prepared by treating them with alcohols or phenols.[745] Quaternary ammonium salts can sometimes also be used.[746]

OS **VIII**, 536.

10-16 Hydroxylation via Silanes

$$R{-}SiR^1{}_2Ar \xrightarrow{F^-} R{-}SiR^{1\prime}{}_2F \xrightarrow{\text{Oxidation}} R{-}OH$$

$$R{-}SiR^1{}_2SiR^2{}_3 \xrightarrow{F^-} R{-}SiR^1{}_2F \xrightarrow{\text{Oxidation}} R{-}OH$$

Alkylsilanes can be oxidized, with the silyl unit converted to a hydroxy unit. This usually requires either an aryl group[747] or another silyl group[748] attached to silicon. It has been shown that a strained four-membered ring silane (a siletane) also gives the corresponding alcohol upon oxidation.[749] Treatment with a fluorinating agent such as tetrabutylammonium fluoride or CsF replaces Ar or SiR_3 with F, which is oxidized with hydrogen peroxide

[736] See Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, ***1969***, pp. 224–227, 256–257.
[737] Wu, J.; Hou, X.-L.; Dai, L.-X. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1314.
[738] Lugiņina, J.; Turks, M. *Synlett* ***2017***, *28*, 939.
[739] Hou, X.-L.; Fan, R.-H.; Dai, L.-X. *J. Org. Chem.* ***2002***, *67*, 5295.
[740] Ghorai, M.K.; Das, K.; Shukla, D. *J. Org. Chem.* ***2007***, *72*, 5859.
[741] Yadav, J.S.; Reddy, B.V.S.; Sadashiv, K.; Harikishan, K. *Tetrahedron Lett.* ***2002***, *43*, 2099.
[742] Righi, G.; Potini, C.; Bovicelli, P. *Tetrahedron Lett.* ***2002***, *43*, 5867.
[743] Mita, T.; Fujimori, I.; Wada, R.; Wen, J.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2005***, *127*, 11252.
[744] Xichun, F.; Guofu, Q.; Shucai, L.; Hanbing, T.; Lamei, W.; Xianming, H. *Tetrahedron: Asymmetry* ***2006***, *17*, 1394.
[745] Granik, V.G.; Pyatin, B.M.; Glushkov, R.G. *Russ. Chem. Rev.* ***1971***, *40*, 747 (see p. 749).
[746] See Vogel, D.E.; Büchi, G.H. *Org. Synth.* ***66***, 29. With pyridinium salts, see Poon, K.W.C.; Dudley, G.B. *J. Org. Chem.* ***2006***, *71*, 3923. See also Saitoh, T.; Ichikawa, J. *J. Am. Chem. Soc.* ***2005***, *127*, 9696.
[747] Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshia, J.; Kumada, M. *Tetrahedron* ***1983***, *39*, 983; Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* ***1984***, 29. For the protodesilylation step see Häbich, D.; Effenberger, F. *Synthesis* ***1979***, 841.
[748] Suginome, M.; Matsunaga, S.; Ito, Y. *Synlett*, ***1995***, 941.
[749] Sunderhaus, J.D.; Lam, H.; Dudley, G.B. *Org. Lett.* ***2003***, *5*, 4571.

or a peroxyacid to give the alcohol. This sequence is often called the *Tamao-Fleming oxidation*.[747] There are several variations in substrate that allow versatility in the initial incorporation of the silyl unit.[750] Hydroperoxide oxidation of a cyclic silane leads to a diol.[751]

C. Attack by OCOR at an Alkyl Carbon

10-17 Alkylation of Carboxylic Acid Salts

$$RX + R'COO^- \xrightarrow{HMPA} R'COOR$$

Sodium salts of carboxylic acids, including hindered acids such as mesitoic, rapidly react with primary and secondary bromides and iodides at room temperature in dipolar aprotic solvents, especially HMPA, to give high yields of carboxylic esters.[752] The mechanism is S_N2. Several bases or basic media have been used to generate the carboxylate salt.[753] Sodium salts are often used, but K, Ag, Cs,[754] and substituted ammonium salts have also been used. An important variation uses phase-transfer catalysis,[755] and good yields of esters have been obtained from primary, secondary, benzylic, allylic, and phenacyl halides.[756] Without phase-transfer catalysts and in protic solvents, the reaction is useful only for fairly active R, such as benzylic and allylic (S_N1 mechanism), but not for tertiary alkyl, since elimination occurs instead.[757] Addition of the dry carboxylate salt and the halide to alumina as a solid support, and microwave irradiation gives the ester in a procedure that is applicable to long-chain primary halides.[758] A similar reaction of hexanoic acid and benzyl bromide on solid benzyltributylammonium chloride gave the ester with microwave irradiation.[759] Ionic liquid solvents have been shown to facilitate this alkylation reaction.[760]

The reaction of an alcohol and a carboxylate anion with diethyl azodicarboxylate (EtOOCN=NCOOEt) and Ph_3P[761] is called the *Mitsunobu reaction*.[762] Other azocarboxylates may be used in this reaction, including diisopropyl azodicarboxylate

[750] See Matsumoto, Y.; Hayashi, T.; Ito, Y. *Tetrahedron* ***1994***, *50*, 335; Uozumi, Y.; Kitayama, K.; Hayashi, T.; Yanagi, K.; Fukuyo, E. *Bull. Chem. Soc. Jpn.* ***1995***, *68*, 713.

[751] Liu, D.; Kozmin, S.A. *Angew. Chem. Int. Ed.* ***2001***, *40*, 4757.

[752] Pfeffer, P.E.; Silbert, L.S. *J. Org. Chem.* ***1976***, *41*, 1373.

[753] Bases include DBU (see **17-13**): See Mal, D. *Synth. Commun.* ***1986***, *16*, 331. Cs2CO3: Lee, J.C.; Oh, Y.S.; Cho, S.H.; Lee, J.I. *Org. Prep. Proceed. Int.* ***1996***, *28*, 480. CsF-Celite: Lee, J.C.; Choi, Y. *Synth. Commun.* ***1998***, *28*, 2021.

[754] See Dijkstra, G.; Kruizinga, W.H.; Kellogg, R.M. *J. Org. Chem.* ***1987***, *52*, 4230.

[755] See Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, **1978**, pp. 140–155; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, **1977**, pp. 85–95.

[756] See Clark, J.H.; Miller, J.M. *Tetrahedron Lett.* ***1977***, 599.

[757] See, however, Moore, G.G.; Foglia, T.A.; McGahan, T.J. *J. Org. Chem.* ***1979***, *44*, 2425.

[758] Bram, G.; Loupy, A.; Majdoub, M.; Gutierrez, E.; Ruiz-Hitzky, E. *Tetrahedron* ***1990***, *46*, 5167; Dakka, J.; Sasson, Y.; Khawaled, K.; Bram, G.; Loupy, A. *J. Chem. Soc., Chem. Commun.* ***1991***, 853.

[759] Yuncheng, Y.; Yulin, J.; Dabin, G. *Synth. Commun.* ***1992***, *22*, 3109.

[760] Liu, Z.; Chen, Z.-C.; Zheng, Q.-G. *Synthesis* ***2004***, 33.

[761] Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2380; Camp, D.; Jenkins, I.D. *Aust. J. Chem.* ***1988***, *41*, 1835.

[762] But, T.Y.S.; Toy, P.H. *Chem. Asian J.* ***2007***, *2*, 1340. See Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* ***2002***, *67*, 1751 and references cited therein. See also, Dembinski, R. *Eur. J. Org. Chem.* ***2004***, 2763; Dandapani, S.; Curran, D.P. *Chem. Eur. J.* ***2004***, *10*, 3131; Proctor, A.J.; Beautement, K.; Clough, J.M.; Knight, D.W.; Li, Y. *Tetrahedron Lett.* ***2006***, *47*, 5151.

(DIAD) and di-2-methoxyethyl azodicarboxylate (DMEAD).[763] Other Mitsunobu catalysts are available,[764] including organocatalysts,[765] and polymer-supported reagents have been used.[766] Azadicarbonyl dimorpholide is an effective and water-soluble Mitsunobu reagent.[767] A renewable phosphine ligand has been developed.[768] A redox-free protocol for the Mitsunobu reaction has been developed "using triphenylphosphine oxide, the unwanted by-product in the conventional Mitsunobu reaction, as the precursor to the active P(V) coupling reagent."[769] Photocatalytic reactions have been reported, mediated by flavin and visible light.[770] The rate of the Mitsunobu reaction is faster in nonpolar solvents when ethanol or isopropanol are used with benzoic acid.[771] Note that other functional groups can be generated from alcohols using Mitsunobu conditions. Mitsunobu cyclodehydration of 1,2-diols leads to epoxides.[772] Copper(I) carboxylates give esters with primary (including neopentyl without rearrangement), secondary, and tertiary alkyl, allylic, and vinylic halides.[773] A simple S_N2 mechanism is obviously precluded in this case. Vinylic halides can be converted to vinylic acetates by treatment with sodium acetate if palladium(II) chloride is present.[774]

There are several reports of catalytic Mitsunobu reactions, beginning with the report of Toy and co-workers.[775] Buonomo and Aldrich have proposed a "fully catalytic" Mitsunobu reaction that uses a phosphine–azo reagent that is recyclable by aerobic oxidation.[776] Another investigation showed that "the same result is obtained if the hydrazine catalyst is omitted, indicating that this is not a Mitsunobu reaction."[777] A recyclable Mitsunobu reagent has been reported using an Fe catalyst in the presence of atmospheric oxygen.[778] The Mitsunobu reaction has been carried out using both continuous flow conditions (Sec. 7.D) or microwave conditions.[779] Protected hydrazines ($TsNHNHCOR^3$) undergo Mitsunobu reactions with alcohols to give mono adducts $Ts(R^1R^2CH)NNHCOR^3$.[780]

Lactones can be prepared from halo acids by treatment with base (see **16-62**). This has most often been accomplished with γ- and δ-lactones, but macrocyclic lactones (e.g., 11–17 members) have also been prepared in this way.[781] An interesting variation treated

[763] Sugimura, T.; Hagiya, K. *Chem. Lett.* ***2007***, *36*, *566*.
[764] See Tsunoda, T.; Yamamiya, Y.; Kawamura, Y.; Itô, S. *Tetrahedron Lett.* ***1995***, *36*, 2529; Tsunoda, T.; Nagaku, M.; Nagino, C.; Kawamura, Y.; Ozaki, F.; Hioki, H.; Itô, S. *Tetrahedron Lett.* ***1995***, *36*, 2531. For fluorous reactions and reagents see Dandapani, S.; Curran, D.P. *Tetrahedron* ***2002***, *58*, 3855.
[765] But, T.Y.S.; Toy, P.H. *J. Am. Chem. Soc.* ***2006***, *128*, 9636.
[766] Harned, A.M.; He, H.S.; Toy, P.H.; Flynn, D.L.; Hanson, P.R. *J. Am. Chem. Soc.* ***2005***, *127*, 52.
[767] Lanning, M.E.; Fletcher, S. *Tetrahedron Lett.* ***2013***, *54*, 4624.
[768] Yoakim, C.; Guse, I.; O'Meara, J.A.; Thavonokham, B. *Synlett* ***2003***, 473.
[769] Tang, X.; Chapman, C.; Whiting, M.; Denton, R. *Chem. Commun.* ***2014***, *50*, 7340.
[770] März, M.; Chudoba, J.; Kohout, M.; Cibulka, R. *Org. Biomol. Chem.* ***2017***, *15*, 1970.
[771] Camp, D.; Harvey, P.J.; Jenkins, I.D. *Tetrahedron* ***2015***, *71*, 3932.
[772] García-Delgado, N.; Riera, A.; Verdaguer, X. *Org. Lett.* ***2007***, *9*, 635.
[773] Klumpp, G.W.; Bos, H.; Schakel, M.; Schmitz, R.F.; Vrielink, J.J. *Tetrahedron Lett.* ***1975***, 3429.
[774] Yamaji, M.; Fujiwara, Y.; Asano, R.; Teranishi, S. *Bull. Chem. Soc. Jpn.* ***1973***, *46*, 90.
[775] But, T.Y.B.; Toy, P.H. *J. Am. Chem. Soc.* ***2006***, *128*, 9636; But, T.Y.S.; Lu, J.; Toy, P.H. *Synlett* ***2010***, 1115.
[776] Buonomo, J. A.; Aldrich, C.C. *Angew. Chem. Int. Ed.* ***2015***, *54*, 13041.
[777] Hirose, D.; Gazvoda, M.; Košmrlj, J.; Taniguchi, T. *Org. Lett.* ***2016***, *18*, 4036.
[778] Hirose, D.; Taniguchi, T.; Ishibashi, H. *Angew. Chem. Int. Ed.* ***2013***, *52*, 4613.
[779] Manvar, A.; Shah, A. *Org. Biomol. Chem.* ***2014***, *12*, 8112.
[780] Dunford, D.G.; Chaudhry, F.; Kariuki, B.; Knight, D.W.; Wheeler, R.C. *Tetrahedron Lett.* ***2012***, *53*, 7006.
[781] See Galli, C.; Mandolini, L. *Org. Synth.* ***VI***, 698; Kimura, Y.; Regen, S.L. *J. Org. Chem.* ***1983***, *48*, 1533.

2-ethylbenzoic acid with hypervalent iodine and then $I_2/h\nu$ to give the five-membered ring lactone.[782]

A carboxylic acid (not the salt) can be the nucleophile if F^- is present.[783] Mesylates are readily displaced, for example, by benzoic acid/CsF.[784] Dihalides have been converted to diesters by this method.[783] Dialkyl carbonates can be prepared without phosgene (see **16-60**) by phase-transfer catalyzed treatment of primary alkyl halides with dry $KHCO_3$ and K_2CO_3.[785]

Other leaving groups can also be replaced by OCOR. Alkyl chlorosulfites (ROSOCl) and other derivatives of sulfuric, sulfonic, and other inorganic acids can be treated with carboxylate ions to give the corresponding esters. Treatment with oxalyl chloride allows displacement by carboxylate salts.[786] The use of dimethyl sulfate[787] or trimethyl phosphate[788] allows sterically hindered COOH groups to be methylated. The reaction of benzoic acid with aqueous LiOH and then dimethyl sulfate gave methyl benzoate.[789] Dimethyl carbonate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, see **17-11**) has been used to prepare methyl esters.[790] With certain substrates, carboxylic acids are strong enough nucleophiles for the reaction. Examples of such substrates are trialkyl phosphites $P(OR)_3$[791] and acetals of DMF, $(RO)_2CHNMe_2$.[792] This reaction is an S_N2 process, since inversion is found at R. Another good leaving group is NTs_2 and ditosylamines react quite well with acetate ion in dipolar aprotic solvents:[793]

$$RNTs_2 + OAc^- \rightarrow ROAc$$

Ordinary primary amines have been converted to acetates and benzoates by the *Katritzky pyrylium–pyridinium method* (Sec. 10.G.iii).[794]

In a variation of this reaction, alkyl halides can be converted to carbamates by treatment with a secondary amine and K_2CO_3 under phase-transfer conditions.[795] The reaction of alcohols and alkyl halides can lead to carbonates.[796]

OS **II**, 5; **III**, 650; **IV**, 582; **V**, 580; **VI**, 273, 576, 698.

[782] Togo, H.; Muraki, T.; Yokoyama, M. *Tetrahedron Lett.* ***1995***, *36*, 7089.
[783] Ooi, T.; Sugimoto, H.; Doda, K.; Maruoka, K. *Tetrahedron Lett.* ***2001***, *42*, 9245.
[784] Sato, T.; Otera, J. *Synlett*, ***1995***, 336.
[785] Verdecchia, M.; Frochi, M.; Palombi, L.; Rossi, L. *J. Org. Chem.* ***2002***, *67*, 8287.
[786] Barrett, A.G.M.; Braddock, D.C.; James, R.A.; Koike, N.; Procopiou, P.A. *J. Org. Chem.* ***1998***, *63*, 6273.
[787] Grundy, J.; James, B.G.; Pattenden, G. *Tetrahedron Lett.* ***1972***, 757.
[788] Harris, M.M.; Patel, P.K. *Chem. Ind. (London)* ***1973***, 1002.
[789] Chakraborti, A.K.; Basak, A.; Grover, V. *J. Org. Chem.* ***1999***, *64*, 8014. See also, Avila-Zárraga, J.G.; Martínez, R. *Synth. Commun.* ***2001***, *31*, 2177.
[790] Shieh, W.-C.; Dell, S.; Repič, O. *Tetrahedron Lett.* ***2002***, *43*, 5607.
[791] Szmuszkovicz, *J. Org. Prep. Proceed. Int.* ***1972***, *4*, 51.
[792] Vorbrüggen, H. *Angew. Chem. Int. Ed.* ***1963***, *2*, 211; Brechbühler, H.; Büchi, H.; Hatz, E.; Schreiber, J.; Eschenmoser, A. *Angew. Chem. Int. Ed.* ***1963***, *2*, 212.
[793] Curtis, V.A.; Schwartz, H.S.; Hartman, A.F.; Pick, R.M.; Kolar, L.W.; Baumgarten, R.J. *Tetrahedron Lett.* ***1977***, 1969.
[794] See Katritzky, A.R.; Gruntz, U.; Kenny, D.H.; Rezende, M.C.; Sheikh, H. *J. Chem. Soc., Perkin Trans. 1* ***1979***, 430. Schreiber, J.; Eschenmoser, A. *Angew. Chem. Int. Ed.* ***1963***, *2*, 212.
[795] Gómez-Parra, V.; Sánchez, F.; Torres, T. *J. Chem. Soc., Perkin Trans. 2* ***1987***, 695.
[796] Dueno, E.E.; Chu, F.; Kim, S.-I.; Jung, K.W. *Tetrahedron Lett.* ***1999***, *40*, 1843. Also see Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M. *J. Am. Chem. Soc.* ***2003***, *125*, 4874.

10-18 Cleavage of Ethers

$$R—O—R' + Ac_2O \xrightarrow{FeCl_3} ROAc + R'OAc$$

Dialkyl ethers can be cleaved by treatment with anhydrous ferric chloride in acetic anhydride,[797] or with Me_3SiOTf in acetic anhydride.[798] In this reaction both R groups are converted to acetates and yields are moderate to high. Ethers can also be cleaved by the mixed anhydride acetyl tosylate:[799]

Epoxides give β-hydroxyalkyl carboxylates when treated with a carboxylic acid or a carboxylate ion and a suitable catalyst.[800] Tetrahydrofuran was opened to give *O*-acyl-4-iodobutan-1-ol by treatment with acid chlorides and Sm halides[801] or BCl_3.[802]

OS **VIII**, 13.

10-19 Esterification of Carboxylic Acids With Diazo Compounds

$$R_2CN_2 + R'COOH \longrightarrow R'COOCHR_2$$

Carboxylic acids can be converted to esters with diazo compounds in a reaction essentially the same as **10-11**. In contrast to alcohols, carboxylic acids undergo the reaction quite well at room temperature, since the reactivity of the reagent increases with acidity. The reaction is used where high yields are important or where the acid is sensitive to higher temperatures. Because of availability, diazomethane (CH_2N_2)[693] is commonly used to prepare methyl esters, and diazo ketones are common. The mechanism is as shown in **10-11**.

OS **V**, 797.

D. Other Oxygen Nucleophiles

10-20 Formation of Oxonium Salts

$$RX + R_2O \longrightarrow R_3\overset{+}{O}{}^{-}BF_4 + AgX$$

$$RX + R_2'CO \longrightarrow R_2'C{=}\overset{+}{O}{—}R\ BF_4^- + AgX$$

Alkyl halides can be alkylated by ethers or ketones to give oxonium salts, if a very weak, negatively charged nucleophile is present to serve as a counterion and a Lewis acid is present to combine with X^-.[803] A typical procedure consists of treating the halide with the ether

[797] Ganem, B.; Small Jr., V.M. *J. Org. Chem.* ***1974***, *39*, 3728.
[798] Procopiou, P.A.; Baugh, S.P.D.; Flack, S.S.; Inglis, G.G.A. *Chem. Commun.* ***1996***, 2625.
[799] Karger, M.H.; Mazur, Y. *J. Am. Chem. Soc.* ***1968***, *90*, 3878. See also, Coffi-Nketsia, S.; Kergomard, A.; Tautou, H. *Bull. Soc. Chim. Fr.* ***1967***, 2788.
[800] Otera, J.; Matsuzaki, S. *Synthesis* ***1986***, 1019; Deardorff, D.R.; Myles, D.C. *Org. Synth.* ***67***, 114.
[801] Kwon, D.W.; Kim, Y.H.; Lee, K. *J. Org. Chem.* ***2002***, *67*, 9488.
[802] Malladi, R.R.; Kabalka, G.W. *Synth. Commun.* ***2002***, *32*, 1997.
[803] Meerwein, H.; Hederich, V.; Wunderlich, K. *Arch. Pharm.* ***1958***, *291/63*, 541. See Perst, H. *Oxonium Ions in Organic Chemistry*, Verlag Chemie, Deerfield Beach, FL, ***1971***, pp. 22–39.

or the ketone in the presence of $AgBF_4$ or $AgSbF_6$. The Ag^+ serves to remove X^- and the BF_4^- or SbF_6^- acts as the counterion. Another method involves treatment of the halide with a complex formed between the oxygen compound and a Lewis acid, for example:

$$R_2O \bullet BF_3 + RX \rightarrow R_3O^+BF_4^-$$

although this method is most satisfactory when the oxygen and halogen atoms are in the same molecule so that a cyclic oxonium ion is obtained. Ethers and oxonium ions also undergo exchange reactions.

In the presence of Mn powder, BF_3•OEt_2, and LiCl, *N*-acyl-*N*,*O*-acetals and α-amino acid methyl esters were prepared under 1 atm of CO_2.[804]

OS **V**, 1080, 1096, 1099; **VI**, 1019.

10-21 Preparation of Peroxides and Hydroperoxides

$$RX + {}^-OOH \longrightarrow ROOH$$

Hydroperoxides can be prepared from alkyl halides, esters of sulfuric or sulfonic acids, or alcohols by treatment with hydrogen peroxide in basic solution, where it is actually HOO^-.[805] Sodium peroxide is similarly used to prepare dialkyl peroxides:

$$2RX + Na_2O_2 \rightarrow ROOR$$

Another method, which gives primary, secondary, or tertiary hydroperoxides and peroxides, involves treatment of the halide with H_2O_2 or a peroxide in the presence of silver trifluoroacetate.[806] Peroxides can also be prepared[807] by treatment of alkyl bromides or tosylates with potassium superoxide (KO_2) in the presence of crown ethers (alcohols may be side products).[808]

Diacyl peroxides and acyl hydroperoxides can be prepared[809] from acyl halides or anhydrides. Diacyl peroxides can also be prepared by the treatment of carboxylic acids with H_2O_2 in the presence of DCC,[810] H_2SO_4, methanesulfonic acid, or other dehydrating agents. Mixed alkyl–acyl peroxides (peresters) can be made from acyl halides and hydroperoxides. Bismuth triflate catalyzes the synthesis of 1,1-dihydroperoxides and 1,2,4,5-tetraoxanes.[811] Oxiranes reacted with ethereal $SnCl_4$–H_2O_2 to give the corresponding β-hydroxy hydroperoxides.[812]

OS **III**, 619, 649; **V**, 805, 904; **VI**, 276.

[804] Mita, T.; Chen, J.; Sato, Y. *Org. Lett.* ***2014***, *16*, 2200.
[805] See Hiatt, R. in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1971***, pp. 1–151; Pandiarajan, K. in Pizey, J.S. *Synthetic Reagents*, Vol. 6, Wiley, NY, ***1985***, pp. 60–155.
[806] Cookson, P.G.; Davies, A.G.; Roberts, B.P. *J. Chem. Soc., Chem. Commun.* ***1976***, 1022. Also see Bourgeois, M.; Montaudon, E.; Maillard, B. *Synthesis* ***1989***, 700.
[807] Johnson, R.A.; Nidy, E.G.; Merritt, M.V. *J. Am. Chem. Soc.* ***1978***, *100*, 7960.
[808] See San Filippo Jr., J.; Chern, C.; Valentine, J.S. *J. Org. Chem.* ***1975***, *40*, 1678; Corey, E.J.; Nicolaou, K.C.; Shibasaki, M.; Machida, Y.; Shiner, C.S. *Tetrahedron Lett.* ***1975***, 3183.
[809] See Bouillon, G.; Lick, C.; Schank, K. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 279–309; Hiatt, R.; Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1971***, pp. 799–929.
[810] Greene, F.D.; Kazan, J. *J. Org. Chem.* ***1963***, *28*, 2168.
[811] Sashidhara, K.V.; Avula, S.R.; Singh, L.R.; Palnati, G.R. *Tetrahedron Lett.* ***2012***, *53*, 4880.
[812] Yan, X.; Qiao, C.; Guo, Z. *Synlett* ***2013***, *24*, 502.

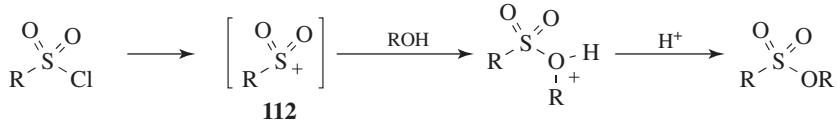
10-22 Preparation of Inorganic Esters

$$\mathrm{ROH + HONO \xrightarrow{H^+} RONO} \qquad \mathrm{ROH + POCl_3 \longrightarrow PO(OR)_3}$$

$$\mathrm{ROH + HONO_2 \xrightarrow{H^+} RONO_2} \qquad \mathrm{ROH + SO_3 \longrightarrow ROSO_2OH}$$

$$\mathrm{ROH + SOCl_2 \longrightarrow ROSOOR} \qquad \mathrm{ROH + (CF_3SO_2)_2O \longrightarrow ROSO_2CF_3}$$

The transformations shown are a few of the many inorganic esters that can be prepared by the reaction of an alcohol with an inorganic acid or, better, its acid halide or anhydride.[813] These similar reactions are grouped together for convenience, but not all involve nucleophilic substitutions at R. The other possible pathway is nucleophilic substitution at the inorganic central atom, such as the attack of the alcohol oxygen at the electrophilic sulfur atom in **112**[814] or a corresponding S_N2-type process (Sec. 16.B.v).



112

In such cases there is no alkyl–*O* cleavage. Mono esters of sulfuric acid (alkylsulfuric acids), which are important industrially because their salts are used as detergents, can be prepared by treating alcohols with SO_3, H_2SO_4, $ClSO_2OH$, or SO_3 complexes.[815] It is possible to prepare a primary sulfonate ester, such as tosylate, in the presence of a secondary alcohol unit when tosic acid reacts with a 1,2-diol in the presence of Fe^{3+} Montmorillonite.[816] Polymer-bound reagents have been used to prepare sulfonate esters.[817] Sulfinic esters are readily prepared from alcohols and sulfinyl chlorides, and in the presence of Cinchona alkaloids the reaction is enantioselective.[818]

Alkyl nitrites[819] can be conveniently prepared by an exchange reaction:

$$\mathrm{ROH + R'ONO \rightarrow RONO + R'OH}$$

where R = *t*-Bu.[820]

Primary amines can be converted to alkyl nitrates ($RNH_2 \rightarrow RONO_2$) by treatment with N_2O_4 at − 78 °C in the presence of an excess of amidine base.[821] Mitsunobu conditions (**10-17**) can be used to prepare phosphate esters or phosphonate esters. The reaction can be done intramolecularly to prepare cyclic phosphonate esters.[822]

[813] See Salomaa, P.; Kankaanperä, A.; Pihlaja, K. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 481–497.
[814] See Aldred, S.E.; Williams, D.L.H.; Garley, M. *J. Chem. Soc., Perkin Trans. 2* ***1982***, 777.
[815] Sandler, S.R.; Karo, W. *Organic Functional Group Preparations*, 2nd ed., vol. 3, Academic Press, NY, ***1989***, pp. 129–151.
[816] Choudary, B.M.; Chowdari, N.S.; Kantam, M.L. *Tetraheron* ***2000***, *56*, 7291.
[817] Vignola, N.; Dahmen, S.; Enders, D.; Bräse, S. *Tetrahedron Lett.* ***2001***, *42*, 7833.
[818] Shibata, N.; Matsunaga, M.; Fukuzumi, T.; Nakamura, S.; Toru, T. *Synlett* ***2005***, 1699.
[819] See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 150–172.
[820] Doyle, M.P.; Terpstra, J.W.; Pickering, R.A.; LePoire, D.M. *J. Org. Chem.* ***1983***, *48*, 3379. See Ref 819.
[821] Barton, D.H.R.; Narang, S.C. *J. Chem. Soc., Perkin Trans. 1* ***1977***, 1114.
[822] Pungente, M.D.; Weiler, L. *Org. Lett.* ***2001***, *3*, 643.

Alkyl halides are often used as substrates instead of alcohols. In such cases, the *salt* of the inorganic acid is usually used and the mechanism is nucleophilic substitution at the carbon atom. An important example is the treatment of alkyl halides with silver nitrate to form alkyl nitrates, which is used as a test for alkyl halides. However, the nitrite ion is an ambident nucleophile that can give nitrites or nitro compounds (see **10-41**).[823] Dialkyl ethers or aryl alkyl ethers can be cleaved with anhydrous sulfonic acids to give a sulfonate ester and an alcohol.[824] For dialkyl ethers, the alcohol is rapidly converted to a symmetrical ether by the sulfonic acid (reaction **10-12**), which in turn is further cleaved to a new sulfonate ester, so that the product is a mixture of two different sulfonate esters. For aryl alkyl ethers, cleavage always takes place to give the phenol, which is not converted to the aryl ether under these conditions. Ethers can also be cleaved in a similar manner by mixed anhydrides of sulfonic and carboxylic acids[825] (prepared as in **16-67**). Phosphinate esters are prepared by transesterification-type reactions (**16-63**) from alcohols and other phosphinates.[826]

OS **II**, 106, 108, 109, 112, 204, 412; **III**, 148, 471; **IV**, 955; **V**, 839; **VIII**, 46, 50, 616. Also see OS **II**, 111.

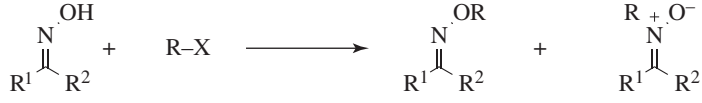
10-23 Alcohols from Amines

$$RNH_2 \longrightarrow ROH$$

A primary amine was reported to react with KOH in diethylene glycol at 210 °C to give an alcohol.[827] The reaction of (*S*)-phenethylamine and the *bis*-sulfonyl chloride of 1,2-benzenesulfonic acid, followed by KNO_2 and 18-crown-6, gave (*R*)-phenethyl alcohol in 70% yield and 40% enantiomeric excess (ee).[828]

Amides have been prepared by the reaction of alcohols and amines, with a Ru–NHC catalyst.[829]

10-24 Alkylation of Oximes[830]



A nitrone

Oximes can be alkylated by alkyl halides or sulfates. *N*-Alkylation is a side reaction, yielding a nitrone.[831] The relative yield of oxime ether and nitrone depends on the nature of the

[823] See Boguslavskaya, L.S.; Chuvatkin, N.N.; Kartashov, A.V. *Russ. Chem. Rev.* ***1988***, *57*, 760.
[824] Klamann, D.; Weyerstahl, P. *Chem. Ber.* ***1965***, *98*, 2070.
[825] Karger, M.H.; Mazur, Y. *J. Org. Chem.* ***1971***, *36*, 532, 540.
[826] Han, L.-B.; Zhao, C.-Q. *J. Org. Chem.* ***2005***, *70*, 10121.
[827] Rahman, S.M.A.; Ohno, H.; Tanaka, T. *Tetrahedron Lett.* ***2001***, *42*, 8007.
[828] Sørbye, K.; Tautermann, C.; Carlsen, P.; Fiksdahl, A. *Tetrahedron: Asymmetry*, ***1998***, *9*, 681.
[829] Chen, C.; Zhang, Y.; Hong, S.H. *J. Org. Chem.* ***2011***, *76*, 10005.
[830] See Abele, E.; Lukevics, E. *Org. Prep. Proceed. Int.* ***2000***, *32*, 235.
[831] See Torssell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH, NY, ***1988***, pp. 75–93; Katritzky, A.R.; Cui, X.; Long, Q.; Yanga, B.; Wilcox, A.L.; Zhang, Y.-K. *Org. Prep. Proceed. Int.* ***2000***, *32*, 175.

reagents, including the configuration of the oxime, and on the reaction conditions.[832] For example, *anti*-benzaldoximes give nitrones, while the *syn* isomers give oxime ethers.[833]

OS **III**, 172; **V**, 1031. Also see OS **V**, 269; **VI**, 199.

10.H.ii. Sulfur Nucleophiles

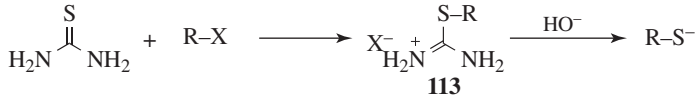
Sulfur compounds[834] are better nucleophiles than their oxygen analogs (Sec. 10.G.ii), so in most cases these reactions take place faster and more smoothly than the corresponding reactions with oxygen nucleophiles. There is evidence that some of these reactions take place by SET mechanisms.[835]

10-25 Attack by SH at an Alkyl Carbon: Formation of Thiols[836]

$$RX + H_2S \longrightarrow RSH_2^+ \longrightarrow RSH + H^+$$
$$RX + HS^- \longrightarrow RSH$$

Sodium sulfhydride (NaSH) is a much better reagent for the formation of thiols (mercaptans) from alkyl halides than H_2S and is used much more often. Bubbling H_2S into an alkaline solution generates NaSH, but hydrosulfide on a supported polymer resin has also been used.[837] The reaction is most useful for primary halides since secondary substrates give much lower yields. The reaction fails completely for tertiary halides because elimination predominates. Sulfuric and sulfonic esters can be used instead of halides. Thioethers (RSR) are often side products.[838] Thiols have also been prepared from alcohols by treatment with H_2S and a catalyst such as Al_2O_3,[839] but this is limited to primary alcohols. Another method involves treatment with *Lawesson's reagent* (see **16-10**).[840]

The conversion can also be accomplished under neutral conditions by treatment of a primary halide with F^- and a tin sulfide such as $Ph_3SnSSnPh_3$.[841] An indirect method for the preparation of a thiol is the reaction of an alkyl halide with thiourea to give an isothiuronium salt (**113**), and subsequent treatment with alkali or a high-molecular-weight amine gives cleavage to the thiol. An indirect method is hydrolysis of *Bunte salts* (see **10-27**).



113

OS **III**, 363, 440; **IV**, 401, 491; **V**, 1046; **VIII**, 592. Also see OS **II**, 345, 411, 573; **IV**, 232; **V**, 223; **VI**, 620.

[832] See Reutov, O.A.; Beletskaya, I.P.; Kurts, A.L. *Ambident Anions*, Plenum, NY, ***1983***, pp. 262–272.
[833] Buehler, E. *J. Org. Chem.* ***1967***, *32*, 261.
[834] See Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, ***1985***; Oae, S. *Organic Chemistry of Sulfur*, Plenum, NY, ***1977***. For selenium compounds, see Krief, A.; Hevesi, L. *Organoselenium Chemistry I*, Springer, NY, ***1988***; Liotta, D. *Organoselenium Chemistry*, Wiley, NY, ***1987***.
[835] See Ashby, E.C.; Park, W.S.; Goel, A.B.; Su, W. *J. Org. Chem.* ***1985***, *50*, 5184.
[836] See Wardell, J.L. in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, ***1974***, pp. 179–211.
[837] Bandgar, B.P.; Sadavarte, V.S.; Uppalla, L.S. *Chem. Lett.* ***2000***, 1304.
[838] See Vasil'tsov, A.M.; Trofimov, B.A.; Amosova, S.V. *J. Org. Chem. USSR* ***1983***, *19*, 1197.
[839] Lucien, J.; Barrault, J.; Guisnet, M.; Maurel, R. *Nouv. J. Chim.* ***1979***, *3*, 15.
[840] Nishio, T. *J. Chem. Soc., Perkin Trans. 1* ***1993***, 1113.
[841] Gingras, M.; Harpp, D.N. *Tetrahedron Lett.* ***1990***, *31*, 1397.

10-26 Attack by S at an Alkyl Carbon: Formation of Thioethers (Sulfides)

$$R\text{–}X + R'\text{–}S^- \longrightarrow R\text{–}S\text{–}R'$$

$$R\text{–}OH + R'\text{–}SH \xrightarrow{\text{Additives}} R\text{–}S\text{–}R'$$

Thioethers (sulfides) can be prepared by treatment of alkyl halides with salts of thiols (thiolate anions).[842] The R′ group may be alkyl or aryl and organolithium bases can be used to deprotonate the thiol.[843] As in **10-25**, RX cannot be a tertiary halide, and sulfuric and sulfonic esters can be used instead of halides. As in the *Williamson reaction* (**10-8**), yields are often improved by phase-transfer catalysis.[844] Leaving groups other than halides can be used, as in the Ru-catalyzed reaction of thiols with propargylic carbonates.[845] Sulfides have been prepared by reaction with allylic carbonates using an iridium catalyst.[846] Vinylic sulfides can be prepared by treating vinylic bromides with PhS^- in the presence of a Ni complex,[847] or in the presence of $Pd(PPh_3)_4$. Alternatively, the Ag salt of an enethiol reacts with iodomethane to give the corresponding methyl vinyl sulfide.[848] A catalytic method for the preparation of sulfides that involves alcohol derivatives, organic halides, and sodium thiosulfate has been developed for aqueous media.[849] A catalyst-free and solvent-free synthesis of allylic thioethers directly from allylic alcohols and thiols under microwave irradiation has been reported.[850]

Symmetrical thioethers (R—S—R) can also be prepared by treatment of an alkyl halide (R—X) with sodium sulfide (Na_2S).[851] Symmetrical thioethers have also been prepared by the reaction of $S(MgBr)_2$ with allylic halides.[852] This reaction can be carried out internally, by treatment of sulfide ions with 1,4-, 1,5-, or 1,6-dihalides, to prepare five-, six-, and seven-membered[853] sulfur-containing heterocyclic rings. Certain larger rings have also been closed in this way.[854]

The sulfides of thioethers are an active area of research. Tertiary alcohols react with thiols in the presence of sulfuric acid to give thioethers, and the reaction works best with tertiary substrates.[855] Iodine catalyzes the allylic alkylation of thiols.[856] Thiophenol reacts with propargylic alcohols in the presence of a Ru catalyst to give propargylic thioether,[857]

[842] See Peach, M.E. in Patai, S. *The Chemistry of the Thiol Groups*, pt. 2, Wiley, NY, ***1974***, pp. 721–735; Ono, N.; Miyake, H.; Saito, T.; Kaji, A. *Synthesis* ***1980***, 952. Ando, W.; Furuhata, T.; Tsumaki, H.; Sekiguchi, A. *Synth. Commun.* ***1982***, *12*, 627.
[843] Yin, J.; Pidgeon, C. *Tetrahedron Lett.* ***1997***, *38*, 5953.
[844] See Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 221–233. Also see Salvatore, R.N.; Smith, R.A.; Nischwitz, A.K.; Gavi, T. *Tetrahedron Lett.* ***2005***, *46*, 8931.
[845] Kondo, T.; Kanda, Y.; Baba, A.; Fukuda, K.; Nakamura, A.; Wada, K.; Morisaki, Y.; Mitsudo, T.-a. *J. Am. Chem. Soc.* ***2002***, *124*, 12960.
[846] Gao, N.; Zheng, S.; Yang, W.; Zhao, X. *Org. Lett.* ***2011***, *13*, 1514.
[847] Cristau, H.J.; Chabaud, B.; Labaudiniere, R.; Christol, H. *J. Org. Chem.* ***1986***, *51*, 875.
[848] Ochiai, M.; Hirobe, M.; Miyamoto, K. *J. Am. Chem. Soc.* ***2006***, *128*, 9046.
[849] Chu, X.-Q.; Xu, X.-P.; Ji, S.-J. *Chem. Eur. J.* ***2016***, *22*, 14181.
[850] Tabarelli, G.; Godoi, M.; Canto, R.F.S.; Mora, J.R.; Nome, F.; Braga, A.L. *Synth. Commun.* ***2014***, *44*, 3441.
[851] For another reagent, see Harpp, D.N.; Gingras, M.; Aida, T.; Chan, T.H. *Synthesis* ***1987***, 1122.
[852] Nedugov, A.N.; Pavlova, N.N. *Zhur. Org. Khim.*, ***1992***, *28*, 1401 (Engl. 1103).
[853] Tan, L.C.; Pagni, R.M.; Kabalka, G.W.; Hillmyer, M.; Woosley, J. *Tetrahedron Lett.* ***1992***, *33*, 7709.
[854] See Singh, A.; Mehrotra, A.; Regen, S.L. *Synth. Commun.* ***1981***, *11*, 409.
[855] See Cain, M.E.; Evans, M.B.; Lee, D.F. *J. Chem. Soc.* ***1962***, 1694.
[856] Zhang, X.; Rao, W.; Chan, P.W.H. *Synlett* ***2008***, 2204.
[857] Inada, Y.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* ***2002***, *124*, 15172.

and the synthesis and applications of thioethers has been reviewed.[858] An alkyne–dicobalt complex, catalyzed by chiral Brønsted acid, has been used for the preparation of propargylic thioethers from propargylic alcohols.[859] A hydroxyl group can be replaced with O, S, or N nucleophiles in the presence of phosphonic acid.[860] The synthesis of α-aryl thioethers has been reported by direct thiolation of ethers with diaryl disulfides, induced by visible light. Continuous flow techniques (Sec. 7-D) have been used for the *O*-alkylation and *S*-alkylation of phenol and thiophenol substrates.[861] Thioethers have been prepared using triethylamine•P_4S_{10}.[862] Thioalkynes are prepared by the reaction of terminal alkynes and thiols in the presence of ethynyl benziodoxolone (EBX) hypervalent iodine reagents.[863]

Enantioenriched allylic thioethers have been synthesized from chiral racemic allylic alcohols in the presence of an Ir–(P,alkene) complex and dibutyl phosphoric acid.[864] The kinetic resolution of allylic acetates by a Ru-catalyzed regioselective allylic etherification has been reported.[865]

Thioethers have been prepared from carboxylates and thiols via a Fe(III)-catalyzed direct displacement of carboxylates by the thiol.[866] Decarboxylation of carboxylic acids in the presence of thiols gave sulfides by the reaction with $InBr_3$ and 1,1,3,3-tetramethyldisiloxane (TMDS).[867] Unsymmetrical dialkyl sulfides were prepared by reaction of carboxylic acids, *t*-butylmercaptan in the presence of InI_3, and TMDS.[868]

The Pd-catalyzed cross coupling of aryl or alkyl halides and $Na_2S_2O_3$•$5H_2O$ gave aromatic thioethers.[869] A photochemical method converted aryl- or heteroarylamines to selenides via diazotization of amines with *tert*-butyl nitrite followed by reaction with diaryl/diheteroaryl/dialkyl diselenides.[870] Unsymmetrical sulfides have been prepared from esters and thiols in the presence of InI_3 using TMDS or $PhSiH_3$ as the reductant.[871]

Diaryl sulfides have been prepared from aryl iodides using potassium thiocyanate as a sulfur-transfer agent.[872] Aryl alkyl sulfides have been prepared using CS_2 and diethylamine in polyethylene glycol (PEG200), using a CuI catalyst.[873] The coupling of terminal alkynes with thiols, in the presence of an MCM-41-supported bidentate nitrogen–Cu complex [MCM-41-2N-CuCl] catalyst and K, gave alkynyl sulfides.[874] 1,3,5-Triazo-2,4,6-triphosphorine-2,2,4,4,6,6-chloride (TAPC) catalyzed the reaction of

[858] Vizer, S.A.; Sycheva, E.S.; Al Quntar, A.A.A.; Kurmankulov, N.B.; Yerzhanov, K.B.; Dembitsky, V.M. *Chem. Rev.* ***2015***, *115*, 1575.
[859] Terada, M.; Ota, Y.; Li, F.; Toda, Y.; Kondoh, A. *J. Am. Chem. Soc.* ***2016***, *138*, 11038.
[860] Bunrit, A.; Dahlstrand, C.; Olsson, S.K.; Srifa, P.; Huang, G.; Orthaber, A.; Sjöberg, P.J.R.; Biswas, S.; Himo, F.; Samec, J.S.M. *J. Am. Chem. Soc.* ***2015***, *137*, 4646.
[861] Reichart, B.; Kappe, C.O.; Glasnov, T.N. *Synlett* ***2013***, *24*, 2393.
[862] Turkoglu, G.; Cinar, M.E.; Ozturk, T. *Synthesis* ***2016***, *48*, 3618.
[863] Frei, R.; Wodrich, M.D.; Hari, D.P.; Borin, P.-A.; Chauvier, C.; Waser, J. *J. Am. Chem. Soc.* ***2014***, *136*, 16563.
[864] Roggen, M.; Carreira, E.M. *Angew. Chem. Int. Ed.* ***2012***, *51*, 8652.
[865] Shinozawa, T.; Terasaki, S.; Mizuno, S.; Kawatsura, M. *J. Org. Chem.* ***2016***, *81*, 5766.
[866] Venkatesham, K.; Rao, C.B.; Dokuburra, C.B.; Bunce, R.A.; Venkateswarlu, Y. *J. Org. Chem.* ***2015***, *80*, 11611.
[867] Sakai, N.; Miyazaki, T.; Sakamoto, T.; Yatsuda, T.; Moriya, T.; Ikeda, R.; Konakahara, T. *Org. Lett.* ***2012***, *14*, 4366.
[868] Sakai, N.; Yoshimoto, S.; Miyazaki, T.; Ogiwara, Y. *Tetrahedron Lett.* ***2016***, *57*, 3117.
[869] Qiao, Z.; Wei, J.; Jiang, X. *Org. Lett.* ***2014***, *16*, 1212.
[870] Kundu, D.; Ahammed, S.; Ranu, B.C. *Org. Lett.* ***2014***, *16*, 1814.
[871] Miyazaki, T.; Kasai, S.; Ogiwara, Y.; Sakai, N. *Eur. J. Org. Chem.* ***2016***, 1043.
[872] Kelly, C.B.; Lee, C.; Leadbeater, N.E. *Tetrahedron Lett.* ***2011***, *52*, 4587.
[873] Firouzabadi, H.; Iranpoor, N.; Samadi, A. *Tetrahedron Lett.* ***2014***, *55*, 1212.
[874] Fang, Z.; He, W.; Cai, M.; Lin, Y.; Zhao, H. *Tetrahedron Lett.* ***2015***, *56*, 6463.

benzylic alcohols with a variety of thiols to give thioethers.[875] The synthesis of alkyl aryl sulfides has been reported by reaction of alkanes with arylsulfonyl hydrazides using di-*tert*-butyl peroxide as an oxidant and $Pd(OAc)_2$ as a catalyst.[876]

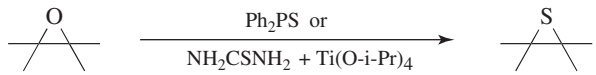
Thiolate ions are also useful for the demethylation of certain ethers,[877] esters, amines, and quaternary ammonium salts. Aryl methyl ethers[878] can be cleaved by heating with EtS^- in the dipolar aprotic solvent DMF:[879]

$$ROAr + EtS^- \rightarrow ArO^- + EtSR$$

Allylic sulfides have been prepared by treating allylic carbonates $ROCO_2Me$ (R = an allylic group) with a thiol and a Pd catalyst.[880] A good method for the demethylation of quaternary ammonium salts consists of refluxing them with PhS^- in butan-2-one to give the amine and methyl phenyl sulfide.[881] A methyl group is cleaved more readily than other simple alkyl groups (such as ethyl), although loss of these groups competes. Benzylic and allylic groups cleave even more easily, and this is a useful procedure for the cleavage of benzylic and allylic groups from quaternary ammonium salts, even if methyl groups are also present.[882]

gem-Dihalides can be converted to dithioacetals $RCH(SR')_2$,[883] and acetals have been converted to dithioacetals.[884] The combination of CS_2 and $NaBH_4$ converted 1,3-dibromopropane to 1,3-dithiane.[885]

Epoxides can also be directly converted to episulfides (thiiranes)[886] by treatment with thiourea and $Ti(O\text{-}i\text{-}Pr)_4$[887] or thiourea and $LiBF_4$ in acetonitrile,[888] with KSCN and $InBr_3$,[889] and with KSCN in ionic liquids (Sec. 9.D.iii).[890]



[875] Bahrami, K.; Khodaei, M.M.; Khodadoustan, N. *Synlett.* ***2011***, *22*, 2206.
[876] Guo, S.; He, W.; Xiang, H.; Yan, Y. *Chem. Commun.* ***2014***, *50*, 8578.
[877] See Evers, M. *Chem. Scr.* ***1986***, *26*, 585.
[878] See Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* ***1980***, *45*, 4275; Evers, M.; Christiaens, L. *Tetrahedron Lett.* ***1983***, *24*, 377; Tiecco, M. *Synthesis* ***1988***, 749.
[879] Feutrill, G.I.; Mirrington, R.N. *Tetrahedron Lett.* ***1970***, 1327, *Aust. J. Chem.* ***1972***, *25*, 1719, 1731.
[880] Goux, C.; Lhoste, P.; Sinou, D. *Tetrahedron* ***1994***, *50*, 10321.
[881] Shamma, M.; Deno, N.C.; Remar, J.F. *Tetrahedron Lett.* ***1966***, 1375. For alternative procedures, see Hutchins, R.O.; Dux, F.J. *J. Org. Chem.* ***1973***, *38*, 1961; Posner, G.H.; Ting, J. *Synth. Commun.* ***1974***, *4*, 355.
[882] Kametani, T.; Kigasawa, T.; Hiiragi, M.; Wagatsuma, N.; Wakisaka, K. *Tetrahedron Lett.* ***1969***, 635.
[883] See, for example, Wähälä, K.; Ojanperä, I.; Häyri, L.; Hase, T.A. *Synth. Commun.* ***1987***, *17*, 137.
[884] Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* ***2001***, *66*, 7527 and references cited therein; Ranu, B.C.; Das, A.; Samanta, S. *Synlett.* ***2002***, 727.
[885] Wan, Y.; Kurchan, A.N.; Barnhurst, L.A.; Kutateladze, A.G. *Org. Lett.* ***2000***, *2*, 1133.
[886] See Fokin, A.V.; Kolomiets, A.F. *Russ. Chem. Rev.* ***1975***, *44*, 138. Key intermediates have been isolated: Kleiner, C.M.; Horst, L.; Würtele, C.; Wende, R.; Schreiner, P.R. *Org. Biomol. Chem.* ***2009***, *7*, 1397. See Das, B.; Reddy, V.S.; Krishnaiah, M. *Tetrahedron Lett.* ***2006***, *47*, 8471.
[887] Gao, Y.; Sharpless, K.B. *J. Org. Chem.* ***1988***, *53*, 4114. Also see Bouda, H.; Borredon, M.E.; Delmas, M.; Gaset, A. *Synth. Commun.* ***1987***, *17*, 943; ***1989***, *19*, 491.
[888] Kazemi, F.; Kiasat, A.R.; Ebrahimi, S. *Synth. Commun.* ***2003***, *33*, 595.
[889] Yadav, J.S.; Reddy, B.V.S.; Baishya, G. *Synlett.* ***2003***, 396.
[890] Yadav, J.S.; Reddy, B.V.S.; Reddy, Ch.S.; Rajasekhar, K. *J. Org. Chem.* ***2003***, *68*, 2525.

Epoxides are converted to thiiranes enantioselectively, which is the basis of a kinetic resolution (Sec. 4.H), in the presence of a thiolactam and the chiral phosphoric acid catalyst, TRIP.[891]

Diaryl selenides have been prepared from aryl boronic acids by reaction with SeO_2 in the presence of potassium carbonate in PEG-400 at 110 °C.[892] Diaryl selenides have also been prepared by the reaction of aryl halides with KSeCN in the presence of nano copper oxide.[893] Aryl–alkyl tellurides have been formed by the reaction of aryl iodides with alkyltellurolates, promoted by CuI.[894]

Selenides (selenoethers) and tellurides can be prepared via RSe^- and RTe^- species,[895] and Se and borohydride exchange resin followed by the halide give the selenoether.[896] The La/I_2-catalyzed reaction of diphenyl diselenide with primary alkyl iodides gave aryl alkyl selenides.[897] An In catalyst has been used with alkyl halides,[898] and a Zn-mediated synthesis of tertiary alkyl selenides is known.[899] Diaryl selenides (Ar—Se—Ar′) have been prepared by coupling aryl iodides with tin reagents ($ArSeSnR_3$) with a Pd catalyst.[900] α-Seleno aldehydes are prepared by the reaction of an aldehyde with PhSe(*N*-phthalimide).[901]

OS **II**, 31, 345, 547, 576; **III**, 332, 751, 763; **IV**, 396, 667, 892, 967; **V**, 562, 780, 1046; **VI**, 5, 31, 268, 364, 403, 482, 556, 601, 683, 704, 737, 833, 859; **VII**, 453; **VIII**, 592. See also OS **VI**, 776.

10-27 Formation of Disulfides[902]

$$2\ RX + S_2^{2-} \longrightarrow RSSR + 2X^-$$

Disulfides[903] can be prepared by treatment of alkyl halides with disulfide ions and also indirectly by the reaction of *Bunte salts* (see **10-25**) with acid solutions of iodide, thiocyanate ion, or thiourea,[904] or by pyrolysis or treatment with hydrogen peroxide. Alkyl halides also give disulfides when heated to reflux with sulfur and NaOH.[905] Some molybdenum compounds convert alkyl halides to disulfides, including $(BnNEt_3)_6Mo_7S_{24}$.[906]

[891] Liao, S.; Leutzsch, M.; Monaco, M.R.; List, B. *J. Am. Chem. Soc.* ***2016***, *138*, 5230.
[892] Kumar, R.U.; Reddy, K.H.V.; Satish, G.; Swapna, K.; Nageswar, Y.V.D. *Tetrahedron Lett.* ***2016***, *57*, 4138.
[893] Reddy, K.H.V.; Reddy, V.P.; Madhav, B.; Shankar, J.; Nageswar, Y.V.D. *Synlett.* ***2011***, *22*, 1268. For a discussion of the nucleophilic reactivity of a copper(I) superoxide complex, see Pirovano, P.; Magherusan, A.M.; McGlynn, C.; Ure, A.; Lynes, A.; McDonald, A.R. *Angew. Chem. Int. Ed.* ***2014***, *53*, 5946.
[894] Silva, M.S.; Comasseto, J.V. *Tetrahedron* ***2011***, *67*, 8763.
[895] Cohen, R.J.; Fox, D.L.; Salvatore, R.N. *J. Org. Chem.* ***2004***, *69*, 4265. Also see Monahan, R.; Brown, D.; Waykole, L.; Liotta, D. in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 207–241.
[896] Yanada, K.; Fujita, T.; Yanada, R. *Synlett* ***1998***, 971.
[897] Nishino, T.; Okada, M.; Kuroki, T.; Watanabe, T.; Nishiyama, Y.; Sonoda, N. *J. Org. Chem.* ***2002***, *67*, 8696. Zinc in aqueous media has also been used: see Bieber, L.W.; de Sá, A.C.P.F.; Menezes, P.H.; Goncalves, S.M.C. *Tetrahedron Lett.* ***2001***, *42*, 4597.
[898] Munbunjong, W.; Lee, E.H.; Chavasiri, W.; Jang, D.O. *Tetrahedron Lett.* ***2005***, *46*, 8769.
[899] Krief, A.; Derock, M.; Lacroix, D. *Synlett* ***2005***, 2832.
[900] Nishiyama, Y.; Tokunaga, K.; Sonoda, N. *Org. Lett.* ***1999***, *1*, 1725.
[901] Wang, J.; Li, H.; Mei, Y.; Lou, B.; Xu, D.; Xie, D.; Guo, H.; Wang, W. *J. Org. Chem.* ***2005***, *70*, 5678.
[902] See Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* ***2003***, *125*, 6624.
[903] For a review, see Musiejuk, M.; Witt, D. *Org. Prep. Proceed. Int.* ***2015***, *47*, 95.
[904] Milligan, B.; Swan, J.M. *J. Chem. Soc.* ***1962***, 2712.
[905] Chorbadjiev, S.; Roumian, C.; Markov, P. *J. Prakt. Chem.* ***1977***, *319*, 1036. For an example using microwave irradiation, see Wang, J.-X.; Gao, L.; Huang, D. *Synth. Commun.* ***2002***, *32*, 963.
[906] See Polshettiwar, V.; Nivsarkar, M.; Acharya, J.; Kaushik, M.P. *Tetrahedron Lett.* ***2003***, *44*, 887.

Unsymmetrical disulfides have been prepared by treatment of alkyl halides with $Na_2S_2Os•5\ H_2O$ in DMSO.[907] The reaction of alcohols and 4,4′-azopyridine and 5,5′-dimethyl-3,3′-azoisooxazole give the corresponding disulfides.[908] Irradiation with visible light led to the oxidative coupling of thiols to the corresponding disulfides in the presence of Rose Bengal dye.[909] Disulfides have been prepared from alkyl halides and sodium sulfide trihydrate and CCl_4 or hexachloroethane in PEG-200.[910] Both disulfides and diselenides were prepared in water by using a copper catalyst.[911]

There are no *Organic Syntheses* references, but a preparation of a polysulfide may be found in OS **IV**, 295.

Primary and secondary, but not tertiary, alkyl halides are converted to *Bunte salts* ($RSSO_3^-$) by treatment with thiosulfate ion.[912] Bunte salts can be hydrolyzed with acids to give the corresponding thiols[913] or converted to disulfides, tetrasulfides, or pentasulfides.[914]

OS **VI**, 235.

10-28 Alkylation of Sulfinic Acid Salts

$$RX + R'SO_2^- \longrightarrow R\text{–}SO_2\text{–}R' + X^-$$

Alkyl halides or alkyl sulfates, treated with the salts of sulfinic acids, give sulfones.[915] Alkyl sulfinates R′SO—OR may be side products.[916] A Pd-catalyzed reaction with a chiral complexing agent led to sulfones with modest asymmetric induction.[917] Sodium tosylsulfinate reacted with allylic acetates in the presence of a Pd catalyst to give the corresponding sulfone.[918] Sulfonic acids themselves can be used, if DBU (see **17-11**) is present.[919] Sulfonyl halides react with allylic halides in the presence of $AlCl_3$–Fe[920] and with benzyl halides in the presence of Sm/$HgCl_2$.[921] The Cu-catalyzed cross coupling of organoboronic acids and sulfinate salts leads to sulfones.[922] Vinyl sulfones were prepared from $PhSO_2Na$ and vinyl iodinium salts C═C—I^+Ph BF_4^-.[923]

OS **IV**, 674; **IX**, 497. See also OS **VI**, 1016.

[907] Abbasi, M.; Mohammadizadeh, M.R.; Saeedi, N. *New J. Chem.* ***2016***, 82.
[908] Iranpoor, N.; Firouzabadi, H.; Khalili, D. *Tetrahedron Lett.* ***2012***, *53*, 6913.
[909] Tankam, T.; Poochampa, K.; Vilaivan, T.; Sukwattanasinitt, M.; Wacharasindhu, S. *Tetrahedron* ***2016***, *72*, 788.
[910] Abbasi, M.; Mohammadizadeh, M.R.; Moosavi, H.; Saeedi, N. *Synlett* ***2015***, *26*, 1185.
[911] Li, Z.; Ke, F.; Deng, H.; Xu, H.; Xiang, H.; Zhou, X. *Org. Biomol. Chem.* ***2013***, *11*, 2943.
[912] For a review of Bunte salts, see Distler, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 544.
[913] Kice, J.L. *J. Org. Chem.* ***1963***, *28*, 957.
[914] Milligan, B.; Saville, B.; Swan, J.M. *J. Chem. Soc.* ***1963***, 3608.
[915] See Schank, K. in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 165–231, pp. 177–188. For a reaction using the MgBr salt of an aryl sulfinate, see Wu, J.-P.; Emeigh, J.; Su, X.-P. *Org. Lett.* ***2005***, *7*, 1223.
[916] See Kielbasinski, P.; Zurawinski, R.; Drabowicz, J.; Mikolajczyk, M. *Tetrahedron* ***1988***, *44*, 6687.
[917] Eichelmann, H.; Gais, H.-J. *Tetrahedron: Asymmetry* ***1995***, *6*, 643.
[918] Felpin, F.-X.; Landais, Y. *J. Org. Chem.* ***2005***, *70*, 6441. Also see Chandrasekhar, S.; Jagadeshwar, V.; Saritha, B.; Narsihmulu, C. *J. Org. Chem.* ***2005***, *70*, 6506.
[919] Biswas, G.; Mal, D. *J. Chem. Res. (S)* ***1988***, 308.
[920] Saikia, P.; Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *Chem. Lett.* ***2001***, 512.
[921] Zhang, J.; Zhang, Y. *J. Chem. Res. (S)* ***2001***, 516.
[922] Huang, F.; Batey, R.A. *Tetrahedron* ***2007***, *63*, 7667.
[923] Ochiai, M.; Oshima, K.; Masaki, Y.; Kunishima, M.; Tani, S. *Tetrahedron Lett.* ***1993***, *34*, 4829.

10-29 Formation of Alkyl Thiocyanates

$$RX + SCN^- \longrightarrow RSCN + X^-$$

Alkyl halides[924] or sulfuric or sulfonic esters can be heated with sodium or potassium thiocyanate to give alkyl thiocyanates,[925] although the attack by the analogous cyanate ion (**10-44**) gives exclusive *N*-alkylation. Primary amines can be converted to thiocyanates by the *Katritzky pyrylium–pyridinium method* (Sec. 10.G.iii).[926] Tertiary chlorides are converted to tertiary thiocyanates with $Zn(SCN)_2$ in pyridine and ultrasound.[927]

The ^-SCN nucleophile reacts at the α position of an amine to form a thiocyanate, following formation of an iminium ion by oxidation induced by visible light, catalyzed by eosin Y.[928] Thiocyanates have been formed from thioethers by treatment with hypervalent iodine reagents, aryl(cyano)-iodonium triflates as the cyanating agent.[929] The CuCN-mediated cyanation of thiophenols and diaryl disulfides with MSCN leads to thiocyanates.[930] Arylboronic acids are converted to aryl thiocyanates using a CuCl-catalyzed oxidative cross coupling in the presence of trimethylsilylisothiocyanate (TMS–NCS) and an oxygen atmosphere.[931] Aryl thiocyanates have been prepared using trichlorocyanuric acid and ammonium thiocyanate in the presence of wet SiO_2.[932] Arylthiocyanates are formed from aromatic compounds by treatment with NH_4SCN in the presence of 2,2′-azobenzothiazole.[933] Alkyl thiocyanates have been prepared from allyl and benzyl halides using $Zn(SCN)_2$ under microwave conditions which accelerated the reaction.[934] The α-thiocyanation of carbonyl compounds has been reviewed.[935]

OS **II**, 366.

10.H.iii. Nitrogen Nucleophiles

A. Attack by NH_2, NHR, or NR_2 at an Alkyl Carbon

10-30 Alkylation and Arylation of Amines

$$3\,RX + NH_3 \longrightarrow R_3N + RX \longrightarrow R_4N^+X^-$$
$$2\,RX + R'NH_2 \longrightarrow R_2R'N + RX \longrightarrow R_3R'N^+X^-$$
$$RX + R''R'NH_2 \longrightarrow RR'R''N + RX \longrightarrow R_2R'R''N^+X^-$$
$$RX + RR'R''N \longrightarrow RR'R''R'''N^+X^-$$

[924] Renard, P.-Y.; Schwebel, H.; Vayron, P.; Leclerc, E.; Dias, S.; Mioskowski, C. *Tetrahedron Lett.* ***2001***, *42*, 8479. Also see Mohanazadeh, F.; Aghvami, M. *Tetrahedron Lett.* ***2007***, *48*, 7240.

[925] See Guy, R.G. in Patai, S. *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 2, Wiley, NY, ***1977***, pp. 819–886.

[926] Katritzky, A.R.; Gruntz, U.; Mongelli, N.; Rezende, M.C. *J. Chem. Soc., Perkin Trans. 1* ***1979***, 1953. See Tamura, Y.; Kawasaki, T.; Adachi, M.; Tanio, M.; Kita, Y. *Tetrahedron Lett.* ***1977***, 4417.

[927] Bettadaiah, B.K.; Gurudutt, K.N.; Srinivas, P. *Synth. Commun.* ***2003***, *33*, 2293.

[928] Yadav, A.K.; Yadav, L.D.S. *Tetrahedron Lett.* ***2015***, *56*, 6696.

[929] Zhu, D.; Chang, D.; Shi, L. *Chem. Commun.* ***2015***, *51*, 7180.

[930] Castanheiro, T.; Gulea, M.; Donnard, M.; Suffert, J. *Eur. J. Org. Chem.* ***2014***, 7814.

[931] Sun, N.; Che, L.; Mo, W.; Hu, B.; Shen, Z.; Hu, X. *Org. Biomol. Chem.* ***2015***, *13*, 691.

[932] Akhlaghinia, B.; Purali, A.-R.; Rahmani, M. *Synth. Commun.* ***2012***, *42*, 1184.

[933] Iranpoor, N.; Firouzabadi, H.; Shahin, R.; Khalili, D. *Synth. Commun.* ***2012***, *42*, 2040.

[934] Bound, D.J.; Bettsadaiah, B.K.; Srinivas, P. *Synth. Commun.* ***2013***, *43*, 1138.

[935] Vekariya, R.H.; Patel, H.D. *Synth. Commun.* ***2017***, *47*, 87.

The reaction between alkyl halides and ammonia or primary amines is not usually a feasible method for the preparation of primary or secondary amines, since the amine products are stronger bases than ammonia or a primary amine, respectively, and preferentially attack the substrate.[936] However, the reaction is very useful for the preparation of tertiary amines[937] and quaternary ammonium salts. As expected, tertiary substrates do not give the reaction at all but undergo preferential elimination upon treatment with a basic amine. If ammonia is the nucleophile,[938] the three or four alkyl groups on the nitrogen of the product must be identical. If a primary, secondary, or tertiary amine is used, then different alkyl groups can be placed on the same nitrogen atom. The conversion of tertiary amines to quaternary salts is called the *Menshutkin reaction*.[939] The limitations of this approach can be seen in the reaction of a saturated solution of ammonia in 90% ethanol with ethyl bromide in a 16:1 molar ratio, which gave 34.2% of the primary amine (at a 1:1 ratio the yield was 11.3%).[940] The immediate product in any particular step is the protonated amine, but it rapidly loses a proton to another molecule of ammonia or amine in an equilibrium process, for example:

$$RX + R_2NH \longrightarrow R_3\overset{+}{N}H + R_2NH \rightleftharpoons R_3N + R_2\overset{+}{N}H_2$$

When a primary or secondary amine must be converted directly to the quaternary salt (*exhaustive alkylation*), the rate can be increased by the addition of a nonnucleophilic strong base that serves to remove the proton from $RR'NH_2^+$ or $RR'R^2NH^+$ and thus liberates the amine to attack another molecule of RX.[941] *N*-Alkylation has been accomplished using alkyl halides in aqueous media.[942]

It is sometimes possible to prepare a primary amine by the use of a large excess of ammonia or a secondary amine by the use of a large excess of primary amine. Ionic liquids have been used to facilitate amination reactions.[943] The use of ammonia in methanol with microwave irradiation has also been effective.[944] Microwave irradiation has also been used in reactions of aniline with allyl iodides.[945] Bromides react faster than chlorides. *tert*-Butylamines can be prepared from isobutylene, HBr, and the amine by heating in a sealed tube.[946] Primary arylamines are easily alkylated, but diaryl- and triarylamines are very poor nucleophiles. However, the reaction has been carried out with diarylamines.[947] Sulfates or sulfonates can be used instead of halides.

[936] Grange, R.L.; Clizbe, E.A.; Evans, P.A. *Synthesis* ***2016***, *48*, 2911.
[937] See Gibson, M.S. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 45–55; Spialter, L.; Pappalardo, J.A. *The Acyclic Aliphatic Tertiary Amines*, Macmillan, NY, ***1965***, pp. 14–29.
[938] See Jeyaraman, R. in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 9–83.
[939] For solvent effects, see Sola, M.; Lledos, A.; Duran, M.; Bertran, J.; Abboud, J.L.M. *J. Am. Chem. Soc.* ***1991***, *113*, 2873. For other parameters, see Persson, J.; Berg, U.; Matsson, O. *J. Org. Chem.* ***1995***, *60*, 5037; Shaik, S.; Ioffe, A.; Reddy, A.C.; Pross, A. *J. Am. Chem. Soc.* ***1994***, *116*, 262.
[940] Werner, E.A. *J. Chem. Soc.* ***1918***, *113*, 899.
[941] Sommer, H.Z.; Lipp, H.I.; Jackson, L.L. *J. Org. Chem.* ***1971***, *36*, 824. See also, Chuang, T.-H.; Sharpless, K.B. *Org. Lett.* ***2000***, *2*, 3555.
[942] Simion, A.M.; Arimura, T.; Miyazawa, A.; Simion, C.; Prakash, G.K.S.; Olah, G.A.; Tashiro, M. *Synth. Commun.* ***2009***, *39*, 2859.
[943] Lyubimov, S.E.; Davankov, V.A.; Gavrilov, K.N. *Tetrahedron Lett.* ***2006***, *47*, 2721.
[944] Saulnier, M.G.; Zimmermann, K.; Struzynski, C.P.; Sang, X.; Velaparthi, U.; Wittman, M.; Frennesson, D.B. *Tetrahedron Lett.* ***2004***, *45*, 397.
[945] Romera, J.L.; Cid, J.M.; Trabanco, A.A. *Tetrahedron Lett.* ***2004***, *45*, 8797.
[946] Gage, J.R.; Wagner, J.M. *J. Org. Chem.* ***1995***, *60*, 2613.
[947] Patai, S.; Weiss, S. *J. Chem. Soc.* ***1959***, 1035.

Bases other than an amine can be used, including sodium carbonate,[948] LiOH,[949] and CsOH,[950] while cesium fluoride has been used with benzylic halides.[951] Fluorinated alcohols were found to act as promoters for this reaction, with a variety of nucleophiles, including amines.[952] Aminoboranes[953] react with sulfonate esters to give a derivative that can be hydrolyzed to a tertiary amine.[954] *N*-Silylalkyl amines are formed from amines by reaction with halotrialkylsilanes and a suitable base.[955] *N*-Chloromethyl lactams also react with amines to give good yields of the *N*-aminomethyl lactam.[956]

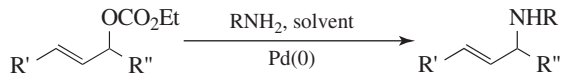
Primary amines are converted to the *N*-methyl derivative with methyl triflate, made possible by using HFIP as the solvent, which "interferes with amines and avoids overmethylation."[957] Chlorobutane reacts with aryl amines in molten quaternary ammonium salts, as the solvent, under base-free conditions.[958] Aniline reacted with benzylic halides in DMF at 150 °C under microflow conditions (Sec. 7.D).[959] Aryltrialkylammonium salts have been prepared by the reaction of tertiary amines with 2-(trimethylsilyl)phenyl triflate in the presence of CsF.[960] Benzylic fluorides react with amines in presence of water as a cosolvent to give *N*-alkyl amines.[961] Allyl bromide reacted with anilines under microwave irradiation, in DMF in the presence of Na_2CO_3 and CTAB.[962] The synthesis of *N*-methylamines is possible by the reaction of amines with carbon dioxide with H_2.[963] Formic acid has been used as a carbon and hydrogen source for the *N*-methylation of aromatic amines.[964]

[948] Faul, M.M.; Kobierski, M.E.; Kopach, M.E. *J. Org. Chem.* ***2003***, *68*, 5739.
[949] Cho, J.H.; Kim, B.M. *Tetrahedron Lett.* ***2002***, *43*, 1273.
[950] Salvatore, R.N.; Schmidt, S.E.; Shin, S.I.; Nagle, A.S.; Worrell, J.H.; Jung, K.W. *Tetrahedron Lett.* ***2000***, *41*, 9705.
[951] Hayat, S.; Rahman, A.-u.; Choudhary, M.I.; Khan, K.M.; Schumann, W.; Bayer, E. *Tetrahedron* ***2001***, *57*, 9951.
[952] Trillo, P.; Baeza, A.; Nájera, C. *J. Org. Chem.* ***2012***, *77*, 7344.
[953] For a review of electrophilic amination reactions, see Corpet, M.; Gosmini, C. *Synthesis* ***2014***, *46*, 2258.
[954] Thomas, S.; Huynh, T.; Enriquez-Rios, V.; Singaram, B. *Org. Lett.* ***2001***, *3*, 3915.
[955] Greene, T.W. *Protective Groups in Organic Synthesis*, Wiley, New York, ***1980***; Wuts, P.G.M.; Greene, T.W. *ProtectiveGroups in Organic Synthesis*, 2nd ed., Wiley, New York, ***1991***; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, New York, ***1999***; Wuts, P.G.M.; Greene, T.W. *Greene's Protective Groups in Organic Synthesis*, 4th ed., Wiley, New Jersey, ***2006***; Wuts, P.G.M. *Greene's Protective Groups in Organic Synthesis*, 5th ed., Wiley, New Jersey, ***2014***.
[956] Chen, P.; Suh, D.J.; Smith, M.B. *J. Chem. Soc., Perkin Trans. 1* ***1995***, 1317; Deskus, J.; Fan, D.-p.; Smith. M.B. *Synth. Commun.* ***1998***, *28*, 1649.
[957] Lebleu, T.; Ma, X.; Maddaluno, J.; Legros, J. *Chem. Commun.* ***2014***, *50*, 1836.
[958] Monopoli, A.; Cotugno, P.; Cortese, M.; Calvano, C.D.; Ciminale, F.; Nacci, A. *Eur. J. Org. Chem.* ***2012***, 3105.
[959] Choi, Y.-S.; Kim, Y.-J.; Shen, L.-L.; Lee, Y.S.; Jeong, J.-H. *Synlett* ***2015***, *26*, 970.
[960] Hirsch, M.; Dhara, S.; Diesendruck, C.E. *Org. Lett.* ***2016***, *18*, 980.
[961] Champagne, P.A.; Pomarole, J.; Thérien, M-È.; Benhassine, Y.; Beaulieu, S.; Legault, C.Y.; Paquin, J.-F. *Org. Lett.* ***2013***, *15*, 2210.
[962] Liu, M.; Wang, X.; Sun, X.; He, W. *Tetrahedron Lett.* ***2014***, *55*, 2711. For a nano-gold catalyzed reaction, see Berrichi, A.; Bachir, R.; Benabdallah, M.; Choukchou-Braham, N. *Tetrahedron Lett.* ***2015***, *56*, 1302.
[963] Li, Y.; Sorribes, I.; Yan, T.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* ***2013***, *52*, 12156. For a Cu-catalyzed reaction using the BICMAP ligand, see Mino, T.; Taguchi, H.; Hashimoto, M.; Sakamoto, M. *Tetrahedron: Asymmetry* ***2013***, *24*, 1520. Also see Das, S.; Bobbink, F.D.; Laurenczy, G.; Dyson, P.J. *Angew. Chem. Int. Ed.* ***2014***, *53*, 12876. For a reaction catalyzed by Pd/$CuZrO_x$, see Cui, X.; Zhang, Y.; Deng, Y.; Shi, F. *Chem. Commun.* ***2014***, *50*, 13521. For a catalyst-free reaction using CO_2, see Niu, H.; Lu, L.; Shi, R.; Chiang, C.-W.; Lei, A. *Chem. Commun.* ***2017***, *53*, 1148–1151. For the use of a Pd-catalyst, see Kon, K.; Hakim Siddiki, S.M.A.; Onodera, W.; Shimizu, K. *Chem. Eur. J.* ***2014***, *20*, 6264. For the use of hydrosilane and a fluoride catalyst, see Liu, X.-F.; Ma, R.; Qiao, C.; Cao, H.; He, L.-N. *Chem. Eur. J.* ***2016***, *22*, 16489.
[964] Savourey, S.; Lefèvre, G.; Berthet, J.-C.; Cantat, T. *Chem. Commun.* ***2014***, *50*, 14033.

Primary amines can be prepared from alkyl halides by the use of hexamethylenetetramine[965] followed by cleavage of the resulting salt with ethanolic HCl. The method, called the *Delépine reaction*, is most successful for active halides such as allylic and benzylic halides and α-halo ketones.

The conjugate bases of ammonia and of primary and secondary amines (NH_2^-, RNH^-, R_2N^-) are generically known as *amide bases*, and are sometimes used as nucleophiles,[966] including amide bases generated from organolithium reagents and amines (R_2NLi).[967] Primary alkyl, allylic, and benzylic bromides, iodides, and tosylates react with sodium bis(trimethylsilyl)amide to give derivatives that are easily hydrolyzed to produce amine salts in high overall yields.[968]

The reaction can be carried out intramolecularly to give cyclic amines; three-, five-, and six-membered rings (but not four-membered) are easily prepared. Thus, 4-chloro-1-aminobutane treated with base gives pyrrolidine, and 2-chloroethylamine gives aziridine[969] (analogous to **10-9**). Three-membered cyclic amines (aziridines) can be prepared from chiral conjugated amides via bromination and reaction with an amine.[970] Four-membered cyclic amines (azetidines) have been prepared from the ditosylate of 1,3-propanediol[971] and from 1,3-dichloropropane.[972] This reaction was also used to close five-, six-, and seven-membered rings. Reduction of *N*-(3-bromopropyl)imines gave a bromo amine *in situ*, which cyclized to the aziridine.[973] *N*-Alkylation of heterocycles is sometimes problematic, but pyrrole was converted to *N*-methylpyrrole with KOH and iodomethane in ionic liquids.[974] Indolines have been prepared from diaryliodonium salts.[975] Copper(I) 3-metylsalicylate has been used for the *N*-arylation of heterocycles.[976] Carbazoles react with alkyl iodides under photolytic conditions, in the presence of a catalytic amount of CuI and Li*O*t-Bu, to give *N*-alkyl carbazoles.[977] An intramolecular amination of propargylic acetates bearing an amino group, with a chiral Cu–pybox complex, leads to optically active 1-ethynyl isoindolines.[978]



[965] See Blazevic, N.; Kolbah, D.; Belin, B.; Sunjic, V.; Kajfez, F. *Synthesis* ***1979***, 161.
[966] See DePue, J.S.; Collum, D.B. *J. Am. Chem. Soc.* ***1988***, *110*, 5524.
[967] Vitale, A.A.; Chiocconi, A.A. *J. Chem. Res. (S)* ***1996***, 336.
[968] Bestmann, H.J.; Wölfel, G. *Chem. Ber.* ***1984***, *117*, 1250.
[969] See Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academc Press, NY, ***1969***, pp. 1–59.
[970] Garner, P.; Dogan, O.; Pillai, S. *Tetrahedron Lett.* ***1994***, *35*, 1653.
[971] Juaristi, E.; Madrigal, D. *Tetrahedron* ***1989***, *45*, 629.
[972] Ju, Y.; Varma, R.S. *J. Org. Chem.* ***2006***, *71*, 135.
[973] DeKimpe, N.; DeSmaele, D. *Tetrahedron Lett*. ***1994***, *35*, 8023. Also see, De Kimpe, N.; Boelens, M.; Piqueur, J.; Baele, J. *Tetrahedron Lett.* ***1994***, *35*, 1925.
[974] Le, Z.-G.; Chen, Z.-C.; Hu, Y.; Zheng, Q.-G. *Synthesis* ***2004***, 1951.
[975] Riedmüller, S.; Nachtsheim, B.J. *Synlett* ***2015***, *26*, 651.
[976] Farahat, A.A.; Boykin, D.W. *Tetrahedron Lett.* ***2014***, *55*, 3049. For a ligand-free Cu-catalyzed reaction, see Wang, D.; Kuang, D.; Zhang, F.; Liu, Y.; Ning, S. *Tetrahedron Lett.* ***2014***, *55*, 7121. See Heidarizadeh, F.; Majdinasab, A. *Tetrahedron Lett.* ***2015***, *56*, 6360; Xu, Z.-L.; Li, H.-X.; Ren, Z-G.; Du, W.-Y.; Xu,W.-C.; Lang, J.-P. *Tetrahedron* ***2011***, *67*, 5282; Yang, Q.; Wang, Y.; Yang, L.; Zhang, M. *Tetrahedron* ***2013***, *69*, 6230. Also see Alakonda, L.; Periasamy, M. *Synthesis* ***2012***, *44*, 1063.
[977] Bissember, A.C.; Lundgren, R.J.; Creutz, S.E.; Peters, J.C.; Fu, G.C. *Angew. Chem. Int. Ed.* ***2013***, *52*, 5129.
[978] Shibata, M.; Nakajima, K.; Nisibayashi, Y. *Chem. Commun.* ***2014***, *50*, 7874.

Metal-catalyzed methods are available to convert primary amines to secondary amines,[979] and secondary amines can be converted to tertiary amines.[980] It is known that Pd compounds react with allylic halides, acetates, or carbonate derivatives to generate π-allyl Pd intermediates that react with amines to give an allylic amine.[981] The Pd-catalyzed internal addition of amine to allylic acetates leads to cyclic products via an S_N2' reaction[982] (also see **10-59**). Propargylic amines can be prepared by similar methodology.[983]

Metal-catalyzed amination is an active area of research. Amines react with allylic acetates in the presence of palladium metallocenyl *P*,*N* ligands to give allylic amines.[984] Cyclopropylamines react with aryl or heteroaryl halides in the presence of allylpalladium catalysts give *N*-aryl or *N*-heteroaryl cyclopropylamines.[985] The Pd-catalyzed synthesis of α,α-disubstituted allylic *N*-aryl amines has been reported by the reaction of vinyl cyclic carbonates and aromatic amines.[986] Allenyl amines were prepared by the enantioselective Pd-catalyzed decarboxylation of allenyl *N*-tosylcarbamates.[987] Secondary amines react with allylic chlorides in the presence of Pd or Ti catalysts, and in the presence of silver triflate, to give *N*-allyl amines.[988]

Ruthenium(II) complexes have been used for the alkylation of aryl amines,[989] as has $NiCl_2 \bullet 6H_2O$ using microwave conditions.[990] Heating primary amines in water with a Ru catalyst gave the corresponding alcohol,[991] and microwave irradiation has been used.[992] *N*-Allylic amines have been generated by the reaction of amines with tertiary allylic acetates, catalyzed by Cp^*RuCl_2/5,5′-dimethyl-2,2′-bipyridine.[993] Secondary amines react with 1-arylallyl acetates in the presence of a $RuCl_3$/(*S,S*)-*ip*-pybox catalyst.[994]

Boronic acid derivatives lead to methylation of aniline derivatives in the presence of cupric acetate.[995] Aryl amines react with alkylborane reagents, in the presence of a catalytic amount of a Cu catalyst and di-*tert*-butyl peroxide, to give alkylated amines.[996] A

[979] Lorentz-Petersen, L.L.R.; Jensen, P.; Madsen, R. *Synthesis* ***2009***, 4110.
[980] Kurosu, M.; Dey, S.S.; Crick, D.C. *Tetrahedron Lett.* ***2006***, *47*, 4871.
[981] Nagano, T.; Kobayashi, S. *J. Am. Chem. Soc.* ***2009***, *131*, 4200. See also, Evans, P.A.; Robinson, J.E.; Moffett, K.K. *Org. Lett.* ***2001***, *3*, 3269. For mechanistic insights, see Watson, I.D.G.; Yudin, A.K. *J. Am. Chem. Soc.* ***2005***, *127*, 17516.
[982] Grellier, M.; Pfeffer, M.; van Koten, G. *Tetrahedron Lett.* ***1994***, *35*, 2877.
[983] Detz, R.J.; Delville, M.M.E.; Hiemstra, H.; van Maarseveen, J.H. *Angew. Chem. Int. Ed.* ***2008***, *47*, 3777. See Park, S.B.; Alper, H. *Chem. Commun.* ***2005***, 1315.
[984] Wu, H.; Xie, F.; Wang, Y.; Zhao, X.; Liu, D.; Zhang, W. *Org. Biomol. Chem.* ***2015***, *13*, 4248.
[985] Gildner, P.G.; DeAngelis, A.; Colacot, T.J. *Org. Lett.* ***2016***, *18*, 1442.
[986] Cai, A.; Guo, W.; Martínez-Rodríguez, L.; Kleij, A.W. *J. Am. Chem. Soc.* ***2016***, *138*, 14194.
[987] Wan, B.; Ma, S. *Angew. Chem. Int. Ed.* ***2013***, *52*, 441.
[988] Walker, W.K.; Anderson, D.L.; Stokes, R.W.; Smith, S.J.; Michaelis, D.J. *Org. Lett.* ***2015***, *17*, 752.
[989] Hollmann, D.; Bähn, S.; Tillack, A.; Parton, R.; Altink, R.; Beller, M. *Tetrahedron Lett.* ***2008***, *49*, 5742.
[990] Gupta, A.K.; Rao, G.T.; Singh, K.N. *Tetrahedron Lett.* ***2012***, *53*, 2218.
[991] Khusnutdinova, J.R.; Ben-David, Y.; Milstein, D. *Angew. Chem. Int. Ed.* ***2013***, *52*, 6269.
[992] Watson, A.J.A.; Maxwell, A.C.; Williams, J.M.J. *J. Org. Chem.* ***2011***, *76*, 2328.
[993] Mizuno, S.; Terasaki, S.; Shinozawa, T; Kawatsura, M. *Org. Lett.* ***2017***, *19*, 504. For the use of IndPHOX (indole phosphine oxazoline) ligand, see Wang, Y.; Vaismaa, M.J.P.; Hämäläinen, A.M.; Tois, J.E.; Franzén, R. *Tetrahedron: Asymmetry* ***2011***, *22*, 524.
[994] Kawatsura, M.; Uchida, K.; Terasaki, S.; Tsuji, H.; Minakawa, M.; Itoh, T. *Org. Lett.* ***2014***, *16*, 1470.
[995] González, I.; Mosquera, J.; Guerrero, C.; Rodríguez, R.; Cruces, J. *Org. Lett.* ***2009***, *11*, 1677. See also Bariwal, J.B.; Ermolat'ev, D.S.; van der Eycken, E.V. *Chem. Eur. J.* ***2010***, *16*, 3281.
[996] Sueki, S.; Kuninobu, Y. *Org. Lett.* ***2013***, *15*, 1544.

glycerol-ingrained Cu catalyst has been used for the *N*-arylation of arylamines.[997] The *N*-arylation of amines with bromoarenes used an Fe–Cu co-catalyst system.[998] Primary amines react with a variety of alkyl halides, in the presence of a SiO_2–CuI, with TBAB and aqueous NaOH, to give *N*-alkylation.[999] The Cu-catalyzed *N*-arylation of allylic amides has been reported using diaryliodonium salts.[1000]

Allylic alcohols are converted to allylic amines by reaction with aqueous ammonia in the presence of a Pt catalyst and a bis-phosphine.[1001] The *N*-alkylation of amines has been accomplished by reaction with carboxylic acids in the presence of $PhSiH_3$ and a Pt catalyst.[1002] Functionalized amines reacted with alcohols, in the presence of an Au catalyst, to give the functionalized amine.[1003] Methylation has been accomplished with dialkyl carbonates and hydrosilanes, catalyzed by Fe complexes.[1004] Allylic amines were formed by the reaction of allylic compounds with aniline derivatives using an Ir catalyst.[1005] A nano-In_2O_3-catalyzed reaction of terminal alkynes, dichloromethane, and secondary amines gave propargylamines in the presence of DABCO.[1006] Propargylamines have been prepared by the reaction of terminal alkynes, dichloromethane, and tertiary amines using a catalytic amount of AgOAc.[1007] A technique labeled "thermodynamic kinetic asymmetric amination" of alcohols with arylamines in the presence of an Ir catalyst and a chiral phosphoric acid has been reported.[1008]

Phosphines behave similarly to the amines, and compounds such as R_3P and $R_4P^+ X^-$ can be prepared.[1009] The reaction between triphenylphosphine and quaternary salts of nitrogen heterocycles in an aprotic solvent is probably the best way of dealkylating the heterocycles, for example, giving the *P*-alkylphosphonium salt.[1010] Other phosphorus compounds can be alkylated. Phosphinate esters, for example, react with a suitable base and then an alkyl halide to give the *P*-substituted product.[1011]

OS **I**, 23, 48, 102, 300, 488; **II**, 85, 183, 290, 328, 374, 397, 419, 563; **III**, 50, 148, 254, 256, 495, 504, 523, 705, 753, 774, 813, 848; **IV**, 84, 98, 383, 433, 466, 582, 585, 980; **V**, 88, 124, 306, 361, 434, 499, 541, 555, 608, 736, 751, 758, 769, 825, 883, 985, 989, 1018,

[997] Khatri, P.K.; Jain, S.L. *Tetrahedron Lett.* ***2013***, *54*, 2740. See Yadav, D.K.T.; Rajak, S.S.; Bhanage, B.M. *Tetrahedron Lett.* ***2014***, *55*, 931.

[998] Liu, X.; Zhang, S. *Synlett* ***2011***, *22*, 1137.

[999] Shamim, T.; Kumar, V.; Paul, S. *Synth. Commun.* ***2014***, *44*, 630.

[1000] Cahard, E.; Male, H.P.J.; Tissot, M.; Gaunt, M.J. *J. Am. Chem. Soc.* ***2015***, *137*, 7986.

[1001] Das, K.; Shibuya, R.; Nakahara, Y.; Germain, N.; Ohshima, T.; Mashim, K. *Angew. Chem. Int. Ed.* ***2012***, *51*, 150.

[1002] Sorribes, I.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* ***2014***, *136*, 14314. For the reaction with a Ru catalyst, see Minakawa, M.; Okubo, M.; Kawatsura, M. *Tetrahedron Lett.* ***2016***, *57*, 4187. For the reaction with $B(C_6F_5)_3$, see Zhang, Q.; Fu, M.-C.; Yu, H.-Z.; Fu, Y. *J. Org. Chem.* ***2016***, *81*, 6235.

[1003] Ohshima, T.; Nakahara, Y.; Ipposhi, J.; Miyamoto, Y.; Mashima, K. *Chem. Commun.* ***2011***, *47*, 8322.

[1004] Zheng, J.; Darcel, C.; Sortais, J.-B. *Chem. Commun.* ***2014***, *50*, 14229.

[1005] Madrahimov, S.T.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2012***, *134*, 8136.

[1006] Rahman, M.; Bagdi, A.Kr.; Majee, A.; Hajra, A. *Tetrahedron Lett.* ***2011***, *52*, 4437. For a $CoBr_2$-catalyzed reaction in the presence of DBU, see Tang, Y.; Xiao, T.; Zhou, L. *Tetrahedron Lett.* ***2012***, *53*, 6199. For an iron (III)-catalyzed reaction, see Gao, J.; Song, Q.-W.; He, L.-N.; Yang, Z.-Z.; Dou, Z.-Y. *Chem. Commun.* ***2012***, *48*, 2024. See Rawat, V.S.; Bathini, T.; Govardan, S.; Sreedhar, B. *Org. Biomol. Chem.* ***2014***, *12*, 6725.

[1007] Chen, X.; Chen. T.; Zhou, Y.; Au, C.-T.; Han, L.-B.; Yin, S.-F. *Org. Biomol. Chem.* ***2014***, *12*, 247.

[1008] Rong, Z.-Q.; Zhang, Y.; Chua, R.H.B.; Pan, H.-J.; Zhao, Y. *J. Am. Chem. Soc.* ***2015***, *137*, 4944.

[1009] See Honaker, M.T.; Sandefur, B.J.; Hargett, J.L.; McDaniel, A.L.; Salvatore, R.N. *Tetrahedron Lett.* ***2003***, *44*, 8373.

[1010] See Deady, L.W.; Finlayson, W.L.; Korytsky, O.L. *Aust. J. Chem.* ***1979***, *32*, 1735.

[1011] Abrunhosa-Thomas, I.; Sellers, C.E.; Montchamp, J.-L. *J. Org. Chem.* ***2007***, *72*, 2851.

1085, 1145; **VI**, 56, 75, 104, 106, 175, 552, 652, 704, 818, 967; **VIII**, 9, 152, 231, 358. Also see OS **II**, 395; **IV**, 950; OS **V**, 121; OS **I**, 203.

For *N*-arylation of amines see **13-5**.

10-31 Amines From Alcohols or Ethers

$$\text{R–OH} \longrightarrow \text{R–NH}_2$$
$$\text{Ar–OR}' \longrightarrow \text{R}'\text{–NH}_2 + \text{ArOH}$$

Alcohols can be converted to alkyl halides, which then react with amines (**10-42**). Alcohols react with various amine reagents that give products convertible to the amine.[1012] The conversion ROH → RNH_2 can be accomplished for primary and secondary alcohols by treatment with hydrazoic acid (HN_3), diisopropyl azodicarboxylate (*i*-Pr-OOCN=NCOO-*i*-Pr), and excess Ph_3P in THF, followed by water or aqueous acid.[1013] This is a type of *Mitsunobu reaction* (see **10-17**).[1014] Primary and secondary alcohols (but not methanol) can be converted to tertiary amines.[1015] Primary amines can be generated directly from primary alcohols and ammonia.[1016] Formation of R'_2NR required treatment of the secondary amine R'_2NH with $(t\text{-BuO})_3Al$ in the presence of Raney nickel.[1017] The use of aniline gives secondary amines PhNHR.

Alcohols react directly with amines to give an amine in the presence of a transition metal catalyst.[1018] Secondary amines were prepared by the reaction of nitroarenes with primary alcohols with a Ru-complex catalyst.[1019] Allylic alcohols react with amines in

[1012] See Cami-Kobeci, G.; Williams, J.M.J. *Chem. Commun.* ***2004***, 1072. See also, Salehi, P.; Motlagh, A.R. *Synth. Commun.* ***2000***, *30*, 671; Lakouraj. M.M.; Movassagh, B.; Fasihi, J. *Synth. Commun.* ***2000***, *30*, 821.

[1013] Fabiano, E.; Golding, B.T.; Sadeghi, M.M. *Synthesis* ***1987***, 190. See also, Klepacz, A.; Zwierzak, A. *Synth. Commun.* ***2001***, *31*, 1683.

[1014] See Edwards, M.L.; Stemerick, D.M.; McCarthy, J.R. *Tetrahedron Lett.* ***1990***, *31*, 3417.

[1015] See Huh, K.; Tsuji, Y.; Kobayashi, M.; Okuda, F.; Watanabe, Y. *Chem. Lett.* ***1988***, 449.

[1016] Gunanathan, C.; Milstein, D. *Angew. Chem. Int. Ed.* ***2008***, *47*, 8661. For a Ru-catalyzed reaction of primary and secondary alcohols with ammonia, see Imm, S.; Bähn, S.; Neubert, L.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* ***2010***, *49*, 8126.

[1017] Botta, M.; De Angelis, F.; Nicoletti, R. *Synthesis* ***1977***, 722.

[1018] For reaction with a **Co** catalyst, see Mastalir, M.; Tomsu, G.; Pittenauer, E.; Allmaier, G.; Kirchner, K. *Org. Lett.* ***2016***, *18*, 3462. For a **Ru** catalsyt, see Luo, J.; Wu, M.; Xiao, F.; Deng, G. *Tetrahedron Lett.* ***2011***, *52*, 2706; Baumann, W.; Spannenberg, A.; Pfeffer, J.; Haas, T.; Köckritz, A.; Martin, A.; Deutsch, J. *Chem. Eur. J.* ***2013***, *19*, 17702. For a **Re** catalyst, see Abdukader, A.; Jin, H.; Cheng, Y.; Zhu, C. *Tetrahedron Lett.* ***2014***, *55*, 4172. For a **Cu** catalyst, see Martínez-Asencio, A.; Ramón, D.J.; Yus, M. *Tetrahedron* ***2011***, *67*, 3140; Li, Q.; Fan, S.; Sun, Q.; Eian, H.; Yu, X.; Xu, Q. *Org. Biomol. Chem.* ***2012***, *10*, 2966. For a **Au** catalyst, see Yang, H.; Mao, R.; Luo, C.; Lu, C.; Cheng, G. *Tetrahedron* ***2014***, *70*, 8829. For the use of **Pt-Sn/γ-Al_2O_3** as a catalyst, see Wu, K.; He, W.; Sun, C.; Yu, Z. *Tetrahedron* ***2016***, *72*, 8516. For the use of a cyclometalated **Pd** pre-catalyst, see Mamidala, R.; Mukundam, V.; Dhanunjayarao, K.; Venkatasubbaiah, K. *Tetrahedron* ***2017***, *73*, 2225; Sun, G.-J.; Wang, Y.; Kang, Q. *Synthesis* ***2015***, *47*, 2931. Banerjee, D.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* ***2014***, *53*, 13049. For an **Ir** catalyst, see Wetzel, A.; Wöckel, S.; Schelwies, M.; Brinks, M.K.; Rominger, F.; Hofmann, P.; Limbach, M. *Org. Lett.* ***2013***, *15*, 266; Zhang, Y.; Lim, C.-S.; Sim, D.S.B.; Pan, H.-J.; Zhao, Y. *Angew. Chem. Int. Ed.* ***2014***, *53*, 1399; Apsunde, T.D.; Trudell, M.L. *Synthesis* ***2014***, *46*, 230; Li, J.-Q.; Andersson, P.G. *Chem. Commun.* ***2013***, *49*, 6131; Ruch, S.; Irrgang, T.; Kempe, R. *Chem. Eur. J.* ***2014***, *20*, 13279; Zou, Q.; Wang, C.; Smith, J.; Xue, D.; Xiao, J. *Chem. Eur. J.* ***2015***, *21*, 9656. For an **Fe** catalyst, see Emayavaramban, B.; Roy, M.; Sundararaju, B. *Chem. Eur. J.* ***2016***, *22*, 3952.; Trillo, P.; Baeza, A.; Nájera, C. *Eur. J. Org. Chem.* ***2012***, 2929. For an **Fe/amino acid**-catalyzed reaction, see Zhao, Y.; Foo, S.W.; Saito, S. *Angew. Chem. Int. Ed.* ***2011***, *50*, 3006.

[1019] Lee, C.-C.; Liu, S.-T. *Chem. Commun.* ***2011***, *47*, 6981.

the presence of Pt[1020] or Pd[1021] complexes, to give allylic amines.[1022] Amines can be *N*-alkylated by reaction with alcohols in a sealed tube with microwave irradiation,[1023] and also by Ru-catalyzed,[1024] Ir-catalyzed,[1025] Au-catalyzed,[1026] or Ti-mediated[1027] reactions. The Ru-catalyzed reaction of amines and diols leads to cyclic amines.[1028] Alcohols react with TEMPA-BAIB and then amines and $NaBH(OAc)_3$ to give the corresponding amine, where BAIB is [bis(acetoxy)-iodo]benzene.[1029] Alcohols reacted with $R_3NH^-\ K^+$ with a catalytic amount of KOH to give the amine.[1030]

β-Amino alcohols give aziridines (**10-35**) when treated with triphenylphosphine dibromide in the presence of triethylamine.[1031] The fact that inversion takes place at the OH carbon indicates that an S_N2 mechanism is involved, with $OPPh_3$ as the leaving group.

Alcohols can be converted to amines in an indirect manner.[1032] The alcohols are converted to alkyloxyphosphonium perchlorates, which in DMF successfully *monoalkylate* not only secondary but also primary amines.[1033] Therefore, secondary as well as tertiary amines can be prepared in good yields. Benzylic alcohols can be converted to an azide and then treated with triphenylphosphine to give the amine (**19-50**).[1034]

$$\mathrm{ROH} \xrightarrow[2.\ NH_4ClO_4]{1.\ CCl_4-p(NMe_2)_3} \mathrm{ROP}\overset{+}{(}\mathrm{NMe_2})_3\ ClO_4^- \xrightarrow[R'R^2NH]{DMF} RR'R^2N + O{=}P(NMe_2)_3$$

N-Alkyl amides or imides can also be prepared starting from alcohols by treatment of the latter with equimolar amounts of the amide or imide, Ph_3P, and diethyl azodicarboxylate ($EtO_2CN{=}NCO_2Et$) at room temperature (the *Mitsunobu reaction*, **10-17**).[1035] A related reaction treats an alcohol with $ClCH{=}NMe_2^+\ Cl^-$, followed by potassium phthalimide and treatment with hydrazine to give the amine.[1036] Metal-catalyzed syntheses of amides via oxidative coupling of alcohols and amines are known. Variations include the use of a Ru

[1020] Utsunomiya, M.; Miyamoto, Y.; Ipposhi, J.; Ohshima, T.; Mashima, K. *Org. Lett.* ***2007***, *9*, 3371.
[1021] Yamashita, Y.; Gopalarathnam, A.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2007***, *129*, 7508.
[1022] Tsuji, Y.; Takeuchi, R.; Ogawa, H.; Watanabe, Y. *Chem. Lett.* ***1986***, 293.
[1023] Jiang, Y.-L.; Hu, Y.-Q.; Feng, S.-Q.; Wu, J.-S.; Wu, Z.-W.; Yuan, Y.-C.; Liu, J.-M.; Hao, Q.-S.; Li, D.-P. *Synth. Commun.* ***1996***, *26*, 161.
[1024] Tillack, A.; Hollmann, D.; Mevius, K.; Michalik, D.; Bähn, S.; Beller, M. *Eur. J. Org. Chem.* ***2008***, 4745.
[1025] Fujita, K.; Enoki, Y.; Yamaguchi, R. *Tetrahedron* ***2008***, *64*, 1943.
[1026] Guo, S.; Song, F.; Liu, Y. *Synlett* ***2007***, 964.
[1027] Ramanathan, B.; Odom, A.L. *J. Am. Chem. Soc.* ***2006***, *128*, 9344.
[1028] Fujita, K.-i.; Fujii, T.; Yamaguchi, R. *Org. Lett.* ***2004***, *6*, 3525.
[1029] Guérin, C.; Bellosta, V.; Guillamot, G.; Cossy, J. *Org. Lett.* ***2011***, *13*, 3534.
[1030] Li, Q.-Q.; Xiao, Z.-F.; Yao, C.-Z.; Zheng, H.-X.; Kang, Y.-B. *Org. Lett.* ***2015***, *17*, 5328.
[1031] Okada, I.; Ichimura, K.; Sudo, R. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 1185. See also, Pfister, J.R. *Synthesis* ***1984***, 969; Suzuki, H.; Tani, H. *Chem. Lett.* ***1984***, 2129; Marsella, J.A. *J. Org. Chem.* ***1987***, *52*, 467.
[1032] Also see Hendrickson, J.B.; Joffee, I. *J. Am. Chem. Soc.* ***1973***, *95*, 4083; Trost, B.M.; Keinan, E. *J. Org. Chem.* ***1979***, *44*, 3451; Koziara, A.; Osowska-Pacewicka, K.; Zawadzki, S.; Zwierzak, A. *Synthesis* ***1985***, 202; ***1987***, 487.
[1033] Castro, B.; Selve, C. *Bull. Soc. Chim. Fr.* ***1971***, 4368. For a similar method, see Tanigawa, Y.; Murahashi, S.; Moritani, I. *Tetrahedron Lett.* ***1975***, 471.
[1034] Reddy, G.V.S.; Rao, G.V.; Subrmanyam, R.V.K.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 2233.
[1035] Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* ***1972***, *94*, 679; Grunewald, G.L.; Kolasa, T.; Miller, M.J. *J. Org. Chem.* ***1987***, *52*, 4978; Sammes, P.G.; Thetford, D. *J. Chem. Soc., Perkin Trans. 1* ***1989***, 655.
[1036] Barrett, A.G.M.; Braddock, D.C.; James, R.A.; Procopiou, P.A. *Chem. Commun.* ***1997***, 433.

complex,[1037] an $FeCl_3$ complex,[1038] an Ir complex reaction,[1039] and an $InCl_3$-catalyzed coupling of alcohols with ToSMIC (toluenesulfonylmethyl isocyanide).[1040]

A solution of the sodium salt of *N*-methylaniline in HMPA can be used to cleave the methyl group from aryl methyl ethers:[1041]

$$ArOMe + PhNMe^- \rightarrow ArO^- + PhNMe_2$$

This reagent also cleaves benzylic groups. In a similar reaction, methyl groups of aryl methyl ethers can be cleaved with lithium diphenylphosphide, Ph_2PLi.[1042] This reaction is specific for methyl ethers and can be carried out in the presence of ethyl ethers with high selectivity.

OS **II**, 29, 231; **IV**, 91, 283; **VI**, 567, 788; **VII**, 501. Also see OS **I**, 473; **III**, 272, 471.

10-32 Transamination

$$RNH_2 + R'NH^- \longrightarrow RR'NH + NH_2^-$$

Where the nucleophile is the conjugate base of a primary amine, NH_2 can be a leaving group. The method has been used to prepare secondary amines.[1043] In another process, primary amines are converted to secondary amines in which both R groups are the same[1044]

$$2RNH_2 \rightarrow R_2NH + NH_3$$

by refluxing in xylene in the presence of Raney nickel.[1045] Quaternary salts can be dealkylated with ethanolamine,[1046] and methyl groups are cleaved in preference to other saturated alkyl groups. A similar reaction takes place between a *Mannich base* (see **16-17**) and a secondary amine, where the mechanism is elimination–addition (Sec. 10.F). Benzylamine has also been used in this reaction for transamination,[1047] and 2-hydroxybenzylamine has been used as an amine source.[1048]

Transamination has been accomplished using yeast alcohol dehydrogenase.[1049] Enzymatic transamination of an α-keto ester leads to the transformation of an amino

[1037] Nordstrøm, L.U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* ***2008***, *130*, 17672. See also Dam, J.H.; Osztrovszky, G.; Nordstrøm, L.U.; Madsen, R. *Chem. Eur. J.* ***2010***, *16*, 6820; Ghosh, S.C.; Hong, S.-H. *Eur. J. Org. Chem.* ***2010***, 4266.
[1038] Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett.* ***2008***, *49*, 858.
[1039] Fujita, K.; Komatsubara, A.; Yamaguchi, R. *Tetrahedron* ***2009***, *65*, 3624.
[1040] Krishna, P.R.; Sekhar, E.R.; Prapurna, Y.L. *Tetrahedron Lett.* ***2007***, *48*, 9048.
[1041] Loubinoux, B.; Coudert, G.; Guillaumet, G. *Synthesis* ***1980***, 638.
[1042] Ireland, R.E.; Walba, D.M. *Org. Synth.* ***VI***, 567.
[1043] Baltzly, R.; Blackman, S.W. *J. Org. Chem.* ***1963***, *28*, 1158.
[1044] See Geller, B.A. *Russ. Chem. Rev.* ***1978***, *47*, 297.
[1045] De Angelis, F.; Grgurina, I.; Nicoletti, R. *Synthesis* ***1979***, 70; See also, Bank, S.; Jewett, R. *Tetrahedron Lett.* ***1991***, *32*, 303.
[1046] Hünig, S.; Baron W. *Chem. Ber.* ***1957***, *90*, 395, 403.
[1047] Xue, F.; Xiao, X.; Wang, H.; Shi, Y. *Tetrahedron* ***2012***, *68*, 6862.
[1048] Xie, L.; Pan, H.; Xia, X.; Li, S.; Shi, Y. *Org. Biomol. Chem.* ***2012***, *10*, 8960.
[1049] Cassimjee, K.E.; Branneby, C.; Abedi, V.; Wells, A.; Berglund, P. *Chem. Commun.* ***2010***, 5569.

acid, with loss of CO_2, to a new amino acid and benzophenone, catalyzed by pyridoxal/pyridoxamine.[1050] Chiral amines have been prepared using ω-transaminase, with a high enantiomeric purity.[1051] It was discovered that *ortho*-substitution of acetophenone reaction partners had a positive effect, and formation of a six-membered ring favored the transformation, whereas formation of a conjugated five-membered ring was unfavorable.[1051] A transaminase from *Halomonas elongata* was recombinantly produced in *E. coli* and applied to the amination of nitro-substituted acetophenone, giving the (*S*)-amine with high enantioselectivity.[1052] Transamination of α-amino nitriles has been reported.[1053] See also, **19-5**.

OS **V**, 1018.

10-33 Alkylation of Amines With Diazo Compounds

$$CR_2N_2 + R_2'NH \xrightarrow{BF_3} CHR_2NR_2'$$

The reaction of diazo compounds with amines is similar to **10-11**.[1054] The acidity of amines is not great enough for the reaction to proceed without a catalyst, but BF_3, which converts the amine to the $F_3B{-}NHR'_2$ complex, enables the reaction to take place. Cuprous cyanide can also be used as a catalyst.[1055] Ammonia has been used rather than an amine but, as in the case of **10-30**, mixtures of primary, secondary, and tertiary amines are obtained. However, a highly chemoselective reaction of amines in water has been reported.[1056] Primary aliphatic amines give mixtures of secondary and tertiary amines. Secondary amines give successful alkylation. Primary aromatic amines also give the reaction, but diaryl or arylalkylamines react very poorly.

10-34 Reaction of Epoxides With Nitrogen Reagents[1057]

+ 2° and 3° amine by-products

The reaction between epoxides and ammonia[1058] (or ammonium hydroxide)[1059] is a general and useful method for the preparation of β-hydroxyamines, including ethanolamines. Primary and secondary amines react with epoxides to give, respectively, secondary and tertiary

[1050] Liu, Y.E.; Lu, Z.; Li, B.; Tian, J.; Liu, F.; Zhao, J.; Hou, C.; Li, Y.; Niu, L.; Zhao, B. *J. Am. Chem. Soc.* ***2016***, *138*, 10730; Shi, L.; Tao, C.; Yang, Q.; Liu, Y.E.; Chen, J.; Chen, J.; Tian, J.; Liu, F.; Li, B.; Du, Y; Zhao, B. *Org. Lett.* ***2015***, *17*, 5784. This reaction can be catalyzed by other pyridoxamines: see Lan, X.; Tao, C.; Liu, X.; Zhang, A.; Zhao, B. *Org. Lett.* ***2016***, *18*, 3658; Chen, J.; Zhao, J.; Gong, X.; Xu, D.; Zhao, B. *Tetrahedron Lett.* ***2016***, *57*, 4612.

[1051] Gundersen, M.T.; Abu, R.; Schürmann, M.; Woodley, J.M. *Tetrahedron: Asymmetry* ***2015***, *26*, 567.

[1052] Contente, M.L.; Planchestainer, M.; Moinari, E.; Paradisi, F. *Org. Biomol. Chem.* ***2016***, *14*, 9306.

[1053] Popov, Yu.V.; Mkhov, V.M.; Tankabekyan, N.A. *Russ. J. Org. Chem.* ***2014***, *50*, 21.

[1054] Müller, E.; Huber-Emden, H.; Rundel, W. *Liebigs Ann. Chem.* ***1959***, *623*, 34.

[1055] Saegusa, T.; Ito, Y.; Kobayashi, S.; Hirota, K.; Shimizu, T. *Tetrahedron Lett.* ***1966***, 6131.

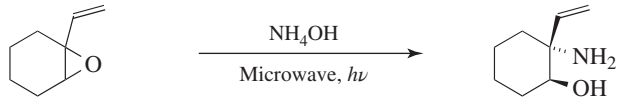
[1056] Azizi, N.; Saidi, M.R. *Org. Lett.* ***2005***, *7*, 3649.

[1057] Lu, P. *Tetrahedron* ***2010***, *66*, 2549.

[1058] See Charrada, B.; Hedhli, A.; Baklouti, A. *Tetrahedron Lett.* ***2000***, *41*, 7347.

[1059] Pastó, M.; Rodríguez, B.; Riera, A.; Pericàs, M.A. *Tetrahedron Lett.* ***2003***, *44*, 8369.

amines.[1060] With epoxides derived from terminal alkenes, the reaction with ammonia gives largely the primary amine, but secondary and tertiary amine products are possible from the appropriate epoxide. The reaction of **114** with ammonium hydroxide with microwave irradiation, for example, gave **115**.[1061]



114 **115**

Similar ring-opening occurs with alkyl and aromatic amines.[1062] For another way of accomplishing this conversion, see **10-39**. Ring opening has been accomplished with aniline on silica gel,[1063] and with aromatic amines in the presence of heteropoly acids in water.[1064] The reaction of α-nitroepoxides, cyanamide, and amines in propan-1-ol gave 2-aminoimidazole derivatives.[1065]

Aniline reacts with epoxides in the presence of aqueous β-cyclodextrin[1066] in 5 M $LiClO_4$ in ether,[1067] in fluoro-alcohol solvents,[1068] or using a V[1069] or a Cu catalyst.[1070] *N*-Boc-amine (H_2N-CO_2t-Bu) reacted with epoxides in the presence of a cobalt-salen catalyst to give the amido alcohol.[1071] Solvent-free reactions using a catalytic amount of $SnCl_4$ are known.[1072]

Enantioselective ring-opening reactions typically use a metal catalyst in the presence of a chiral additive. Amines react with epoxides using a catalytic amount of a Nb complex, in the presence of a BINOL derivative, to give chiral amino alcohols.[1073] Other metal-catalyzed ring-opening reactions of epoxides with amines have been reported,[1074] often with high enantioselectivity. Other enantioselective ring-opening reactions include V-salen

[1060] For a review, see Saddique, F.A.; Zahoor, A.F.; Faiz, S.; Naqvi, S.A.R.; Usman, M.; Ahmad, M. *Synth. Commun.* ***2016***, *46*, 831.

[1061] Lindström, U.M.; Olofsson, B.; Somfai, P. *Tetrahedron Lett.* ***1999***, *40*, 9273.

[1062] See Harrack, Y.; Pujol, M.D. *Tetrahedron Lett.* ***2002***, *43*, 819; Steiner, D.; Sethofer, S.G.; Goralski, C.T.; Singaram, B. *Tetrahedron: Asymmetry* ***2002***, *13*, 1477. For a reaction catalyzed by LiBr, see Chakraborti, A.K.; Rudrawar, S.; Kondaskar, A. *Eur. J. Org. Chem.* ***2004***, 3597.

[1063] Chakraborti, A.K.; Rudrawar, S.; Kondaskar, A. *Org. Biomol. Chem.* ***2004***, *2*, 1277.

[1064] Azizi, N.; Saidi, M.R. *Tetrahedron* ***2007***, *63*, 888.

[1065] Guo, X.; Chen, W.; Chen, B.; Huang, W.; Qi, W.; Zhang, G.; Yu, Y. *Org. Lett.* ***2015***, *17*, 1157.

[1066] Reddy, L.R.; Reddy, M.A.; Chanumathi, N.; Rao, K.R. *Synlett* ***2000***, 339.

[1067] Heydari, A.; Mehrdad, M.; Malecki, A.; Ahmadi, N. *Synthesis* ***2004***, 1563.

[1068] Das, U.; Crousse, B.; Kesavan, V.; Bonnet-Delpon, D.; Bégue, J.P. *J. Org. Chem.* ***2000***, *65*, 6749.

[1069] Sabitha, G.; Reddy, G.S.K.K.; Reddy, K.B.; Yadav, J.S. *Synthesis* ***2003***, 2298.

[1070] Kamal, A.; Ramu, R.; Azhar, M.A.; Khanna, G.B.R. *Tetrahedron Lett.* ***2005***, *46*, 2675.

[1071] Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Mechiorre, P.; Sambri, L. *Org. Lett.* ***2004***, *6*, 3973.

[1072] Zhao, P.-Q.; Xu, L.-W.; Xia, C.-G. *Synlett* ***2004***, 846.

[1073] Arai, K.; Lucarini, S.; Salter, M.M.; Ohta, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* ***2007***, *129*, 8103; Arai, K.; Salter, K.M.; Yamashita, Y.; Kobayashi, S. *Angew. Chem. Int. Ed.* ***2007***, *46*, 955.

[1074] Examples of catalysts include **Al**: Robinson, M.W.C.; Timms, D.A.; Williams, S.M.; Graham, A.E. *Tetrahedron Lett.* ***2007***, *48*, 6249. **Bi**: Ollevier, T.; Nadeau, E. *Tetrahedron Lett.* ***2008***, *49*, 1546. **Ce**: Reddy, L.R.; Reddy, M.A.; Bhanumathi, N.; Rao, K.R. *Synthesis* ***2001***, 831. **Co**: Sundararajan, G.; Viyayakrishna, K.; Varghese, B. *Tetrahedron Lett.* ***2004***, *45*, 8253. **Er**: Procopio, A.; Gaspari, M.; Nardi, M.; Oliverio, M.; Rosati, O. *Tetrahedron Lett.* ***2008***, *49*, 2289. **Fe**: Yadav, G.D.; Chauhan, M.S.; Singh, S. *Synthesis* ***2014***, *46*, 629; Plancq, B.; Ollevier, T. *Chem. Commun.* ***2012***, *48*, 3806. **Ga**: Wang, C.; Yamamoto, H. *Angew. Chem. Int. Ed.* ***2015***, *54*, 8760. **In**: Rodríguez, J.R.; Navarro, A. *Tetrahedron Lett.* ***2004***, *45*, 7495. **Mg**: Jafari, A.A.; Moradgholi *Synth. Commun.* ***2010–2011***, *41*, 594. **Ni**: Wang, C.; Yamamoto, H. *J. Am. Chem. Soc.* ***2015***, *137*, 4308. **Sc**: Azoulay, S.; Manabe,

catalyzed[1075] or Mg-BINOL complex[1076] reactions. The ring opening of enantiopure epoxides with sodium azide in hot water led to azido alcohols.[1077] Halohydrin dehalogenase (*Arthrobacter* sp. AD2) catalyzed the reaction of NaN_3 with epoxides with high regioselectivity and low to moderate enantioselectivity, but the reaction with aromatic epoxides catalyzed by HheA-N178A proceeded with complete enantioselectivity.[1078] Chiral sulfonamides were used as an organocatalyst for the reaction of *meso* epoxides with anilines to give chiral β-amino alcohols.[1079]

Amide bases react differently with epoxides. Lithium 2,2,6,6-tetramethylpiperidide (LTMP), for example, reacted with epoxides, but the product was the corresponding enamine.[1080] In the latter reaction, an initially formed lithio-epoxide reacts with another equivalent of lithium amide to give an enamine, and, if desired, subsequent hydrolysis will liberate an aldehyde.[1081]

An indirect method for generating an amino alcohol is to open an epoxide with azide to give the azido alcohol,[1082] and subsequent reduction (**19-54**) gives the amine group.[1083] The cerium ammonium nitrate-catalyzed reaction of epoxides and sodium azide, for example, gave the azido alcohol with selectivity for the azide group on the more substituted position.[1084] Cerium chloride has also been used, giving the azide on the less substituted carbon.[1085] Under *Mitsunobu conditions* (**10-17**), epoxides are converted to 1,2-diazides with HN_3.[1086] The reaction of trimethylsilyl azide and an epoxide was reported using an ionic solvent.[1087] Vinyl epoxides reacted with $TMSN_3/BF_3$ to give the corresponding azido alcohol.[1088] It is also noted that sodium nitrite ($NaNO_2$) reacts with epoxides in the presence of $MgSO_4$ to give the nitro alcohol.[1089] The nitro group can also be reduced to give the amine (**19-45**).[1090]

Episulfides (thiiranes), which can be generated *in situ* in various ways, react similarly to give β-amino thiols,[1091] and aziridines react with amines to give 1,2-diamines (**10-37**).

K.; Kobayashi, S. *Org. Lett.* ***2005***, *7*, 4593; **Sm**: Carrée, F.; Gil, R.; Collin, J. *Org. Lett.* ***2005***, *7*, 1023. **Sn**: Sekar, G.; Singh, V.K. *J. Org. Chem.* ***1999***, *64*, 287. **W**: Wang, C.; Yamamoto, H. *Angew. Chem. Int. Ed.* ***2014***, *53*, 13920. **Zn**: Bonollo, S.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synlett* ***2008***, 1574; Pujala, B.; Rana, S.; Chakraborti, A.K. *J. Org. Chem.* ***2011***, *76*, 8768. **Zr**: Shinde, S.S.; Said, M.S.; Surwase, T.B. Kumar, P. *Tetrahedron Lett.* ***2015***, *56*, 5916.

[1075] Sun, J.; Dai, Z.; Yang, M.; Pan, X.; Zhu, C. *Synthesis* ***2008***, 2100.

[1076] Bao, H.; Wu, J.; Li, H.; Wang, Z.; You; T.; Ding, K. *Eur. J. Org. Chem.* ***2010***, 6722.

[1077] Wang, H.-Y.; Huang, K.; De Jesús, M.; Espinosa, S.; Piñero-Santiago, L.E.; Barnes, C.L.; Ortiz-Marciales, M. *Tetrahedron: Asymmetry* ***2016***, *27*, 91.

[1078] Mikleušević, A.; Primožič, I.; Hrenar, T.; Salopek-Sondi, B.; Tang, L.; Majerić Elenkov, M. *Tetrahedron: Asymmetry* ***2016***, *27*, 930.

[1079] Kumar, M.; Kureshy, R.I.; Saravanan, S.; Verma, S.; Jakhar, A.; Khan, N.H.; Abdi, S.R.; Bajaj, H.C. *Org. Lett.* ***2014***, *16*, 2798.

[1080] Hodgson, D.M.; Bray, C.D.; Kindon, N.D. *J. Am. Chem. Soc.* ***2004***, *126*, 6870.

[1081] Yanagisawa, A.; Yasue, K.; Yamamoto, H. *J. Chem. Soc., Chem. Commun.* ***1994***, 2103.

[1082] Kazemi, F.; Kiasat, A.R.; Ebrahimi, S. *Synth. Commun.* ***2003***, *33*, 999. For a reaction done under phase-transfer conditions, see Tamami, B.; Mahdavi, H. *Tetrahedron Lett.* ***2001***, *42*, 8721.

[1083] Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, p. 815.

[1084] Iranpoor, N.; Kazemi, F. *Synth. Commun.* ***1999***, *29*, 561.

[1085] Sabitha, G.; Babu, R.S.; Rajkumar, M.; Yadav, J.S. *Org. Lett.* ***2002***, *4*, 343.

[1086] Göksu, S.; Socen, H.; Sütbeyaz, Y. *Synthesis* ***2002***, 2373.

[1087] Song, C.E.; Oh, C.R.; Roh, E.J.; Choo, D.J. *Chem. Commun.* ***2000***, 1743.

[1088] Righi, G.; Manni, L.S.; Bovicelli, P.; Pelagalli, R. *Tetrahedron Lett.* ***2011***, *52*, 3895.

[1089] Kalita, B.; Barua, N.C.; Bezbarua, M.; Bez, G. *Synlett* ***2001***, 1411.

[1090] Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, **1999**, p. 821.

[1091] Dong, Q.; Fang, X.; Schroeder, J.D.; Garvey, D.S. *Synthesis* ***1999***, 1106.

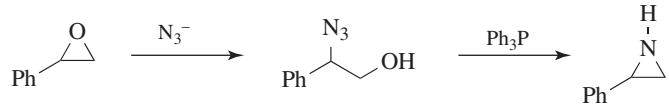
Triphenylphosphine similarly reacts with epoxides to give an intermediate that undergoes elimination to give alkenes (see the *Wittig reaction*, **16-44**). Thiiranes react regioselectively with ammonia and amines.[1092]

OS **X**, 29. See OS **VI**, 652 for a related reaction.

10-35 Formation of Aziridines from Epoxides

It is possible to prepare aziridines, which are synthetically important molecules, directly from the corresponding epoxide. Reaction of $Ph_3P{=}NPh$ with an epoxide in the presence of $ZnCl_2$ gives the *N*-phenyl aziridine.[1093] Guanidines have also been used to prepare aziridines from epoxides.[1094] Tosylamines react with epoxides to give the *N*-tosyl aziridine.[1095] Various methods are available to convert an aminomethyl epoxide to a hydroxymethyl aziridine.[1096]

Ring-opening reactions of epoxides with nitrogen nucleophiles were discussed in **10-34**. However, it is appropriate to discuss epoxide-opening reactions involving azides. Epoxides react with NaN_3, under various conditions and media, including in ionic liquids.[1097] Other reagents include $TMSN_3$ (TMS = trimethylsilyl) and SmI_2[1098] or $(i\text{-Bu})_2AlHN_3Li$[1099] to give β-azido alcohols, which are easily converted to aziridines.[1100]



It is noted that cyclodehydration of β-hydroxy sulfonamides with R_FSO_2F and NEt_3 gave the corresponding aziridine.[1101]

10-36 Ring Opening of Oxetanes With Nucleophiles

[1092] Li, X.; Xu, J. *Tetrahedron.* ***2011***, *67*, 1681.
[1093] Kühnau, D.; Thomsen, I.; Jørgensen, K.A. *J. Chem. Soc., Perkin Trans. 1*, ***1996***, 1167.
[1094] Tsuchiya, Y.; Kumamoto, T.; Ishikawa, T. *J. Org. Chem.* ***2004***, *69*, 8504.
[1095] Albanese, D.; Landini, D.; Penso, M.; Petricci, S. *Tetrahedron* ***1999***, *55*, 6387.
[1096] See Moulines, J.; Bats, J.-P.; Hautefaye, P.; Nuhrich, A.; Lamidey, A.-M. *Tetrahedron Lett.* ***1993***, *34*, 2315.
[1097] Yadav, J.S.; Reddy, B.V.S.; Jyothirmai, B.; Murty, M.S.R. *Tetrahedron Lett.* ***2005***, *46*, 6559.
[1098] van de Weghe, P.; Collin, J. *Tetrahedron Lett.* ***1995***, *36*, 1649.
[1099] Youn, Y.S.; Cho, I.S.; Chung, B.Y. *Tetrahedron Lett.* ***1998***, *39*, 4337.
[1100] See Ittah, Y.; Sasson, Y.; Shahak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* ***1978***, *43*, 4271. See Pöchlauer, P.; Müller, E.P.; Peringer, P. *Helv. Chim. Acta* ***1984***, *67*, 1238.
[1101] Yan, Z.; Guan, C.; Yu, Z.; Tian, W. *Tetrahedron Lett.* ***2013***, *54*, 5788.

Oxetanes are significantly less reactive with nucleophiles due to diminished ring strain.[1102] Under certain conditions, however, amines can open oxetanes to give amino alcohols. *tert*-Butyl amine reacts with oxetanes in the presence of $Yb(OTf)_3$, for example, to give 3-hydroxy amines.[1103] Lithium tetrafluoroborate has also been used for this purpose.[1104]

Hydroxynitriles are generated by reaction of epoxides with NaCN in aqueous media, in the presence of a phase-transfer catalyst, SiO_2-PEG-ImBr (silica-bound 3-{2-[poly(ethylene glycol)]ethyl}-1-methyl-1*H*-imidazol-3-ium bromide).[1105]

10-37 Ring Opening of Aziridines With Nucleophiles

Just as epoxides can be opened by amines to give hydroxy amines, aziridines can be opened to give diamines.[1106] Amines react with *N*-tosyl aziridines, in the presence of various catalysts or additives, to give the corresponding diamine derivative.[1107] *N*-Tosyl aziridines react with aniline derivatives under aqueous conditions.[1108] *N*-Tosyl aziridines reacted with alkylzinc reagents in the presence of a nickel catalyst.[1109] Tosyl aziridines react with azide ion to generate azido tosylamines,[1110] and a clay-catalyzed variation[1111] has been reported. Reduction of the azide (**19-54**) gave the diamine.

Allylic amines are prepared by the reaction of aziridine-2-alcohols with PPh_3/imidazole.[1112] *N*-Aryl or *N*-alkyl aziridines react with amines in the presence of T-Binolate,[1113] $Sn(OTf)_2$,[1114] or $B(C_6F_5)_3$[1115] to give the diamine. With bicyclic

[1102] For a review, see Ahmad, S.; Yousaf, M.; Mansha, A.; Rasool, N.; Zahoor, A.F.; Hafeez, F.; Ali Rizvi, S.M. *Synth. Commun.* ***2016***, *46*, 1397.

[1103] Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* ***1994***, *35*, 7089.

[1104] Chini, M.; Crotti, P.; Favero, L.; Macchia, F. *Tetrahedron Lett.* ***1994***, *35*, 761.

[1105] Kiasat, A.-R.; Ayashi, N.; Fallah-Mehrjardi, M. *Helv. Chim. Acta* ***2013***, *96*, 275.

[1106] See Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, ***1969***, pp. 262–268. For the influence of DMSO on this reaction, see Isobe, T.; Oriyama, T. *Tetrahedron Lett.* ***2016***, *57*, 2849. See also, Scheuermann, J.E.W.; Ilyashenko, G.; Griffiths, D.V.; Watkinson, M. *Tetrahedron: Asymmetry* ***2002***, *13*, 269. For an iron-catalyzed reaction, see Marti, A.; Richter, L.; Schneider, C. *Synlett* ***2011***, *22*, 2513. For a Ti-BINOL catalyst, see Peruncheralathan, S.; Aurich, S.; Teller, H.; Schneider, C. *Org. Biomol. Chem.* ***2013***, *11*, 2793.

[1107] Examples include aqueous media with **β-cyclodextrin**: Reddy, M.A.; Reddy, L.R.; Bhanamathi, N.; Rao, K.R. *Chem. Lett.* ***2001***, 246. **BiCl3**: Swamy, N.R.; Venkateswarlu, Y. *Synth. Commun.* ***2003***, *33*, 547. **$InBr_3$**: Yadav, J.S.; Reddy, B.V.S.; Rao, K.; Raj, K.S.; Prasad, A.R. *Synthesis* ***2002***, 1061. **$InCl_3$**: Yadav, J.S.; Reddy, B.V.S.; Abraham, S.; Sabitha, G. *Tetrahedron Lett.* ***2002***, *43*, 1565; **$LiClO_4$**: Yadav, J.S.; Reddy, B.V.S.; Jyothirmai, B.; Murty, M.S.R. *Synlett* ***2002***, 53; Yadav, J.S.; Reddy, B.V.S.; Parimala, G.; Reddy, P.V. *Synthesis* ***2002***, 2383. **PBu_3**: Fan, R.-H.; Hou, X.-L. *J. Org. Chem.* ***2003***, *68*, 726. **$TaCl_5$/SiO_2**: Chandrasekhar, S.; Prakash, S.J.; Shyamsunder, T.; Ramachandar, T. *Synth. Commun.* ***2004***, *34*, 3865. **$Yb(OTf)_3$**: Meguro, M.; Yamamoto, Y. *Heterocycles* ***1996***, *43*, 2473.

[1108] Zhu, M.; Moasser, B. *Tetrahedron Lett.* ***2012***, *53*, 2289.

[1109] Jensen, K.L.; Standley, E.A.; Jamison, T.F. *J. Am. Chem. Soc.* ***2014***, *136*, 11145.

[1110] Bisai, A.; Pandey, G.; Pandey, M.K.; Singh, V.K. *Tetrahedron Lett.* ***2003***, *44*, 5839.

[1111] Nadir, U.K.; Singh, A. *Tetrahedron Lett.* ***2005***, *46*, 2083.

[1112] Chavan, S.P.; Khairnar, L.B.; Chavan, P.N. *Tetrahedron Lett.* ***2014***, *55*, 5905.

[1113] Peruncheralathan, S.; Teller, H.; Schneider, C. *Angew. Chem. Int. Ed.* ***2009***, *48*, 4849.

[1114] Sekar, G.; Singh, V.K. *J. Org. Chem.* ***1999***, *64*, 2537.

[1115] Watson, I.D.G.; Yudin, A.K. *J. Org. Chem.* ***2003***, *68*, 5160.

aziridines, the major product is usually the *trans*-diamine. Activated aziridines undergo regioselective ring opening with organoalanes.[1116] The reaction of $LiNTf_2$ and an amine, in the presence of an *N*-alkyl aziridine, gives the diamine.[1117] Silylated nucleophiles open *N*-tosyl aziridines in the presence of a polystyrene-supported TBD catalyst (TBD = 1,5,7-triazabicyclo[4,4,0]dec-5-ene polystyrene).[1118]

Treatment of benzoyl fluoride and an alcohol with DBN generates an amine–HF that acts as a latent HF source, leading to hydrofluorination of aziridines to give β-fluoroamines.[1119] Under flow conditions (Sec. 7-D), *N*-sulfonyl aziridines were prepared from 1,2-amino alcohols, and the aziridines are further ring opened with oxygen, carbon, and halide nucleophiles.[1120] The enantioselective desymmetrization of aziridines with aromatic thiols has been reported.[1121]

10-38 Amination of Alkanes

$$R_3CH + NCl_3 \xrightarrow[0-10\ ^\circ C]{AlCl_3} R_3CNH_2$$

Alkanes, arylalkanes, and cycloalkanes can be aminated, at tertiary positions only, by treatment with trichloroamine and aluminum chloride at 0–10 °C.[1122] For example, *p*-$MeC_6H_4CHMe_2$ gives *p*-$MeC_6H_4CMe_2NH_2$, methylcyclopentane gives 1-amino-1-methylcyclopentane, and adamantane gives 1-aminoadamantane, all in good yields. A Ag-catalyzed reaction has also been reported.[1123] There are not many other methods for the preparation of *tert*-alkylamines. The mechanism has been rationalized as an S_N1 process with H^- as the leaving group.[1122] It is noted than under photochemical conditions, ammonia opens cyclopropane derivatives to give the corresponding alkyl amine.[1124] See also **12-12**.

A four-coordinate iron(III) complex was used to catalyze the reaction of toluene with alkyl azides to give the corresponding benzylic amine compound, or the reaction with styrene to give the aziridine (**15-50**).[1125]

OS **V**, 35.

10-39 Formation of Isonitriles (Isocyanides)

$$CHCl_3 + RNH_2 \xrightarrow{-OH} R - \overset{+}{N}\equiv C^-$$

There are several methods available for the preparation of isonitriles, also known as isocyanides.[1126] Reaction with chloroform under basic conditions is a common test for primary

[1116] Bertolini, F.; Woodward, S.; Crotti, S.; Pineschi, M. *Tetrahedron Lett.* ***2009***, *50*, 4515.
[1117] Cossy, J.; Bellosta, V.; Alauze, V.; Desmurs, J.-R. *Synthesis* ***2002***, 2211.
[1118] Matsukawa, S.; Harada, T.; Yasuda, S. *Org. Biomol. Chem.* ***2012***, *10*, 4886. Matsukawa, S.; Takahashi, H.; Harada, T. *Synth. Commun.* ***2013***, *43*, 406.
[1119] Kalow, J.A.; Schmitt, D.E.; Doyle, A.G. *J. Org. Chem.* ***2012***, *77*, 4177.
[1120] Hsueh, N.; Clarkson, G.J.; Shipman, M. *Org. Lett.* ***2015***, *17*, 3632.
[1121] Zhang, J.; Cao, D.; Wang, H.; Zhao, G.; Shang, Y. *Tetrahedron* ***2015***, *71*, 1785.
[1122] Wnuk, T.A.; Chaudhary, S.S.; Kovacic, P. *J. Am. Chem. Soc.* ***1976***, *98*, 5678, and references cited therein.
[1123] Li, Z.; Capretto, D.A.; Rahaman, R.; He, C. *Angew. Chem. Int. Ed.* ***2007***, *46*, 5184.
[1124] Yasuda, M.; Kojima, R.; Tsutsui, H.; Utsunomiya, D.; Ishii, K.; Jinnouchi, K.; Shiragami, T.; Yamashita, T. *J. Org. Chem.* ***2003***, *68*, 7618.
[1125] King, E.R.; Hennessy, E.T.; Betley, T.A. *J. Am. Chem. Soc.* ***2011***, *133*, 4917.
[1126] For a method for the preparation of benzyl isocyanides, see Kitano, Y.; Manoda, T.; Miura, T.; Chiba, K.; Tada, M. *Synthesis* ***2006***, 405. For review, see Bode, M.L.; Gravestock, D.; Rousseau, A.L. *Org. Prep. Proceed. Int.* ***2016***, *48*, 89; Moderhack, D. *Tetrahedron* ***2012***, *68*, 5949.

amines, both aliphatic and aromatic, since isonitriles have very strong bad odors. The reaction probably proceeds by an S_N1cB mechanism with dichlorocarbene as an intermediate. Yields are generally not high,[1127] but an improved procedure has been reported.[1128] When secondary amines are involved, the dichloroamino adduct cannot lose 2 molar equivalents of HCl, so it is hydrolyzed to an *N*,*N*-disubstituted formamide.[1129]

The reaction of *N*-substituted formamides with chlorophosphate compounds and tertiary amines gave isocyanides.[1130] Isonitriles have been prepared in one step from a primary amine, chloroform, sodium hydride, and 15-crown-5 ether as a phase-transfer catalyst, in benzene.[1131] Isonitriles have also been prepared from alcohols by treatment with (i) TSCN and MsOH, (ii) 10 equivalents of NEt_3, and then (iii) 3 equivalents of pyridine.[1132] Isonitriles have been formed from *N*-substituted formamides using Ph_3P and I_2.[1133]

A completely different way of preparing isocyanides involves the reaction of epoxides or oxetanes with trimethylsilyl cyanide and zinc iodide to give the isocyanide.[1134] The products can be hydrolyzed to protected hydroxy amines. The metal-mediated and metal-catalyzed reactions of isonitriles have been reviewed.[1135] The addition of organolithium reagents to nitriles, followed by reaction with isopropylformate and dehydration with phosphoryl chloride, gave alkene isocyanides.[1136]

OS **VI**, 232.

B. Attack by NHCOR

10-40 *N*-Alkylation or *N*-Arylation of Amides and Imides

$$RX + {}^{-}NHCOR' \longrightarrow RNHCOR'$$
$$ArX + {}^{-}NHCOR' \longrightarrow ArNHCOR'$$

Amides are very weak nucleophiles,[1137] far too weak to attack alkyl halides, so they must first be converted to their conjugate bases, the anion. By this method, unsubstituted amides can be converted to *N*-substituted amides, or *N*-substituted amides to *N*,*N*-disubstituted amides.[1138] Esters of sulfuric or sulfonic acids can also be substrates. Tertiary substrates give elimination and *O*-alkylation is at times a side reaction.[1139] Both amides and

[1127] See Periasamy, M.P.; Walborsky, H.M. *Org. Prep. Proced. Int.* ***1979***, *11*, 293.
[1128] Weber, W.P.; Gokel, G.W. *Tetrahedron Lett.* ***1972***, 1637; Weber, W.P.; Gokel, G.W.; Ugi, I. *Angew. Chem. Int. Ed.* ***1972***, *11*, 530.
[1129] Saunders, M.; Murray, R.W. *Tetrahedron* ***1959***, *6*, 88; Frankel, M.B.; Feuer, H.; Bank, J. *Tetrahedron Lett.* ***1959***, no. 7, 5.
[1130] Kobayashi, G.; Saito, T.; Kitano, Y. *Synthesis* ***2011***, *43*, 3225.
[1131] Bardsley, K.; Hagigeorgiou, M.; Lengyel, I.; Cesare, V. *Synth. Commun.* ***2013***, *43*, 1727.
[1132] Okada, I.; Kitano, Y. *Synthesis* ***2011***, *43*, 3997.
[1133] Wang, X.; Wang, Q.-G.; Luo, Q.-L. *Synthesis* ***2015***, *47*, 49.
[1134] Gassman, P.G.; Haberman, L.M. *Tetrahedron Lett.* ***1985***, *26*, 4971, and references cited therein.
[1135] Boyarskiy, V.P.; Bokach, N.A.; Luzyanin, K.V.; Kukushkin, V.Yu. *Chem. Rev.* ***2015***, *115*, 2698.
[1136] Li, Y.; Fleming, F.F. *Angew. Chem. Int. Ed.* ***2016***, *55*, 14770.
[1137] Brace, N.O. *J. Org. Chem.* ***1993***, *58*, 1804.
[1138] For procedures, see Yamawaki, J.; Ando, T.; Hanafusa, T. *Chem. Lett.* ***1981***, 1143; Sukata, K. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 838.
[1139] See Challis, B.C.; Challis, J.A., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 734–754.

sulfonamides have been alkylated under phase-transfer conditions.[1140] Metal-catalyzed amidations are known, including an Ir(I)-catalyzed allylic amidation.[1141] Amides react with aryl iodides using a catalytic amount of Cu_2O and tetrabutylammonium bromide, with excess K_3PO_4, in heated water.[1142]

The *N*-alkylation of primary amides with bis(trialkylsilyl) peroxides using a copper catalyst has been reported, presumably proceeding via an aryne (**13.D**).[1143] The reaction of secondary amines and primary alcohols with KO*t*-Bu and a Ru catalyst gave the tertiary amine.[1144] Under photolytic conditions, with a CuI catalyst and with 2 equivalents of *t*-BuOLi, alkyl and aryl amides react with 2 equivalents of alkyl bromides and iodides to give the *N*-alkyl amide.[1145] β-Lactams were prepared from *N*,*N*-dibenzyl β-chloroamides using a Pd catalyst, where debenzylation allowed an intramolecular substitution reaction to give the β-lactam.[1146] *N*-Methoxyamides undergo an insertion reaction at a benzylic position, with an iodoarene and mcpba as an oxidant, giving the corresponding lactam.[1147] Internal *N*-alkylation has been used to prepare the highly strained, three-membered ring α-lactams.[1148]

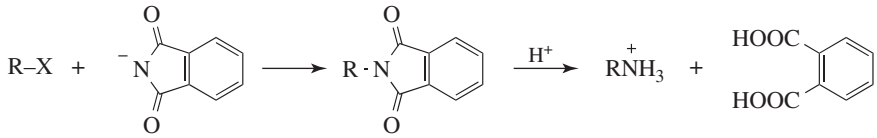
The reaction of a primary amide and benzaldehyde, in the presence of a silane and trifluoroacetic acid, leads to the corresponding *N*-benzyl amide.[1149] This transformation is a reductive alkylation (**16-15**). *N*-Alkynyl amides have been prepared by the Cu-catalyzed reaction of 1-bromoalkynes and secondary amides.[1150] Ynamides have been prepared by the coupling of terminal alkynes with amides, using $Cu(OH)_2$ with air as the oxidant.[1151] 1-Haloalkynes are typically prepared by base-induced elimination of 1,1-dihaloalkenes[1152] or by direct halogenation of an alkyne with sodium or potassium hypohalite, prepared by reaction of the appropriate base with the halogen.[1153]

Lactams can be alkylated using similar procedures. Ethyl pyroglutamate (5-carboethoxy 2-pyrrolidinone) and related lactams were converted to *N*-alkyl derivatives via treatment with NaH (short contact time) followed by addition of the halide.[1154] Other pyrrolidin-2-one derivatives can be alkylated using a similar procedure.[1155] *N*-Cyclopropyl lactams are

[1140] Salvatore, R.N.; Shin, S.I.; Flanders, V.L.; Jung, K.w. *Tetrahedron Lett.* ***2001***, *42*, 1799.
[1141] Singh, O.V.; Han, H. *Tetrahedron Lett.* ***2007***, *48*, 7094.
[1142] Yong, F.F.; Teo, Y.-C.; Chua, G.-L.; Lim, G.S.; Lin, Y. *Tetrahedron Lett.* ***2011***, *52*, 1160.
[1143] Sakamoto, R.; Sakurai, S.; Maruoka, K. *Chem. Commun.* ***2017***, *53*, 6484. See Haber, J.C.; Lynch, M.A.; Spring, S.L.; Pechulis, A.D.; Raker, J.; Wang, Y. *Tetrahedron Lett.* ***2011***, *52*, 5847.
[1144] Enyong, A.B.; Moasser, B. *J. Org. Chem.* ***2014***, *79*, 7553.
[1145] Do, H.-Q.; Bachman, S.; Bissember, A.C.; Peters, J.C.; Fu, G.C. *J. Am. Chem. Soc.* ***2014***, *136*, 2162.
[1146] Pedroni, J.; Boghi, M.; Saget, T.; Cramer, N. *Angew. Chem. Int. Ed.* ***2014***, *53*, 9064.
[1147] Zhu, C.; Liang, Y.; Hong, X.; Sun, H.; Sun, W.-Y.; Houk, K.N.; Shi, Z. *J. Am. Chem. Soc.* ***2015***, *137*, 7564.
[1148] See Quast, H.; Leybach, H. *Chem. Ber.* ***1991***, *124*, 849. For a review of α-lactams, see Lengyel, I.; Sheehan, J.C. *Angew. Chem. Int. Ed.* ***1968***, *7*, 25.
[1149] Dubé, D.; Scholte, A.A. *Tetrahedron Lett.* ***1999***, *40*, 2295.
[1150] Zhang, Y.; Hsung, R.P.; Tracey, M.R.; Kurtz, K.C.M.; Vera, E.L. *Org. Lett.* ***2004***, *6*, 1151.
[1151] Jin, X.; Yamaguchi, K.; Mizuno, N. *Chem. Commun.* ***2012***, *48*, 4974.
[1152] For an example involving Br, see Besstmann, H.-J.; Frey, H. *Liebigs Ann. Chem.* ***1980***, *12*, 2061.
[1153] For examples with hypobromite, see Mozuraitis, R.; Buda, V.; Liblikas, I.; Unelius, C.R.; Borg-Karlson, A.-K. *J. Chem. Ecol.* ***2002***, *28*, 1191.
[1154] Simandan, T.; Smith, M.B. *Synth. Commun.* ***1996***, *26*, 1827.
[1155] Liu, H.; Ko, S.-B.; Josien, H.; Curran, D.P. *Tetrahedron Lett.* ***1995***, *36*, 8917.

prepared using a Bi reagent in the presence of cupric acetate.[1156] Chiral tetrahydroisoquinolines have been prepared by the intramolecular displacement of carbonates by a trifluoroacetamide unit, catalyzed by an Ir complex.[1157]

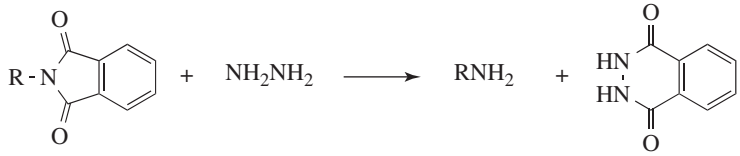
The *N*-arylation of 2-pyridones using diaryliodonium salts with a CuCl catalyst has been reported.[1158] Secondary amines undergo *N*-arylation with iodonium salts, which function as aryne precursors (Sec. 13.D).[1159] Aryl chlorides react with a zinc amide (ArNHZnCl) in the presence of a $ZnCl_2$•TMEDA/2 PhMgBr, catalyzed by $Fe(acac)_3$/1,2-dichloroisobutane.[1160] Oxindoles have been prepared from 2-(2-bromoaryl)acetamides using a Cu_2O/benzene-1,2-diamine in *t*-butanol at 100 °C.[1161] Aryltrimethylgermanes have been used for the Pd-catalyzed *N*-arylation of amides and of amines.[1162] The Ni-catalyzed *N*-arylation of primary amides and lactams has been reported, using heteroaryl electrophiles.[1163] A β-lactam synthesis has been reported from aryl amides with a substituent that contains at least one hydrogen atom at the β position, using a CuI-mediated reaction with O_2 and sodium carbonate.[1164] *N*-Aryl lactams can be prepared using Ph_3Bi and $Cu(OAc)_2$.[1165] *N*-Arylation of sulfonamides has been reported using a Pd catalyst,[1166] and this method has been applied to the intramolecular displacement of arylation leading to bicyclic lactams.[1167] A related Pd-catalyzed vinylation of lactams was repeated using vinyl ethers as a substrate.[1168] Oxazolidin-2-ones (a cyclic carbamate) can be *N*-alkylated using an alkyl halide with KF/Al_2O_3.[1169]



The *Gabriel synthesis*[1170] for converting halides to primary amines is based on this reaction. The halide is treated with potassium phthalimide and the resulting product hydrolyzed (**16-59**). It is obvious that the primary amines formed in this reaction will be uncontaminated by secondary or tertiary amines (unlike **10-30**). The reaction is usually rather slow, but the rate can be conveniently increased by the use of a dipolar aprotic solvent such as

[1156] Gagnon, A.; St-Onge, M.; Little, K.; Duplessis, M.; Barabé, F. *J. Am. Chem. Soc.* ***2007***, *129*, 44.
[1157] Teichert, J.F.; Fañanás-Mastral, M.; Feringa, B.L. *Angew. Chem. Int. Ed.* ***2011***, *50*, 688.
[1158] Jung, S.-H.; Sung, D.-B.; Park, C.-H.; Kim, W.-S. *J. Org. Chem.* ***2016***, *81*, 7717. See Hao, X.; Xu, Z.; Lu, H.; Dai, X.; Yang, T.; Lin, X.; Ren, F. *Org. Lett.* ***2015***, *17*, 3382.
[1159] Wang, M.; Huang, Z. *Org. Biomol. Chem.* ***2016***, *14*, 10185.
[1160] Nakamura, Y.; Ilies L.; Nakamura, E. *Org. Lett.* ***2011***, *13*, 5998.
[1161] Jhan, Y.-H.; Kang, T.-W.; Hsieh, J.-C. *Tetrahedron Lett.* ***2013***, *54*, 1155.
[1162] Zhang, Q.; Liu, C.; Shi, J.; Xu, Q.; Jin, L.; Zhao, C.; Zhang, T. *Synlett* ***2016***, *27*, 1945.
[1163] Lavoie, C.M.; MacQueen, P.M.; Stradiotto, M. *Chem. Eur. J.* ***2016***, *22*, 18752.
[1164] Wang, C.; Yang, Y.; Qin, D.; He, Z.; You, J. *J. Org. Chem.* ***2015***, *80*, 8424.
[1165] Chan, D.M.T. *Tetrahedron Lett.* ***1996***, *37*, 9013.
[1166] Ikawa, T.; Barder, T.E.; Biscoe, M.R.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2007***, *129*, 13001.
[1167] Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* ***2008***, *130*, 14058. See also Poondra, R.R.; Turner, N.J. *Org. Lett.* ***2005***, *7*, 863.
[1168] Brice, J.L.; Meerdink, J.E.; Stahl, S.S. *Org. Lett.* ***2004***, *6*, 1845.
[1169] Blass, B.E.; Drowns, M.; Harris, C.L.; Liu, S.; Portlock, D.E. *Tetrahedron Lett.* ***1999***, *40*, 6545.
[1170] For a review, see Gibson, M.S.; Bradshaw, R.W. *Angew. Chem. Int. Ed.* ***1968***, *7*, 919.

DMF[1171] or with a crown ether.[1172] Hydrolysis of the phthalimide, whether acid- or base-catalyzed (acid catalysis is used far more frequently), is also usually very slow, and better procedures are generally used. A common one is the *Ing-Manske procedure*,[1173] in which the phthalimide is heated with hydrazine in an exchange reaction.[1174]



Hydrazide

However, other methods have been introduced, using Na_2S in aq. THF or acetone,[1175] and 40% aqueous methylamine.[1176] The palladium-catalyzed alkylation of thioamides has been reported.[1177]

Salts of sulfonamides ($ArSO_2NH^-$) can be used to attack alkyl halides to prepare *N*-alkyl sulfonamides ($ArSO_2NHR$) that can be further alkylated to $ArSO_2NRR'$. Hydrolysis of the latter is a good method for the preparation of secondary amines. *N*-Arylation of sulfonimidamides has been reported using a Cu catalyst.[1178] Diaryliodonium salts with a Cu catalyst have also been used for the *N*-arylation of *N*-aryl sulfonamides.[1179] The Cu-catalyzed *N*-arylation of sulfonamides has been reported.[1180]

OS **I**, 119, 203, 271; **II**, 25, 83, 208; **III**, 151; **IV**, 810; **V**, 1064; **VI**, 951; **VII**, 501.

C. Other Nitrogen Nucleophiles

10-41 Formation of Nitro Compounds[1181]

$$RX + NO_2^- \longrightarrow RNO_2$$

Sodium nitrite ($NaNO_2$) can be used to prepare nitro compounds from primary or secondary alkyl bromides or iodides, but the method is of limited scope. Silver nitrite ($AgNO_2$) gives nitro compounds only when RX is a primary bromide or iodide.[1182] Nitrite esters are an important side product in all these cases (**16-22**) and become the major product (by an S_N1 mechanism) when secondary or tertiary halides are treated with silver nitrite. Alkyl nitro compounds can be prepared from the alkyl halide via the corresponding azide, by treatment

[1171] See Sheehan, J.C.; Bolhofer, W.A. *J. Am. Chem. Soc.* ***1950***, *72*, 2786. See also, Landini, D.; Rolla, F. *Synthesis* ***1976***, 389.
[1172] Soai, K.; Ookawa, A.; Kato, K. *Bull. Chem. Soc. Jpn.* ***1982***, *55*, 1671.
[1173] Ing, H.R.; Manske, R.H.F. *J. Chem. Soc.* ***1926***, 2348.
[1174] See Khan, M.N. *J. Org. Chem.* ***1995***, *60*, 4536 for the kinetics of hydrazinolysis of phthalimides.
[1175] Kukolja, S.; Lammert, S.R. *J. Am. Chem. Soc.* ***1975***, *97*, 5582.
[1176] Wolfe, S.; Hasan, S.K. *Can. J. Chem.* ***1970***, *48*, 3572.
[1177] Rong, B.; Ding, L.; Yu, H.; Yang, Q.; Liu, X.; Xu, D.; Li, G.; Zhao, B. *Tetrahedron Lett.* ***2013***, *54*, 6501.
[1178] Battula, S.R.K.; Subbareddy, G.V.; Chakravarthy, I.E. *Tetrahedron Lett.* ***2014***, *55*, 518.
[1179] Geng, X.; Mao, S.; Chen, L.; Yu, J.; Han, J.; Hua, J.; Wang, L. *Tetrahedron Lett.* ***2014***, *55*, 3856.
[1180] Teo, Y.-C.; Yong, F.-F. *Synlett* ***2011***, *22*, 837.
[1181] See Larson, H.O. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, ***1969***, pp. 325–339; Kornblum, N. *Org. React.* ***1962***, *12*, 101.
[1182] See Ballini, R.; Barboni, L.; Giarlo, G. *J. Org. Chem.* ***2004***, *69*, 6907.

with HOF in acetonitrile.[1183] Benzylic halides react with silver nitrite in ether to give the corresponding nitro compounds.[1184]

Nitro compounds can be prepared from alcohols using $NaNO_2$/AcOH/HCl.[1185]

OS **I**, 410; **IV**, 368, 454, 724.

10-42 Formation of Azides

$$RX + N_3^- \longrightarrow RN_3$$
$$RCOX + N_3^- \longrightarrow RCON_3$$

Alkyl azides can be prepared by treatment of the appropriate halide with azide ion.[1186] Phase-transfer catalysis[1187] and the use of ultrasound[1188] are important variations. Substrates with leaving groups other than halogen have been used,[1189] including OMs, OTs,[1190] and OAc.[1191] There are protocols for the conversion of alcohols to azides.[1192] Benzylic hydrogen atoms have been replaced by N_3 by treatment with HN_3 in $CHCl_3$ in the presence of DDQ (see **19-1**).[1193]

Alkyl azides have been prepared by the decarboxylative azidation of aliphatic carboxylic acids with tosyl azide or pyridine-3-sulfonyl azide, using $AgNO_3$ as the catalyst and $K_2S_2O_8$ as the oxidant.[1194] 2-(1-Hydroxyprop-2-en)phenol derivatives reacted with $TMSN_2/BF_3{\bullet}OEt_2$ to give the allylic azide, 2-(3-azidoprop-1-ene).[1195] Amines, in the presence of DIPEA, gave alkyl azides when treated with imidazole-1-sulfonyl azide hydrogen sulfate in a copper tube flow reactor (Sec. 7.D).[1196]

2-Azido-1,2,2-triarylethanones have been prepared by the reaction of $TMSN_3$ and 2-hydroxy-1,2,2-triarylethanones with a catalytic amount of $InBr_3$.[1197] Alkyl azides have been prepared by treating alcohols with 2-azido-1,3-dimethylimidazolnium hexafluorophosphate.[1198] Benzylic alcohols are converted to benzylic azides by treatment with trimethylsilyl azide and bismuth(III) triflate.[1199] Benzylic alcohol silyl ethers are converted to benzylic azides using $TMSN_3$ in the presence of an iron catalyst.[1200] Tertiary alkyl azides can be

[1183] Rozen, S.; Carmeli, M. *J. Am. Chem. Soc.* ***2003***, *125*, 8118.
[1184] Alaime, T.; Delots, A.; Pasquinet, E.; Suzenet, F.; Guillaumet, G. *Tetrahedron* ***2016***, *72*, 1337.
[1185] Baruah, A.; Kalita, B.; Barua, N.C. *Synlett* ***2000***, 1064.
[1186] See Scriven, E.F.V.; Turnbull, K. *Chem. Rev.* ***1988***, *88*, 297; Biffin, M.E.C.; Miller, J.; Paul, D.B. in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 57–119; For a review, see Banert, K. *Synthesis* ***2016***, *48*, 2361.
[1187] Marti, M.J.; Rico, I.; Ader, J.C.; de Savignac, A.; Lattes, A. *Tetrahedron Lett.* ***1989***, *30*, 1245.
[1188] Priebe, H. *Acta Chem. Scand. Ser. B* ***1984***, *38*, 895.
[1189] See Murahashi, T.; Tanigawa, Y.; Imada, Y.; Taniguchi, Y. *Tetrahedron Lett.* ***1986***, *27*, 227.
[1190] Scriven, E.F.V.; Turnbull, K. *Chem. Rev.* ***1988***, *88*, 297 (see p. 306).
[1191] Murahashi, S.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* ***1989***, *54*, 3292.
[1192] Hajipour, A.R.; Rajaei, A.; Ruoho, A.E. *Tetrahedron Lett.* ***2009***, *50*, 708.
[1193] Guy, A.; Lemor, A.; Doussot, J.; Lemaire, M. *Synthesis* ***1988***, 900.
[1194] Liu, C.; Wang, X.; Li, Z.; Cuiand, L.; Li, C. *J. Am. Chem. Soc.* ***2015***, *137*, 9820.
[1195] Srinu, G.; Srihari, P. *Tetrahedron Lett.* ***2013***, *54*, 2382.
[1196] Nuyts, K.; Ceulemans, M.; Parac-Vogt, T.N.; Bultynck, G.; De Borggraeve, W.M. *Tetrahedron Lett.* ***2015***, *56*, 1687.
[1197] Kumar, A.; Sharma, R.K.; Singh, T.V.; Venugopalan, P. *Tetrahedron* ***2013***, *69*, 10724.
[1198] Kitamura, M.; Koga, T.; Yano, M.; Okauchi, T. *Synlett* ***2012***, *23*, 1335.
[1199] Tummatorn, J.; Thongsornkleeb, C.; Ruchirawat, S.; Thongaram, P.; Kaewmee, B. *Synthesis* ***2015***, *47*, 323.
[1200] Sawama, Y.; Nagata, S.; Yabe, Y.; Morita, K.; Monguchi, Y.; Sajiki, H. *Chem. Eur. J.* ***2012***, *18*, 1668.

prepared by stirring tertiary alkyl chlorides with NaN_3 and $ZnCl_2$ in CS_2,[1201] or by treating tertiary alcohols with NaN_3 and CF_3COOH,[1202] or with HN_3 and $TiCl_4$[1203] or BF_3.[1204] Geminal diazides have been prepared from 1,3-dicarbonyl compounds by reaction with NaN_3 in the presence of molecular I_2.[1205]

This conversion has been used as a key step in the preparation of optically active aziridines from optically active 1,2-diols (prepared by **15-44**).[1206] The enantioselective nucleophilic addition to the azidocarbenium ion intermediate with various nucleophiles gave primary and secondary benzyl azides from aldehydes.[1207] The Mukaiyama reagent (2-chloro-1-methylpyridinium iodide) and sodium nitrite in the presence of wet SiO_2 converted hydrazines to azides.[1208] The reaction of C—H compounds and NaN_3 in the presence of a chiral manganese salen catalyst gave the corresponding azide.[1209]

Aryl azides are prepared from aryl amines by reaction with *t*-BuONO and moist NaN_3 in *t*-BuOH.[1210] Aryl azides have been prepared from aniline derivatives by treatment with sodium nitrite and hydrazine hydrate at room temperature, along with a few drops of acetic acid.[1211] Aryl compounds that have a benzylic position reacted with azidoiodinane reagent in the presence of a copper catalyst with visible light to give benzylic azides.[1212] Aryl halides are converted to aryl azides with NaN_3 in the presence of Cu_2O/tetraethylammonium prolinate.[1213] Arenediazonium tosylates react with sodium azide in water to give arene azides.[1214] Anisole is converted to 4-azidoanisole with sonication using aqueous $NaICl_2$ and NaN_3.[1215]

Acyl azides, which can be used in the *Curtius reaction* (**18-14**), are generally prepared from acyl halides, anhydrides,[1216] esters,[1217] or other acyl derivatives.[1218] Acyl benzotriazoles are also precursors to acyl azides.[1219] Acyl azides can also be prepared from aldehydes using $SiCl_4/NaN_3$–MnO_2,[1220] or the *Dess-Martin periodinane* (see **19-3**, category 5) with NaN_3.[1221]

[1201] Miller, J.A. *Tetrahedron Lett.* ***1975***, 2959. See also, Koziara, A.; Zwierzak, A. *Tetrahedron Lett.* ***1987***, *28*, 6513.
[1202] Balderman, D.; Kalir, A. *Synthesis* ***1978***, 24.
[1203] Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* ***1984***, *49*, 4237.
[1204] See, for example, Adam, G.; Andrieux, J.; Plat, M. *Tetrahedron* ***1985***, *41*, 399.
[1205] Erhardt, H.; Häring, A.P.; Kotthaus, A.; Roggel, M.; Tong, M.L.; Biallas, P.; Jübermann, M.; Mohr, F.; Kirsch, S.F. *J. Org. Chem.* ***2015***, *80*, 12460.
[1206] Lohray, B.B.; Gao, Y.; Sharpless, K.B. *Tetrahedron Lett.* ***1989***, *30*, 2623.
[1207] Pramanik, S.; Ghorai, P. *Org. Lett.* ***2014***, *16*, 2104.
[1208] Azadi, R.; Kolivand, K. *Tetrahedron Lett.* ***2015***, *56*, 5613.
[1209] Huang, X.; Bergsten, T.M.; Groves, J.T. *J. Am. Chem. Soc.* ***2015***, *137*, 5300.
[1210] Das, J.; Patil, S.N.; Awasthi, R.; Narasimhulu, C.P.; Trehan, S. *Synthesis* ***2005***, 1801.
[1211] Siddiki, A.A.; Takale, B.S.; Telvekar, V.N. *Tetrahedron Lett.* ***2013***, *54*, 1294.
[1212] Rabet, P.T.G.; Fumagalli, G.; Boyd, S.; Greaney, M.F. *Org. Lett.* ***2016***, *18*, 1646.
[1213] Hajipour, A.R.; Mohammadsaleh, F. *Tetrahedron Lett.* ***2014***, *55*, 6799.
[1214] Kutonova, K.V.; Trusova, M.E.; Postnikov, P.S.; Filimonov, V.D.; Parello, J. *Synthesis* ***2013***, *45*, 2706.
[1215] Telvekarm V.N.; Sasane, K.A. *Synth. Commun.* ***2012***, *42*, 1085.
[1216] See Lwowski, W. in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 503–554.
[1217] Rawal, V.H.; Zhong, H.M. *Tetrahedron Lett.* ***1994***, *35*, 4947.
[1218] Affandi, H.; Bayquen, A.V.; Read, R.W. *Tetrahedron Lett.* ***1994***, *35*, 2729. For a preparation using triphosgene, see Gumaste, V.K.; Bhawal, B.M.; Deshmukh, A.R.A.S. *Tetrahedron Lett.* ***2002***, *43*, 1345.
[1219] Katritzky, A.R.; Widyan, K.; Kirichenko, K. *J. Org. Chem.* ***2007***, *72*, 5802.
[1220] Elmorsy, S.S. *Tetrahedron Lett.* ***1995***, *36*, 1341.
[1221] Bose, D.S.; Reddy, A.V.N. *Tetrahedron Lett.* ***2003***, *44*, 3543.

OS **III**, 846; **IV**, 715; **V**, 273, 586; **VI**, 95, 207, 210, 910; **VII**, 433; **VIII**, 116; **IX**, 220; **X**, 378. See also OS **VII**, 206.

10-43 Formation of Cyanates, Thiocyanates, Isocyanates, and Isothiocyanates

$$RX + NCO^- \longrightarrow RNCO$$
$$RX + NCS^- \longrightarrow RNCS$$

When the reagent is the thiocyanate ion, *S*-alkylation is an important side reaction (**10-30**), but the cyanate ion practically always gives exclusive *N*-alkylation.[538] Primary alkyl halides have been converted to isocyanates by treatment with sodium nitrocyanamide $NaN(CN)NO_2$ and *m*-chloroperoxybenzoic acid, followed by heating of the initially produced $RN(NO_2)CN$.[1222] When alkyl halides are treated with NCO^- in the presence of ethanol, carbamates can be prepared directly (see **16-7**).[1223] Acyl halides give the corresponding acyl isocyanates and isothiocyanates.[1224] For the formation of isocyanides (isonitriles), see **10-76**. Isonitriles, in the presence of sulfur and a Rh catalyst, are converted to isothiocyanate,[1225] as are amines.[1226]

The *Mukaiyama reagent* (2-chloro-*N*-methylpyridinium iodide) and ammonium thiocyanate (NH_4SCN) reacted with benzylic alcohols to give benzylic thiocyanates.[1227] Both alkyl and arylamines are converted to isothiocyanates using acetone–carbon disulfide as a solvent with DABCO to generate a dithiocarbamate, and subsequent reaction with triphosgene as dehydrosulfurization reagent.[1228] Dialkyl disulfides reacted with nitromethane in the presence of I_2 and KOAc to give thiocyanates.[1229]

OS **III**, 735.

10-44 Formation of Azoxy Compounds

The reaction between alkyl halides and alkanediazotates (**116**) gives azoxyalkanes.[1230] The R and R′ groups may be the same or different, but neither may be aryl or tertiary alkyl. The reaction is regioselective; only the isomer shown is obtained.

[1222] Manimaran, T.; Wolford, L.T.; Boyer, J.H. *J. Chem. Res. (S)* ***1989***, 331.
[1223] Effenberger, F.; Drauz, K.; Förster, S.; Müller, W. *Chem. Ber.* ***1981***, *114*, 173.
[1224] See Tsuge, O. in Patai, S. *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 1, Wiley, NY, ***1977***, pp. 445–506; Nuridzhanyan, K.A. *Russ. Chem. Rev.* ***1970***, *39*, 130.
[1225] Arisawa, M.; Ashikawa, M.; Suwa, A.; Yamaguchi, M. *Tetrahedron Lett.* ***2005***, *46*, 1727.
[1226] Munch, H.; Hansen, J.S.; Pittelkow, M.; Christensen, J.B.; Boas, U. *Tetrahedron Lett.* ***2008***, *49*, 3117.
[1227] Mokhtari, B.; Azadi, R.; Mardani, E. *Tetrahedron Lett.* ***2012***, *53*, 491.
[1228] Liu, P.; Li, C.; Zhang, J.; Xu, X. *Synth. Commun.* ***2013***, *43*, 3342.
[1229] Wang, Z.-H.; Ji, X.-M.; Hu, M.-L.; Tang, R.-Y. *Tetrahedron Lett.* ***2015***, *56*, 5067.
[1230] See Yandovskii, V.N.; Gidaspov, B.V.; Tselinskii, I.V. *Russ. Chem. Rev.* ***1980***, *49*, 237; Moss, R.A. *Acc. Chem. Res.* ***1974***, *7*, 421.

10.H.iv. Halogen Nucleophiles[1231]

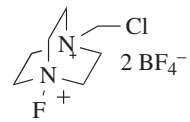
10-45 Halide Exchange

$$RX + X'^{-} \rightleftharpoons RX' + X^{-}$$

Halide exchange, sometimes call the *Finkelstein reaction*, is an equilibrium process, but it is often possible to shift the equilibrium.[1232] The reaction is most often applied to the preparation of iodides and fluorides. Iodides can be prepared from chlorides or bromides by taking advantage of the fact that sodium iodide, but not the bromide or chloride, is soluble in acetone. When an alkyl chloride or bromide is treated with a solution of NaI in acetone, the equilibrium is shifted by the precipitation of NaCl or NaBr. Since the mechanism is S_N2, the reaction is much more successful for primary halides than for secondary or tertiary halides; sodium iodide in acetone can be used as a test for primary bromides or chlorides.

Tertiary chlorides can be converted to iodides by treatment with excess NaI in CS_2, with $ZnCl_2$ as catalyst.[1233] Vinylic bromides give vinylic iodides with retention of configuration when treated with KI and a nickel bromide/zinc catalyst,[1234] or with KI and CuI in hot HMPA.[1235]

Fluorides[1236] are prepared by treatment of other alkyl halides with any of a number of fluorinating agents,[1237] among them anhydrous HF (which is useful only for reactive substrates, e.g., benzylic or allylic), AgF, KF,[1238] HgF_2, Selectfluor (1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate),[1239] or $Et_3N{\bullet}2HF$.[1240]



Selectfluor

The Pd-catalyzed conversion of chlorides to fluorides has also been reported.[1241] The equilibria in these cases are shifted because the alkyl fluoride once formed has little

[1231] See Hudlicky, M.; Hudlicky, T. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 2, Wiley, NY, ***1983***, pp. 1021–1172.

[1232] For a list of reagents for alkyl halide interconversion, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 667–671.

[1233] Miller, J.A.; Nunn, M.J. *J. Chem. Soc., Perkin Trans. 1* ***1976***, 416.

[1234] Takagi, K.; Hayama, N.; Inokawa, S. *Chem. Lett.* ***1978***, 1435.

[1235] Suzuki, H.; Aihara, M.; Yamamoto, H.; Takamoto, Y.; Ogawa, T. *Synthesis* ***1988***, 236.

[1236] See Mann, J. *Chem. Soc. Rev.* ***1987***, *16*, 381; Rozen, S.; Filler, R. *Tetrahedron* ***1985***, *41*, 1111; Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, pt. 2, Ellis Horwood, Chichester, ***1976***, pp. 24–169; Sheppard, W.A.; Sharts, C.M. *Organic Fluorine Chemistry*, W.A. Benjamin, NY, ***1969***, pp. 52–184, 409–430.

[1237] See Sharts, C.M.; Sheppard, W.A. *Org. React.* ***1974***, *21*, 125; Hudlicky, M. *Chemistry of Organic Fluorine Compunds*, pt. 2, Ellis Horwood, Chichester, ***1976***, pp. 91–136.

[1238] See Makosza, M.; Bujok, R. *Tetrahedron Lett.* ***2002***, *43*, 2761.

[1239] Banks, R.E.; Mohialdin-Khaffaf, S.N.; Lal, G.S.; Sharif, I.; Syvret, R.G. *J. Chem. Soc., Chem. Commun.* ***1992***, 595; Differring, E.; Wehrli, M. *Tetrahedron Lett*. ***1991***, *32*, 3819.

[1240] Giudicelli, M.B.; Picq, D.; Veyron B. *Tetrahedron Lett.* ***1990***, *31*, 6527. Also see Sawaguchi, M.; Ayuba, S.; Nakamura, Y.; Fukuhara, J.; Hara, S.; Yoneda, N. *Synlett* ***2000***, 999.

[1241] Katcher, M.H.; Doyle, A.G. *J. Am. Chem. Soc.* ***2010***, *132*, 17402.

tendency to react, owing to the extremely poor leaving-group ability of fluorine. Phase-transfer catalysis of the exchange reaction is a particularly effective way of preparing both fluorides and iodides.[1242]

Primary alkyl chlorides can be converted to bromides with LiBr under phase-transfer conditions[1243] and with $Bu_4N^+ Br^-$.[1244] Primary bromides were converted to chlorides with TMSCl/imidazole in hot DMF.[1245] For secondary and tertiary alkyl chlorides, treatment with excess gaseous HBr and an anhydrous $FeBr_3$ catalyst in CH_2Cl_2 gave the bromide[1246] and iodides have also been prepared. Alkyl chlorides or bromides can be prepared from iodides by treatment with HCl or HBr in the presence of HNO_3, making use of the fact that the leaving I^- is oxidized to I_2 by the HNO_3.[1247] Primary iodides give the chlorides when treated with PCl_5 in $POCl_3$.[1248] Primary alkyl halides are converted to the corresponding fluoride with tetrabutylammonium fluoride in *tert*-butanol.[1249] Alkyl fluorides and chlorides are converted to the bromides and iodides (and alkyl fluorides to the chlorides) by heating with the corresponding HX in excess amounts.[1250]

Benzylic C—H groups are converted to C—F units with visible light activation to abstract a benzylic hydrogen atom with Selectfluor as a fluorine radical donor to give the benzylic fluoride and regenerate the catalyst.[1251] The fluorination of internal allylic bromides and chlorides has been developed using $Et_3N{\bullet}3HF$ as the fluorine source, with a CuBr catalyst. A functional group must be part of the substrate for the allylic fluorination to proceed.[1252] Bromobenzene is converted to iodobenzene using NaI, 10% of I_2 with UV irradiation.[1253] Aryl iodides are also prepared by the zinc(II) catalyzed reaction via an aryl Finkelstein reaction.[1254] Alkyl halides are converted to alkyl fluorides with KF and [IPrCuOTf] as a phase-transfer agent, where IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.[1255]

OS **II**, 476; **IV**, 84, 525; **VIII**, 486; **IX**, 502.

10-46 Formation of Alkyl Halides from Esters of Sulfuric and Sulfonic Acids

$$ROSO_2R' + X^- \longrightarrow RX$$

Alkyl sulfates, tosylates, and other esters of sulfuric and sulfonic acids can be converted to alkyl halides with any of the four halide ions.[1256] Alkyl tosylates are converted to the

[1242] See Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***, pp. 112–125; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 117–124. See also, Bram, G.; Loupy, A.; Pigeon, P. *Synth. Commun.* ***1988***, *18*, 1661.

[1243] Loupy, A.; Pardo, C. *Synth. Commun.* ***1988***, *18*, 1275.

[1244] Bidd, I.; Whiting, M.C. *Tetrahedron Lett.* ***1984***, *25*, 5949.

[1245] Peyrat, J.-F.; Figadère, B.; Cavé, A. *Synth. Commun.* ***1996***, *26*, 4563.

[1246] Yoon, K.B.; Kochi, J.K. *J. Org. Chem.* ***1989***, *54*, 3028.

[1247] Svetlakov, N.V.; Moisak, I.E.; Averko-Antonovich, I.G. *J. Org. Chem. USSR* ***1969***, *5*, 971.

[1248] Bartley, J.P.; Carman, R.M.; Russell-Maynard, J.K.L. *Aust. J. Chem.* ***1985***, *38*, 1879.

[1249] Kim, D.W.; Jeong, H.-J.; Lim, S.T.; Sohn, M.-H. *Tetrahedron Lett.* ***2010***, *51*, 432.

[1250] Namavari, M.; Satyamurthy, N.; Phelps, M.E.; Barrio, J.R. *Tetrahedron Lett.* ***1990***, *31*, 4973.

[1251] Xia, J.-B.; Zhu, C.; Chen, C. *J. Am. Chem. Soc.* ***2013***, *135*, 17494.

[1252] Zhang, Z.; Wang, F.; Mu, X.; Chen, P.; Liu, G. *Angew. Chem. Int. Ed.* ***2013***, *52*, 7549.

[1253] Li, L.; Liu, W.; Zeng, H.; Mu, X.; Cosa, G.; Mi, Z.; Li, C.-J. *J. Am. Chem. Soc.* ***2015***, *137*, 8328.

[1254] Ueberschaar, N.; Heine, D.; Hertweck, C. *Synlett* ***2016***, *27*, 1794. Also see Meyer-Eppler, G.; Küchler, L.; Tenten, C.; Benkhäuser, C.; Brück, S.; Lützen, A. *Synthesis* ***2014***, *46*, 1085; Yamashita, K.-I.; Tsuboi, M.; Asano, M.S.; Sugiura, K.-I. *Synth. Commun.* ***2012***, *42*, 170.

[1255] Dang, H.; Mailig, M.; Lalic, G. *Angew. Chem. Int. Ed.* ***2014***, *53*, 6473.

[1256] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 697–700.

corresponding alkyl iodide, solvent free, with microwave irradiation, using excess NaI at 120 °C.[1257] Neopentyl tosylate, for example, reacts with Cl^-, Br^-, or I^- without rearrangement in HMPA.[1258] Similarly, allylic tosylates can be converted to chlorides without allylic rearrangement by reaction with LiCl in the same solvent.[1259] Inorganic esters are intermediates in the conversion of alcohols to alkyl halides with $SOCl_2$, PCl_5, PCl_3, etc. (**10-47**), but those esters are seldom isolated.

Aryl triflates, alkenyl sulfonates, and alkenyl phosphates were transformed to aryl or alkenyl bromides/iodides by treating them with LiBr/NaI and $[Cp^*Ru(MeCN)_3]OTf$.[1260] Heating alkyl phenylsulfonates with LiCl and a catalytic amount of $MnCl_2$ gave the corresponding chloride.[1261] Allylic carbonates have been converted to allylic fluorides with TBAF in *t*-BuOH using a Pd catalyst.[1262]

OS **I**, 25; **II**, 111, 404; **IV**, 597, 753; **V**, 545.

10-47 Formation of Alkyl Halides from Alcohols

$$\mathrm{ROH + HX \longrightarrow RX}$$
$$\mathrm{ROH + SOCl_2 \longrightarrow RCl}$$

Alcohols can be converted to alkyl halides with several reagents,[1263] the most common of which are halogen acids (HX) and inorganic acid halides, such as $SOCl_2$,[1264] PCl_5, PCl_3, and $POCl_3$.[1265] When the reagent is HX, the mechanism is S_N1cA or S_N2cA; that is, the leaving group is not ^-OH, but OH_2 (Sec. 10.G.iii). Since ^-OH is such a poor leaving group, the alcohol is first converted to an inorganic ester, for example, ROSOCl with $SOCl_2$ (**16-22**). The leaving group is therefore ^-OSOCl or a similar group (**10-46**). These may react by the S_N1 or S_N2 mechanism and, in the case of ROSOCl, by the S_Ni mechanism[1266] (Sec. 10.D).

Primary alcohols give good yields of chlorides upon treatment with HCl in HMPA.[1267] The reagent HBr is typically used to prepare alkyl bromides[1268] and HI is used for alkyl iodides. These reagents are often generated *in situ* from the halide ion and an acid such as phosphoric acid or sulfuric acid. The use of HI sometimes results in reduction of the alkyl iodide to the alkane (**19-57**) and, if the substrate is unsaturated, can also reduce the double bond.[1269] The reaction can be used to prepare primary, secondary, or tertiary

[1257] Cao, J.; Perlmutter, P. *Aust. J. Chem.* ***2014***, *67*, 1360.
[1258] Stephenson, B.; Solladié, G.; Mosher, H.S. *J. Am. Chem. Soc.* ***1974***, *96*, 3171.
[1259] Stork, G.; Grieco, P.A.; Gregson, M. *Tetrahedron Lett.* ***1969***, 1393.
[1260] Imazaki, Y.; Shirakawa, E.; Ueno, R.; Hayashi, T. *J. Am. Chem. Soc.* ***2012***, *134*, 14760.
[1261] Cahiez, G.; Lefèvre, N.; Poizat, M.; Moyeux, A. *Synthesis* ***2013***, *45*, 231.
[1262] Hollingworth, C.; Hazari, A.; Hopkinson, M.N.; Tredwell, M.; Benedetto, E.; Huiban, M.; Gee, A.D.; Brown, J.M.; Gouverneur, V. *Angew. Chem. Int. Ed.* ***2011***, *50*, 2613.
[1263] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 689–697. See Munyemana, F.; George, I.; Devos, A.; Colens, A.; Badarau, E.; Frisque-Hesbain, A.-M.; Loudet, A.; Differding, E.; Damien, J.-M.; Rémion, J.; van Uytbergen, J.; Ghosez, L. *Tetrahedron* ***2016***, *72*, 420.
[1264] See Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 321–357. See Mohanazadeh, F.; Momeni, A.R. *Org. Prep. Proceed. Int.* ***1996***, *28*, 492 for the use of $SOCl_2$ on silica gel.
[1265] See Salomaa, P.; Kankaanperä, A.; Pihlaja, K. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 595–622.
[1266] Schreiner, P.R.; Schleyer, P.v.R.; Hill, R.K. *J. Org. Chem.* ***1993***, *58*, 2822.
[1267] Fuchs, R.; Cole, L.L. *Can. J. Chem.* ***1975***, *53*, 3620.
[1268] Chong, J.M.; Heuft, M.A.; Rabbat, P. *J. Org. Chem.* ***2000***, *65*, 5837.
[1269] Jones, R.; Pattison, J.B. *J. Chem. Soc. C* ***1969***, 1046.

halides, but alcohols of the isobutyl or neopentyl type often give large amounts of rearrangement products.[1270] Tertiary chlorides are easily made with concentrated HCl, but primary and secondary alcohols react with HCl so slowly that a catalyst, such as zinc chloride, is required.[1271] Iodides have been prepared by simply heating the alcohol with iodine.[1272]

The inorganic acid chlorides $SOCl_2$,[1273] PCl_3, and so on give primary, secondary, or tertiary alkyl chlorides with much less rearrangement than is observed with HCl. Inorganic bromides and iodides, especially PBr_3, have also been used, but they are more expensive and used less often than HBr or HI, although some of them may also be generated in situ (e.g., PBr_3 from phosphorus and bromine). Secondary alcohols always give *some* rearranged bromides if another secondary position is available, even with PBr_3, PBr_5, or $SOBr_2$; thus pentan-3-ol gives both 2- and 3-bromopentane. Such rearrangements can be avoided by the use of phase-transfer catalysis.[1274] Tertiary alcohols can be converted to the bromide with BBr_3 at 0 °C.[1275] Pivaloyl chloride–DMF has been used to convert alcohols to chlorides.[1276] Sodium iodide and Amberlyst-15[1277] or tosic acid and KI with microwave irradiation[1278] converts primary alcohols to the iodide.

Ionic liquids can be used for halogenation, and bmim-Cl (1-*n*-butyl-3-methylimidazolium chloride) generates the chloride directly from the alcohol without any additional reagent.[1279] Triphenylphosphine and iodine will convert alcohols to iodides in ionic liquids, under solvent-free conditions.[1280] *tert*-Butyl halides halogenate alcohols in the ionic liquid [pmim]Br with sonication.[1281]

Other reagents[1282] have also been used, including Me_3SiCl and $InCl_3$,[1283] $GaCl_3$-tartrate,[1284] or simply Me_3SiCl in DMSO.[1285] 1,2-Dipyridiniumditribromide-ethane is an efficient brominating agent, and simply grinding the reagent and an alcohol in a porcelain mortar at room temperature with no solvent gives the product.[1286] Other specialized reagents give the halide without rearrangement.[1287] A mixture of PPh_3 and CCl_4[1288] (or

[1270] See Di Deo, M.; Marcantoni, E.; Torregiani, E.; Bartoli, G.; Bellucci, M.C.; Bosco, M.; Sambri, L. *J. Org. Chem.* ***2000***, *65*, 2830.
[1271] Other phase-transfer catalysts have been used: Landini, D.; Montanari, F.; Rolla, F. *Synthesis* ***1974***, 37.
[1272] Joseph, R.; Pallan, P.S.; Sudalai, A.; Ravindranathan, T. *Tetrahedron Lett.* ***1995***, *36*, 609.
[1273] See Chaudhari, S.S.; Akamanchi, K.G. *Synlett* ***1999***, 1763.
[1274] Dakka, G.; Sasson, Y. *Tetrahedron Lett.* ***1987***, *28*, 1223.
[1275] Pelletier, J.D.; Poirier, D. *Tetrahedron Lett.* ***1994***, *35*, 1051.
[1276] Dubey, A.; Upadhyay, A.K.; Kumar, P. *Tetrahedron Lett.* ***2010***, *51*, 744.
[1277] Tajbakhsh, M.; Hosseinzadeh, R.; Lasemi, Z. *Synlett* ***2004***, 635.
[1278] Lee, J.C.; Park, J.Y.; Yoo, E.S. *Synth. Commun.* ***2004***, *34*, 2095.
[1279] Ren, R.X.; Wu, J.X. *Org. Lett.* ***2001***, *3*, 3727.
[1280] Hajipour, A.R.; Mostafavi, M.; Ruoho, A.E. *Org. Prep. Proceed. Int.* ***2009***, *41*, 87.
[1281] Ranu, B.C.; Jana, R. *Eur. J. Org. Chem.* ***2005***, 755.
[1282] Also see Munyemana, F.; Frisque-Hesbain, A.; Devos, A.; Ghosez, L. *Tetrahedron Lett.* ***1989***, *30*, 3077; Ernst, B.; Winkler, T. *Tetrahedron Lett.* ***1989***, *30*, 3081.
[1283] Yasuda, M.; Yamasaki, S.; Onishi, Y.; Baba, A. *J. Am. Chem. Soc.* ***2004***, *126*, 7186.
[1284] Yasuda, M.; Shimizu, K.; Yamasaki, S.; Baba, A. *Org. Biomol. Chem.* ***2008***, *6*, 2790.
[1285] Snyder, D.C. *J. Org. Chem.* ***1995***, *60*, 2638.
[1286] Kavala, V.; Naik, S.; Patel, B.K. *J. Org. Chem.* ***2005***, *70*, 4267.
[1287] See Castro, B.R. *Org. React.* ***1983***, *29*, 1; Mackie, R.K. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 433–466.
[1288] See Appel, R. *Angew. Chem. Int. Ed.* ***1975***, *14*, 801; Appel, R.; Halstenberg, M. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 387–431. Also see Rajendran, K.V.; Kennedy, L.; O'Connor, C.T.; Bergin, E.; Gilheany, D.G. *Tetrahedron Lett.* ***2013***, *54*, 7009. For a

CBr_4[1289]) gave good results, and PPh_3/Cl_3CCONH_2 is an efficient chlorinating reagent.[1290] The reaction of an alcohol with PPh_3 and CCl_4 has been called the *Appel reaction*.[1288] It is known that PPh_3–CCl_3CN converts neopentyl alcohol to neopentyl chloride.[1291] The reaction of triphosgene ($Cl_3COCO_2CCl_3$) and pyridine converts alcohols to alkyl chlorides.[1292] A mixture of tetraethylammonium halide, $Et_4N^+ X^-$ (X = Br, Cl), and $[Et_2NSF_2]BF_4$ (known as XtalFluor-E) converts alcohols to the corresponding chloride or bromide.[1293]

The PPh_3–CCl_4 or –CBr_4 method converts allylic alcohols[1294] to the corresponding halides without allylic rearrangements,[1295] and also converts cyclopropylcarbinyl alcohols to the halides without ring opening.[1296] A mixture of triphenylphosphine and iodine converts alcohols to iodides under solvent-free conditions, using microwave irradiation.[1297] Hexabromoacetone–ethyltribromoacetate is an efficient brominating reagent.[1298]

Allylic and benzylic alcohols can also be converted to bromides or iodides with NaX–BF_3 etherate,[1299] and to iodides with AlI_3.[1300] A mixture of methanesulfonic acid and NaI also converts benzylic alcohols to benzylic iodides.[1301] A simple method that is specific for benzylic and allylic alcohols (and does not give allylic rearrangement) involves reaction with *N*-chloro- or *N*-bromosuccinimide and methyl sulfide.[1302] Thiols are converted to alkyl bromides by a similar procedure using PPh_3 and NBS.[1303]

Alcohols reacted with oxalyl chloride with a triphenylphosphine oxide catalyst to give the alkyl chloride with inversion of configuration. The addition of LiBr to this reaction led to the alkyl bromide with inversion of configuration.[1304] 1-*n*-Butyl-3-methylimidazolium fluoride ([bmim][F]), an ionic liquid (Sec. 9.G), converted sulfonate esters and alkyl halides to alkyl fluorides with microwave irradiation.[1305] Alcohols are converted to the corresponding alkyl iodides and bromides by reaction with KI or KBr and P_2O_5.[1306] Alkyl halides were

discussion of a key intermediate in the asymmetric Appel process, see Rajendran, K.V.; Gilheany, D.G. *Chem. Commun.* ***2012***, *48*, 10040.

[1289] Wagner, A.; Heitz, M.; Mioskowski, C. *Tetrahedron Lett.* ***1989***, *30*, 557. See also, Desmaris, L.; Percina, N.; Cottier, L.; Sinou, D. *Tetrahedron Lett.* ***2003***, *44*, 7589.

[1290] Pluempanupat, W.; Chavasiri, W. *Tetrahedron Lett.* ***2006***, *47*, 6821. Also see Cui, X.-M.; Guan, Y.-H.; Li, N.; Lv, H.; Fu, L.-A.; Guo, K.; Fan, X. *Tetrahedron Lett.* ***2014***, *55*, 90.

[1291] Matveeva, E.D.; Yalovskaya, A.I.; Cherepanov, I.A.; Kurts, A.L.; Bundel', Yu.G. *J. Org. Chem. USSR* ***1989***, *25*, 587.

[1292] Villalpando, A.; Ayala, C.E.; Watson, C.B.; Kartika, R. *J. Org. Chem.* ***2013***, *78*, 3989. Triethylamine has been used also: see Ayala, C.E.; Villalpando, A.; Nguyen, A.L.; McCandless, G.T.; Kartika, R. *Org. Lett.* ***2012***, *14*, 3676.

[1293] Pouliot, M.-F.; Mahé, O.; Hamel, J.-D.; Desroches, J.; Paquin, J.-F. *Org. Lett.* ***2012***, *14*, 5428.

[1294] See Magid, R.M. *Tetrahedron* ***1980***, *36*, 1901 (pp. 1924–1926).

[1295] Axelrod, E.H.; Milne, G.M.; van Tamelen, E.E. *J. Am. Chem. Soc.* ***1973***, *92*, 2139.

[1296] Hrubiec, R.T.; Smith, M.B. *Synth. Commun.* ***1983***, *13*, 593.

[1297] Hajipour, A.R.; Falahati, A.R.; Ruoho, A.E. *Tetrahedron Lett.* ***2006***, *47*, 4191.

[1298] Tongkate, P.; Pluempanupat, W.; Chavasiri, W. *Tetrahedron Lett.* ***2008***, *49*, 1146.

[1299] Bandgar, B.P.; Sadavarte, V.S.; Uppalla, L.S. *Tetrahedron Lett.* ***2001***, *42*, 951.

[1300] Sarmah, P.; Barua, N.C. *Tetrahedron* ***1989***, *45*, 3569.

[1301] Kamal, A.; Ramesh, G.; Laxman, N. *Synth. Commun.* ***2001***, *31*, 827.

[1302] Corey, E.J.; Kim, C.U.; Takeda, M. *Tetrahedron Lett.* ***1972***, 4339.

[1303] Iranpoor, N.; Firouzabadi, H.; Aghapour, G. *Synlett* ***2001***, 1176.

[1304] Denton, R.M.; An, J.; Adeniran, B.; Blake, A.J.; Lewis, W.; Poulton, A.M. *J. Org. Chem.* ***2011***, *76*, 6749; Tang, X.; An, J.; Denton, R.M. *Tetrahedron Lett.* ***2014***, *55*, 799.

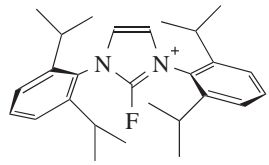
[1305] Bouvet, S.; Pégot, B.; Marrot, J.; Magnier, E. *Tetrahedron Lett.* ***2014***, *55*, 826.

[1306] Khazdooz, L.; Zarei, A.; Aghaei, H.; Azizi, G.; Gheisari, M.M. *Tetrahedron Lett.* ***2016***, *57*, 168.

prepared from alcohols by reaction with dihaloimidazolidinediones that contain geminal dibromides, dichlorides, or diiodides.[1307]

The preparation of alkyl fluorides can be problematic, and specialized reagents are usually required. HF does not generally convert alcohols to alkyl fluorides.[1308] An important reagent for this purpose is the commercially available diethylaminosulfur trifluoride (Et_2NSF_3, DAST),[1309] which converts primary, secondary, tertiary, allylic, and benzylic alcohols to fluorides in high yields under mild conditions.[1310] Selectfluor has been used (**10-46**), as in the preparation of propargylic fluorides from allenylsilanes.[1311] Fluorides have also been prepared from alcohols by treatment with nonaflyl fluoride,[1312] tetrabutylammonium difluoride,[1313] CsI/BF_3,[1314] and, indirectly, by conversion to a sulfate or tosylate, and so on (**10-46**). Primary alcohols are converted to primary fluorides by reaction with a mixture of IF_5, NEt_3, and excess KF,[1315] or by reaction with $(Cl_3CO)_2C{=}O$ (bis(trichloromethyl)carbonate) and KF (which gives COF_2 *in situ*) with 18-crown-6.[1316] Alcohols are converted to the corresponding alkyl fluoride using AlkylFluor.[1317] Chiral alcohols are converted to chiral alkyl chlorides, with inversion of configuration, using $SOCl_2$ and 10% CaF_2.[1318]

$$ROH + Ph_3P + CCl_4 \longrightarrow RCl + Ph_3PO + HCCl_3$$



AlkylFluor

OS **I**, 25, 36, 131, 142, 144, 292, 294, 533; **II**, 91, 136, 159, 246, 308, 322, 358, 399, 476; **III**, 11, 227, 370, 446, 698, 793, 841; **IV**, 106, 169, 323, 333, 576, 681; **V**, 1, 249, 608; **VI**, 75, 628, 634, 638, 781, 830, 835; **VII**, 210, 319, 356; **VIII**, 451. Also see OS **III**, 818; **IV**, 278, 383, 597.

10-48 Formation of Alkyl Halides from Ethers

$$ROR' + HI \longrightarrow RI + R'OH$$

[1307] Moerdyk, J.P.; Bielawski, C.W. *Chem. Eur. J.* ***2014***, *20*, 13487.
[1308] For an exception, see Hanack, M.; Eggensperger, H.; Hähnle, R. *Liebigs Ann. Chem.* ***1962***, *652*, 96. See also, Politanskii, S.F.; Ivanyk, G.D.; Sarancha, V.N.; Shevchuk, V.U. *J. Org. Chem. USSR* ***1974***, *10*, 697.
[1309] See Hudlicky, M. *Org. React.* ***1988***, *35*, 513.
[1310] Middleton, W.J. *J. Org. Chem.* ***1975***, *40*, 574.
[1311] Carroll, L.; Pacheco, Mª C.; Garcia, L.; Gouverneur, V. *Chem. Commun.* ***2006***, 4113.
[1312] Vorbrüggen, H. *Synthesis* ***2008***, 1165.
[1313] Kim, K.-Y.; Kim, B.C.; Lee, H.B.; Shin, H. *J. Org. Chem.* ***2008***, *73*, 8106. See also Zhao, X.; Zhuang, W.; Fang, D.; Xue, X.; Zhou, J. *Synlett* ***2009***, 779.
[1314] Hayat, S.; Atta-ur-Rahman; Khan, K.M.; Choudhary, M.I.; Maharvi, G.M.; Zia-Ullah; Bayer, E. *Synth. Commun.* ***2003***, *33*, 2531.
[1315] Yoneda, N.; Fukuhara, T. *Chem. Lett.* ***2001***, 222.
[1316] Flosser, D.A.; Olofson, R.A. *Tetrahedron Lett.* ***2002***, *43*, 4275.
[1317] Goldberg, N.W.; Shen, X.; Li, J.; Ritter, T. *Org. Lett.* ***2016***, *18*, 6102.
[1318] Zhang, J.; Wang, H.; Ma, Y.; Wang, Y.; Zhou, Z.; Tang, C. *Tetrahedron Lett.* ***2013***, *54*, 2261.

Ethers can be cleaved by heating with concentrated HI or HBr,[1319] but HCl is seldom successful.[1320] Although HBr reacts more slowly than HI, it is often a superior reagent since it causes fewer side reactions. Phase-transfer catalysis has also been used,[1321] and 47% HBr in ionic liquids has proven effective.[1322] Dialkyl ethers and alkyl aryl ethers can be cleaved. In the latter case the alkyl–oxygen bond is the one broken. As in **10-47**, the actual leaving group is not $^{-}OR'$, but HOR'. Although alkyl aryl ethers always cleave so as to give an alkyl halide and a phenol, there is no general rule for dialkyl ethers, although attack of the halide nucleophile is usually biased toward the less-substituted alkyl group. Methyl ethers are usually cleaved so that methyl iodide or bromide is a product, for example. Cleavage often occurs from both sides, and a mixture of two alcohols and two alkyl halides is obtained. An excess of HI or HBr converts the alcohol product into alkyl halide, so that dialkyl ethers (but not alkyl aryl ethers) are converted to 2 equivalents of alkyl halide.

O-Benzyl ethers are readily cleaved to the alcohol and the hydrocarbon via hydrogenolysis (**19-61**), and the most common methods are hydrogenation[1323] or dissolving metal conditions (Na or K in ammonia).[1324] Heating with In metal in aqueous ethanol[1325] also cleaves benzyl ethers.

Cyclic ethers (usually tetrahydrofuran derivatives) can be similarly cleaved (see **10-49** for epoxides). Treatment of 2-methyltetrahydrofuran with acetyl chloride and $ZnCl_2$ gave primarily *O*-acetyl-4-chloropentan-1-ol.[1326] A mixture of Et_2NSiMe_3/2 MeI cleaved tetrahydrofuran to give the *O*-trimethylsilyl ether of 4-iodobutan-1-ol.[1327] When treated with CBr_4 and 2 PPh_3, cyclic ethers are converted to α,ω-dibromides.[1328] Ethers have also been cleaved with Lewis acids such as BF_3, $Ce(OTf)_4$,[1329] BBr_3,[1330] or $AlCl_3$.[1331] In such cases, the departure of the OR is assisted by complex formation with the Lewis acid ($R_2O^+ \rightarrow {}^{-}BF_3$). The reagent NaI–$BF_3$ etherate selectively cleaves ethers in the order benzylic ethers > alkyl methyl ethers > aryl methyl ethers.[1332]

Dialkyl and alkyl aryl ethers are cleaved with NaI/Me_3SiCl[1333] or Me_3SiI.[1334] A more convenient and less expensive alternative, which gives the same products, is a mixture of Me_3SiCl and NaI.[1335] Alkyl aryl ethers can also be cleaved with LiI to give alkyl iodides

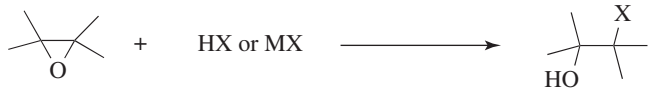
[1319] See Bhatt, M.V.; Kulkarni, S.U. *Synthesis* ***1983***, 249; Staude, E.; Patat, F. in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, p. 22; Tiecco, M. *Synthesis* ***1988***, 749.
[1320] Also see Jursic, B. *J. Chem. Res. (S)* ***1989***, 284.
[1321] Landini, D.; Montanari, F.; Rolla, F. *Synthesis* ***1978***, 771.
[1322] Boovanahalli, S.K.; Kim, D.W.; Chi, D.Y. *J. Org. Chem.* ***2004***, *69*, 3340.
[1323] Heathcock, C.H.; Ratcliffe, R. *J. Am. Chem. Soc.* ***1971***, *93*, 1746.
[1324] Reist, E.J.; Bartuska, V.J.; Goodman, L. *J. Org. Chem.* ***1964***, *29*, 3725.
[1325] Moody, C.J.; Pitts, M.R. *Synlett* ***1999***, 1575.
[1326] Mimero, P.; Saluzzo, C.; Amouroux, R. *Tetrahedron Lett.* ***1994***, *35*, 1553.
[1327] Ohshita, J.; Iwata, A.; Kanetani, F.; Kunai, A.; Yamamoto, Y.; Matui, C. *J. Org. Chem.* ***1999***, *64*, 8024.
[1328] Billing, P.; Brinker, U.H. *J. Org. Chem.* ***2012***, *77*, 11227.
[1329] Khalafi-Nezhad, A.; Alamdari, R.F. *Tetrahedron* ***2001***, *57*, 6805.
[1330] Niwa, H.; Hida, T.; Yamada, K. *Tetrahedron Lett.* ***1981***, *22*, 4239.
[1331] Johnson, F. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 4, Wiley, NY, ***1965***, pp. 1–109.
[1332] Vankar, Y.D.; Rao, C.T. *J. Chem. Res. (S)* ***1985***, 232. See also, Sharma, G.V.M.; Reddy, Ch.G.; Krishna, P.R. *J. Org. Chem.* ***2003***, *68*, 4574.
[1333] Kamal, A.; Laxman, E.; Rao, N.V. *Tetrahedron Lett.* ***1999***, *40*, 371.
[1334] See Jung, M.E.; Lyster, M.A. *J. Org. Chem.* ***1977***, *42*, 3761; *Org. Synth.* ***VI***, 353; Olah, G.A.; Prakash, G.K.S.; Krishnamurti, R. *Adv. Silicon Chem.* ***1991***, *1*, 1.
[1335] Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R. *J. Org. Chem.* ***1979***, *44*, 1247; Amouroux, R.; Jatczak, M.; Chastrette, M. *Bull. Soc. Chim. Fr.* ***1987***, 505.

and salts of phenols[1336] in a reaction similar to **10-51**. Allyl aryl ethers[1337] are efficiently cleaved with $NbCl_5$.[1338] Cleavage in ionic liquids is also known.[1339]

A closely related reaction is cleavage of oxonium salts where $R_3O^+X^-$ gives RX and ROR. For these substrates, HX is not required and X can be any of the four halide ions.

OS **I**, 150; **II**, 571; **III**, 187, 432, 586, 692, 753, 774, 813; **IV**, 266, 321; **V**, 412; **VI**, 353. See also OS **VIII**, 161, 556.

10-49 Formation of Halohydrins from Epoxides (Oxiranes) or Oxetanes



This reaction is frequently used for the preparation of halohydrins.[1340] In contrast to the situation with open-chain ethers and with larger rings, epoxides are more reactive due to ring strain (Sec. 4.Q.i) and react with hydrohalic acids. However, HF[1341] does not react with simple aliphatic and cycloalkyl epoxides,[1342] although more rigid epoxides, such as those in steroid systems, do react. The reaction can be applied to simple epoxides[1343] if polyhydrogen fluoride–pyridine is the reagent. The reagent NEt_3•3HF converts epoxides to fluorohydrins with microwave irradiation.[1344] Organocatalysts have been used to convert epoxides to fluorohydrins using an acetyl fluoride/fluorous alcohol combination.[1345] Chloro-, bromo-, and iodohydrins can also be prepared[1346] by treating epoxides with Ph_3P and X_2,[1347] with ceric ammonium nitrate/KBr,[1348] with I_2 and a SmI_2 catalyst,[1349] and wth LiI on silica gel.[1350] Epoxides are converted to the corresponding chlorohydrin upon treatment with the ionic liquid [AcMIm]Cl.[1351] Meso epoxides were cleaved enantioselectively with the chiral B-halodiisopinocampheylboranes (see **15-11**), where the halogen was Cl, Br, or I.[1352]

[1336] Harrison, I.T. *Chem. Commun.* ***1969***, 616.
[1337] See Ishizaki, M.; Yamada, M.; Watanabe, S.-i.; Hoshino, O.; Nishitani, K.; Hayashida, M.; Tanaka, A.; Hara, H. *Tetrahedron* ***2004***, *60*, 7973.
[1338] Yadav, J.S.; Ganganna, B.; Bhunia, D.C.; Srihari, P. *Tetrahedron Lett.* ***2009***, *50*, 4318.
[1339] Park, J.; Chae, J. *Synlett* ***2010***, 1651; Cheng, L.; Aw, C.; Ong, S.S.; Lu, Y. *Bull. Chem. Soc. Jpn.* ***2007***, *80*, 2008.
[1340] Wang, T.; Ji, W.-H.; Xu, Z.-Y.; Zeng, B.-B. *Synlett* ***2009***, 1511.
[1341] See Sharts, C.M.; Sheppard, W.A. *Organic Fluorine Chemistry*, W.A. Benjamin, NY, ***1969***, pp. 52–184, 409–430. For a related review, see Yoneda, N. *Tetrahedron* ***1991***, *47*, 5329.
[1342] Shahak, I.; Manor, S.; Bergmann, E.D. *J. Chem. Soc. C* ***1968***, 2129.
[1343] Olah, G.A.; Meidar, D. *Isr. J. Chem.* ***1978***, *17*, 148.
[1344] Inagaki, T.; Fukuhara, T.; Hara, S. *Synthesis* ***2003***, 1157.
[1345] Kalow, J.A.; Doyle, A.G. *J. Am. Chem. Soc.* ***2010***, *132*, 3268.
[1346] See Bonini, C.; Righi, G. *Synthesis* ***1994***, 225; Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Tetrahedron* ***1992***, *48*, 3805.
[1347] Palumbo, G.; Ferreri, C.; Caputo, R. *Tetrahedron Lett.* ***1983***, *24*, 1307. See Afonso, C.A.M.; Vieira, N.M.L.; Motherwell, W.B. *Synlett* ***2000***, 382.
[1348] Lu, Z.; Wu, W.; Peng, L.; Wu, L. *Can. J. Chem.* ***2008***, *86*, 142.
[1349] Kwon, D.W.; Cho, M.S.; Kim, Y.H. *Synlett* ***2003***, 959. Thiophenol promotes ring openeing by iodine, see Wu, J.; Sun, X.; Sun, W.; Ye, S. *Synlett* ***2006***, 2489.
[1350] Kotsuki, H.; Shimanouchi, T. *Tetrahedron Lett.* ***1996***, *37*, 1845.
[1351] Ranu, B.C.; Banerjee, S. *J. Org. Chem.* ***2005***, *70*, 4517.
[1352] Srebnik, M.; Joshi, N.N.; Brown, H.C. *Isr. J. Chem.* ***1989***, *29*, 229.

Bicyclic epoxides are usually opened to the *trans*-halohydrin but unsymmetrical epoxides are usually opened to give mixtures of regioisomers. In a typical reaction, the halogen is delivered to the less sterically hindered carbon of the epoxide and in the absence of this structural feature, and in the absence of a directing group, relatively equal mixtures of regioisomeric halohydrins are expected. The phenyl is a directing group, and in the reaction of 1-phenyl-2-alkyl epoxides with $POCl_3$/DMAP (DMAP = 4-dimethylaminopyridine) the chlorohydrin with the chlorine on the carbon bearing the phenyl predominated.[1353] When done in an ionic liquid with Me_3SiCl, styrene epoxide gave 2-chloro-2-phenylethanol.[1354] The reaction of thionyl chloride and poly(vinylpyrrolidinone) converts epoxides to the corresponding 2-chloro-1-carbinol.[1355] Bromine with a phenylhydrazine catalyst, however, converts epoxides to the 1-bromo-2-carbinol.[1356] Epoxy carboxylic acids reacted with NaI at pH 4 to give the 2-iodo-3-hydroxy compound as the major regioisomer, but when $InCl_3$ is added, the major product was the 3-iodo-2-hydroxy carboxylic acid.[1357] Vinyl epoxides are opened by reaction with boron trichloride or tribromide to give the vicinal chlorohydrin or bromohydrin with high regioselectivity.[1358]

A reaction with episulfides leads to 2-chlorothio esters.[1359] Aziridines have been opened with PPh_3 and halogenating agents,[1360] and also by $MgBr_2$, to give 2-haloamides in a related reaction[1361] *N*-Tosyl aziridines react with $KF{\bullet}2H_2O$ to give the 2-fluoro tosylamine product.[1362] Aziridinium salts are opened by bromide ion.[1363] Oxetanes reacted with $(EtO)_3SiCl$ in the presence of 5Å MS and water, in toluene, to give 3-chloroproan-1-ol derivatives with moderate enantioselectivity.[1364]

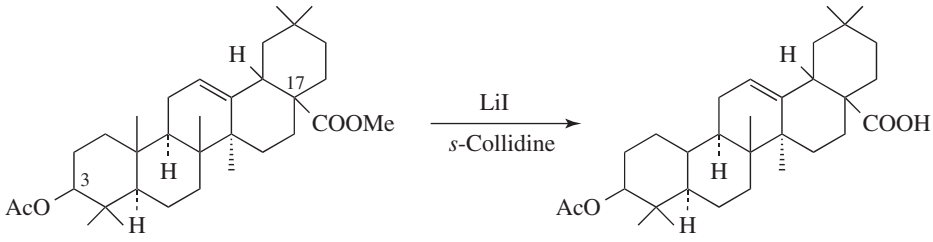
OS **I**, 117; **VI**, 424; **IX**, 220.

10-50 Cleavage of Carboxylic Esters with Lithium Iodide

$$R'COOR + LiI \xrightarrow[\Delta]{\text{Pyridine}} RI + R'COOLi$$

Carboxylic esters, where R is methyl or ethyl, can be cleaved by heating with lithium iodide in refluxing pyridine or a higher-boiling amine.[1365] The reaction is useful where a molecule is sensitive to acid and base (so that **16-58** cannot be used) or where it is desired to cleave selectively only one ester group in a molecule containing two or more. For example, heating *O*-acetyloleanolic acid methyl ester with LiI in *s*-collidine at reflux led to cleavage of only the 17-carbomethoxy group, not the 3-acetyl group, as shown.[1366]

[1353] Sartillo-Piscil, F.; Quinero, L.; Villegas, C.; Santacruz-Juárez, E.; de Parrodi, C.A. *Tetrahedron Lett.* ***2002***, *43*, 15.
[1354] Xu, L.-W.; Li, L.; Xia, C.-G.; Zhao, P.-Q. *Tetrahedron Lett.* ***2004***, *45*, 2435.
[1355] Tamami, B.; Ghazi, I.; Mahdavi, H. *Synth. Commun.* ***2002***, *32*, 3725.
[1356] Sharghi, H.; Eskandari, M.M. *Synthesis* ***2002***, 1519.
[1357] Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* ***2001***, *66*, 4719. Also see Concellón, J.M.; Bardales, E.; Concellón, C.; García-Granda, S.; Díaz, M.R. *J. Org. Chem.* ***2004***, *69*, 6923.
[1358] Weseliński, Ł.J.; Grillo, M.J.; Tanasova, M. *Tetrahedron Lett.* ***2016***, *57*, 4477.
[1359] Kameyama, A.; Kiyota, M.; Nishikubo, T. *Tetrahedron Lett.* ***1994***, *35*, 4571.
[1360] Kumar, M.; Pandey, S.K.; Gandhi, S.; Singh, V.K. *Tetrahedron Lett.* ***2009***, *50*, 363.
[1361] Righi, G.; D'Achille, R.; Bonini, C. *Tetrahedron Lett.* ***1996***, *37*, 6893.
[1362] Fan, R.-H.; Zhou, Y.-G.; Zhang, W.-X.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* ***2004***, *69*, 335.
[1363] D'hooghe, M.; Speybroeck, V.V.; Waroquier, M.; De Kimpe, N. *Chem. Commun.* ***2006***, 1554.
[1364] Yang, W.; Wang, Z.; Sun, J. *Angew. Chem. Int. Ed.* ***2016***, *55*, 6954.
[1365] See McMurry, J. *Org. React.* ***1976***, *24*, 187.
[1366] Elsinger, F.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* ***1960***, *43*, 113.



Esters RCO_2R' and lactones can also be cleaved with a mixture of Me_3SiCl and NaI to give R′I and RCO_2H.[1367] The reaction of acetyl chloride and an allylic acetate leads to the allylic chloride.[1368]

10-51 Conversion of Diazo Ketones to α-Halo Ketones

$$RCOCHN_2 + HBr \longrightarrow RCOCH_2Br$$

When diazo ketones are treated with HBr or HCl they give the respective α-halo ketones. HI does not give the reaction, since the product is reduced to a methyl ketone (**19-71**). α-Fluoro ketones can be prepared by addition of the diazo ketone to polyhydrogen fluoride–pyridine.[1369] This method is also successful for diazoalkanes.

Diazotization of α-amino acids in the above solvent at room temperature gives α-fluoro carboxylic acids.[1370] If this reaction is run in the presence of excess KCl or KBr, the corresponding α-chloro or α-bromo acid is obtained instead.[1371]

OS **III**, 119.

10-52 Conversion of Amines to Halides

$$R–NH_2 \longrightarrow R–X$$

Primary alkyl amines RNH_2 can be converted[1372] to alkyl halides by conversion to $RNTs_2$ (Sec. 10.G.ii) and treatment of this with I^- or Br^- in DMF,[441] or to *N*(Ts)-NH_2 derivatives followed by treatment with *N*-bromosuccinimide under photolysis conditions.[1373] Alternatively, diazotization with *tert*-butylnitrite and a metal halide such as $TiCl_4$ in DMF gave the halide.[1374] The *Katritzky pyrylium–pyridinium method* (Sec. 10.G.ii) can be used.[1375]

[1367] Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R. *J. Org. Chem.* ***1979***, *44*, 1247. See also, Kolb, M.; Barth, J. *Synth. Commun.* ***1981***, *11*, 763.
[1368] Yadav, V.K.; Babu, K.G. *Tetrahedron* ***2003***, *59*, 9111.
[1369] Olah, G.A.; Welch, J.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979***, *44*, 3872.
[1370] Olah, G.A.; Prakash, G.K.S.; Chao, Y.L. *Helv. Chim. Acta* ***1981***, *64*, 2528; Barber, J.; Keck, R.; Rétey, J. *Tetrahedron Lett.* ***1982***, *23*, 1549.
[1371] Olah, G.A.; Shih, J.; Prakash, G.K.S. *Helv. Chim. Acta* ***1983***, *66*, 1028.
[1372] For another method, see Lorenzo, A.; Molina, P.; Vilaplana, M.J. *Synthesis* ***1980***, 853.
[1373] Collazo, L.R.; Guziec Jr., F.S.; Hu, W.-X.; Pankayatselvan, R. *Tetrahedron Lett.* ***1994***, *35*, 7911.
[1374] Doyle, M.P.; Bosch, R.J.; Seites, P.G. *J. Org. Chem.* ***1978***, *43*, 4120.
[1375] Katritzky, A.R.; Chermprapai, A.; Patel, R.C. *J. Chem. Soc., Perkin Trans. 1* ***1980***, 2901.

Alkyl groups can be cleaved from secondary and tertiary aromatic amines by concentrated HBr in a reaction similar to **10-48**, as in the conversion of *N*,*N*-dialkylaniline derivatives to *N*-alkylanilines.

Tertiary aliphatic amines are also cleaved by HI, but useful products are seldom obtained. Tertiary amines can be cleaved by reaction with phenyl chloroformate:[1376]

$$R_3N + ClCOOPh \rightarrow RCl + R_2NCOOPh$$

α-Chloroethyl chloroformate behaves similarly.[1377] Alkyl halides may be formed when quaternary ammonium salts are heated:[1378]

$$R_4N^+ X^- \rightarrow R_3N + RX$$

OS **VIII**, 119. See also OS **I**, 428.

10-53 Conversion of Tertiary Amines to Cyanamides: *The von Braun Reaction*

$$R_3NH + BrCN \longrightarrow R_2NCN + RBr$$

The *von Braun reaction* involves the cleavage of tertiary amines by cyanogen bromide to give an alkyl bromide and a disubstituted cyanamide, and can be applied to many tertiary amines.[1379] Usually, the R group that cleaves is the one that gives the most reactive halide (e.g., benzyl or allyl). For simple alkyl groups, the smallest are the most readily cleaved. One or two of the groups on the amine may be aryl, but they do not cleave. Cyclic amines have been frequently cleaved by this reaction. Secondary amines also give the reaction, but the results are usually poor.[1380]

The mechanism consists of two successive nucleophilic substitutions, with the tertiary amine as the first nucleophile and the liberated bromide ion as the second:

Step 1 $NC{-}Br + R_3N \longrightarrow NC{-}\overset{+}{N}R_3 + \overset{-}{Br}$

Step 2 $R{-}\overset{+}{N}R_2CN + \overset{-}{Br} \longrightarrow RBr + R_2NCN$

The intermediate *N*-cyanoammonium bromide has been trapped, and its structure confirmed by chemical, analytical, and spectral data.[1381] The BrCN in this reaction has been called a *counterattack reagent*, a reagent that accomplishes, in one flask, two transformations designed to give the product.[1382]

[1376] See Cooley, J.H.; Evain, E.J. *Synthesis* ***1989***, 1.
[1377] Olofson, R.A.; Martz, J.T.; Senet, J.; Piteau, M.; Malfroot, T. *J. Org. Chem.* ***1984***, *49*, 2081; Olofson, R.A.; Abbott, D.E. *J. Org. Chem.* ***1984***, *49*, 2795. See also, Campbell, A.L.; Pilipauskas, D.R.; Khanna, I.K.; Rhodes, R.A. *Tetrahedron Lett.* ***1987***, *28*, 2331.
[1378] See Deady, L.W.; Korytsky, O.L. *Tetrahedron Lett.* ***1979***, 451.
[1379] See Vaccari, D.; Davoli, P.; Spaggiari, A.; Prati, F. *Synlett* ***2008***, 1317.
[1380] See Hageman, H.A. *Org. React.* ***1953***, 205.
[1381] Fodor, G.; Abidi, S.; Carpenter, T.C. *J. Org. Chem.* ***1974***, *39*, 1507. See also, Paukstelis, J.V.; Kim, M. *J. Org. Chem.* ***1974***, *39*, 1494.
[1382] See Hwu, J.R.; Gilbert, B.A. *Tetrahedron* ***1989***, *45*, 1233.

Aryl bromides or iodides reacted with cyanamide with a Pd catalyst, 2 atm of CO or $Mo(CO)_6$, and DBU to give the *N*-cyanobenzamide.[1383] Secondary amines reacted with TMSCN and NaOCl to give the corresponding cyanamide.[1384]

OS **III**, 608.

10.H.v. Carbon Nucleophiles

In any heterolytic reaction in which a new C—C bond is formed,[1385] one carbon atom attacks as a nucleophile and the other as an electrophile. The classification of a given reaction as nucleophilic or electrophilic is a matter of convention and is usually based on analogy. Although not discussed in this chapter, **11-8** to **11-25** and **12-16** to **12-21** are nucleophilic substitutions with respect to one reactant, but following convention, they are classified with respect to the other. Similarly, all the reactions in this section would be called electrophilic substitution (aromatic or aliphatic) if the reagent were considered as the substrate.

In reactions **10-56** to **10-65** the nucleophile is a "carbanion" part of an organometallic compound, often a Grignard reagent. There is much that is still not known about the mechanisms of these reactions, although in recent years the chemistry of organometallic reagents has been an important and growing part of organic chemistry and is a very active area of research. Many of these reactions are not nucleophilic substitutions at all. In those reactions that are nucleophilic substitutions, the attacking carbon brings a pair of electrons with it to the new C—C bond, whether or not free carbanions are actually involved. The connection of two alkyl or aryl groups is called *coupling*. Reactions **10-56** to **10-65** include both symmetrical and unsymmetrical coupling reactions. The latter are also called *cross-coupling reactions*. Other coupling reactions are considered in later chapters.

10-54 Coupling with Silanes

$$\mathrm{R{-}X + R^1{}_3Si{-}CH_2CH{=}CH_2 \longrightarrow R{-}CH_2CH{=}CH_2}$$
$$\mathrm{R{-}X \quad or \quad Ar{-}X \longrightarrow R{-}SiR^1{}_3 + Ar{-}SiR^1}$$

Organosilanes $RSiMe_3$ or $RSiMe_2F$ (where R can be vinylic, allylic, or alkynyl) couple with vinylic, allylic, and aryl bromides and iodides R′X, in the presence of certain catalysts, to give RR′ in good yields.[1386] Allylsilanes react with allylic acetates in the presence of iodine.[1387] The transition metal-catalyzed coupling of silanes, particularly allylsilanes, is a mild method for incorporating alkyl fragments into a molecule.[1388] Vinylsilanes react with allylic carbonates and a Pd catalyst to give dienes.[1389] One variation used a silylmethyltin derivative in a Pd-catalyzed coupling with aryl iodides.[1390] Homoallylsilanes

[1383] Mane, R.S.; Nordeman, P.; Odell, L.R.; Larhed, M. *Tetrahedron Lett.* ***2013***, *54*, 6912.
[1384] Zhu, C.; Xia, J.-B.; Chen, C. *Org. Lett.* ***2014***, *16*, 247.
[1385] See Stowell, J.C. *Carbanions in Organic Synthesis*, Wiley, NY, ***1979***; Noyori, R. in Alper, H. *Transition Metal Organometallics in Organic Synthesis*, Vol. 1, Academic Press, NY, ***1976***, pp. 83–187.
[1386] Sharma, R.; Kumar, R.; Kumar, I.; Singh, B.; Sharma, U. *Synthesis* ***2015***, *47*, 2347.
[1387] Yadav, J.S.; Reddy, B.V.S.; Rao, K.V.; Raj, K.S.; Rao, P.P.; Prasad, A.R.; Gunasekar, D. *Tetrahedron Lett.* ***2004***, *45*, 6505.
[1388] See Kakiuchi, F.; Tsuchiya, K.; Matsumoto, M.; Mizushima, E.; Chatani, N. *J. Am. Chem. Soc.* ***2004***, *126*, 12792; Nii, S.; Terao, J.; Kambe, N. *Tetrahedron Lett.* ***2004***, *45*, 1699.
[1389] Matsuhashi, H.; Asai, S.; Hirabayashi, K.; Hatanaka, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* ***1997***, *70*, 1943.
[1390] Itami, K.; Kamei, T.; Yoshida, J.-i. *J. Am. Chem. Soc.* ***2001***, *123*, 8773.

coupled to Ph_3BiF_2 in the presence of BF_3•OEt_2 to give the phenyl coupling product.[1391] A Ru-catalyzed silylation of unreactive, aliphatic C(sp^3)—H bonds by reaction with Et_3SiH and norbornene gave the alkyltriethylsilane.

The metal-catalyzed (usually Ni) coupling reaction of an alkyl halide or an electrophilic substrate with a silane[1392] is known as *Hiyama coupling*.[1393] A Ni-catalyzed Hiyama cross-coupling reaction with a chiral additive leads to a chiral alkylated ketone.[1394] The nature of the ligand has an important impact on the reaction.[1395] There is a Pd-catalyzed Hiyama cross-coupling reaction.[1396] Palladium-on-carbon[1397] has been used as a catalyst, and a polystyrene-supported Pd catalyst has been used.[1398] A pineno-salen catalyst has been used for an enantioselective Hiyama coupling reaction.[1399] Aryl siloxanes have been used in this reaction.[1400]

There are variations of the Hiyama coupling. Aryl and heteroaryl chlorides, catalyzed by a Pd catalyst, have been coupled to the biaryl cross-coupled products.[1401] Aryltrifluorosilanes reacted with aryl chlorides and heteroaryl chlorides in the presence of a Pd catalyst and TBAF to give the biaryl or aryl–heteroaryl compound.[1402] Trialkoxyarylsilanes reacted with aryldiazonium salts in the presence of $Pd(OAc)_2$ to give the biaryl compound.[1403] Arenesulfonates have been coupled to trialkoxyarylsilanes in the presence of $PdCl_2$ to give the biaryl.[1404] Enaminones,[1405] enolizable carbonyl compounds,[1406] hydroxy-functionalized imidazolium salts with microwave irradiation,[1407] and arylhydrazines[1408] have been used for coupling with silanes. Vinylsilanes have been coupled to aryl halides using a Pd catalyst to give the arylalkene.[1409] Aryl[(2-hydroxymethyl)phenyl]dimethylsilanes have been coupled to 4-benzoate derivatives, in the presence of $PdCl_2$ and CuI, to give the aryl–alkyl

[1391] Matano, Y.; Yoshimune, M.; Suzuki, H. *Tetrahedron Lett.* ***1995***, *36*, 7475.

[1392] For a reaction with a vinyl silane substrate, see Wang, Z.; Pitteloud, J.-P.; Montes, L.; Rapp, M.; Derane, D.; Wnuk, S.F. *Tetrahedron* ***2008***, *64*, 5322.

[1393] Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* ***2002***, *219*, 61; Denmark, S.E.; Sweis, R.F. in *Metal-Catalyzed Cross-Coupling Reactions*, de Meijere, A.; Diederich, F. (eds.), Wiley-VCH, New York, ***2004***, Chap. 4.

[1394] Dai, X.; Strotman, N.A.; Fu, G.C. *J. Am. Chem. Soc.* ***2008***, *130*, 3302.

[1395] Raders, S.M.; Kingston, J.V.; Verkade, J.G. *J. Org. Chem.* ***2010***, *75*, 1744.

[1396] Zhang, L.; Wu, J. *J. Am. Chem. Soc.* ***2008***, *130*, 12250; Zhang, L.; Qing, J.; Yang, P.; Wu, J. *Org. Lett.* ***2008***, *10*, 4971; Ranu, B.C.; Dey, R.; Chattopadhyay, K. *Tetrahedron Lett.* ***2008***, *49*, 3430.

[1397] Monguchi, Y.; Yanase, T.; Mori, S.; Sajiki, H. *Synthesis* ***2013***, *45*, 40. For a reaction in water, see Yanase, T.; Mori, S.; Monguchi, Y.; Sajiki, H. *Chem. Lett.* ***2011***, *40*, 910.

[1398] Diebold, C.; Derible, A.; Becht, J.-M.; Le Drian, C. *Tetrahedron* ***2013***, *69*, 264. Also see Ohtaka, A.; Kotera, T.; Sakon, A.; Ueda, K.; Hamasaka, G.; Uozumi, Y.; Shinagawa, T.; Shimomura, O.; Nomura, R. *Synlett* ***2016***, *27*, 1202.

[1399] Dhondge, A.P.; Shaikh, A.C.; Chen, C. *Tetrahedron: Asymmetry* ***2012***, *23*, 723.

[1400] Chen, S.-N.; Wu, W.-Y.; Tsai, F.-Y. *Tetrahedron* ***2008***, *64*, 8164.

[1401] Yuen, O.Y.; So, C.-M.; Man, H.W.; Kwong, F.Y. *Chem. Eur. J.* ***2016***, *22*, 6471.

[1402] Molander, G.A.; Iannazzo, L. *J. Org. Chem.* ***2011***, *76*, 9182. For a Cu-catalyzed coupling, see Gurung, S.K.; Thapa, S.; Vangala, A.S.; Giri, R. *Org. Lett.* ***2013***, *15*, 5378.

[1403] Cheng, K.; Wang, C.; Ding, Y.; Song, Q; Qi, C.; Zhang, X.-M. *J. Org. Chem.* ***2011***, *76*, 9261.

[1404] Cheng, K.; Hu, S.; Zhao, B.; Zhang, X.-M.; Qi, C. *J. Org. Chem.* ***2013***, *78*, 5022.

[1405] Bi, L.; Georg, G.I. *Org. Lett.* ***2011***, *13*, 5413.

[1406] Königs, C.D.F.; Klare, H.F.T.; Ohki, Y.; Tatsumi, K.; Oestreich, M. *Org. Lett.* ***2012***, *14*, 2842.

[1407] Peñafiel, I.; Pastor, I.M.; Yus, M.; Esteruelas, M.A.; Oliván, M.; Oñate, E. *Eur. J. Org. Chem.* ***2011***, 7174.

[1408] Zhang, H.; Wang, C.; Li, Z.; Wang, Z. *Tetrahedron Lett.* ***2015***, *56*, 5371. Arylsulfonyl hydrazides have also been used: see Miao, H.; Wang, F.; Zhou, S.; Zhang, G.; Li, Y. *Org. Biomol. Chem.* ***2015***, *13*, 4647.

[1409] Rooke, D.A.; Ferreira, E.M. *Org. Lett.* ***2012***, *14*, 3328. For a Cu-catalyzed reaction, see Cornelissen, L.; Cirriez, V.; Vercruysse, S.; Riant, O. *Chem. Commun.* ***2014***, *50*, 8018.

coupling product.[1410] A carbonylative coupling under the balloon pressure of CO has been reported.[1411]

A tertiary silyloxy group was displaced by allyl in the presence of $ZnCl_2$.[1412] Allylic acetates reacted with $Me_3SiSiMe_3$ and LiCl with a Pd catalyst to give the allylsilane.[1413] $RSiF_3$ reagents can also be used in coupling reaction with aryl halides.[1414] Allylsilanes reacted with epoxides, in the presence of BF_3•OEt_2, to give 2-allyl alcohols.[1415]

Silyl epoxides have been prepared from epoxides via reaction with *sec*-butyllithium and chlorotrimethylsilane.[1416] α-Silyl-*N*-Boc amines were prepared in a similar manner from the *N*-Boc amine.[1417] Allylsilanes couple to the α carbon of amines under photolysis conditions.[1418] In the presence of BF_3•etherate, allylsilane and α-methoxy *N*-Cbz amines were coupled.[1419] Allylic alcohols are coupled to allylic silanes to give substituted 1,5-dienes, catalyzed by an Ir catalyst and a $Sc(OTf)_3$ catalyst, in the presence of a phosphoramidite ligand.[1420] α-Silyl esters were prepared from α-diazonium esters and silanes, using heme protein cytochrome C to catalyze the reaction.[1421] Allylic phosphates are converted to allylic silanes by reaction with $Me_2PsSiBPin$, catalyzed by chiral six-membered NHC–copper(I) complexes.[1422] Alkyl iodides and tertiary silanes were coupled using a $Pt(P(t\text{-}Bu)_3)_2$/$(i\text{-}Pr)_2EtN/CH_3CN$ system.

Aryl cyanides have been converted to arylsilanes using a Rh catalyst and $Me_3SiSiMe_3$.[1423] Arylsilanes were prepared by the reaction of aryl pivalate esters with $R_3SiBPin$ in the presence of a Ni or Cu catalyst.[1424] Protected alanine derivatives react with $ArSi(OEt)_3$ and AgF with a Pd catalyst, leading to phenylalanine derivatives via C—H/Ph—C coupling.[1425] Anisole derivatives are converted to arylsilanes by reaction with $R_3SiBPin$ and excess KO*t*-Bu with a $Ni(COD)_2$ catalyst.[1426,1427]

The reaction of a vinyl iodide with $(EtO)_3SiH$ with a Pd catalyst generated a good yield of the corresponding vinylsilane.[1428]

OSCV **V** 10, 531.

[1410] Marcuccio, S.M.; Epa, R.; Moslmani, M.; Hughes, A.B. *Tetrahedron Lett.* ***2011***, *52*, 7178.
[1411] Chang, S.; Jin, Y.; Zhang, X.-R.; Sun, Y.B. *Tetrahedron Lett.* ***2016***, *57*, 2017.
[1412] Yokozawa, T.; Furuhashi, K.; Natsume, H. *Tetrahedron Lett.* ***1995***, *36*, 5243.
[1413] Tsuji, Y.; Funato, M.; Ozawa, M.; Ogiyama, H.; Kajita, S.; Kawamura, T. *J. Org. Chem.* ***1996***, *61*, 5779.
[1414] Hatanaka, Y.; Goda, K.; Hiyama, T. *Tetrahedron Lett.* ***1994***, *35*, 6511; Matsuhashi, H.; Kuroboshi, M.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* ***1994***, *35*, 6507.
[1415] Prestat, G.; Baylon, C.; Heck, M.-P.; Mioskowski, C. *Tetrahedron Lett.* ***2000***, *41*, 3829.
[1416] Hodgson, D.M.; Kirton, E.H.M.; Miles, S.M.; Norsikian, S.L.M.; Reynolds, N.J.; Coote, S.J. *Org. Biomol. Chem.* ***2005***, *3*, 1893.
[1417] Harrison, J.R.; O'Brien, P.; Porter, D.W.; Smith, N.W. *Chem. Commun.* ***2001***, 1202.
[1418] Pandey, G.; Rani, K.S.; Lakshimaiah, G. *Tetrahedron Lett.* ***1992***, *33*, 5107. See Gelas-Mialhe, Y.; Gramain, J.-C.; Louvet, A.; Remuson, R. *Tetrahedron Lett.* ***1992***, *33*, 73.
[1419] Matos, M.R.P.N.; Afonso, C.A.M.; Batey, R.A. *Tetrahedron Lett.* ***2001***, *42*, 7007.
[1420] Hamilton, J.Y.; Hauser, N.; Sarlah, D.; Carreira, E.M. *Angew. Chem. Int. Ed.* ***2014***, *53*, 10759.
[1421] Lütz, S. *Angew. Chem. Int. Ed.* ***2017***, *56*, 3140.
[1422] Delvos, L.B.; Hensel, A.; Oestreich, A. *Synthesis* ***2014***, *46*, 2957.
[1423] Tobisu, M.; Kita, Y.; Ano, Y.; Chatani, N. *J. Am. Chem. Soc.* ***2008***, *130*, 15982.
[1424] Zarate, C.; Martin, R. *J. Am. Chem. Soc.* ***2014***, *136*, 2236.
[1425] He, J.; Takise, R.; Fu, H.; Yu, J.-Q. *J. Am. Chem. Soc.* ***2015***, *137*, 4618.
[1426] Zarate, C.; Nakajima, M.; Martin, R. *J. Am. Chem. Soc.* ***2017***, *139*, 1191.
[1427] Inubushi, H.; Kndo, H.; Lesbani, A.; Miyachi, M.; Yamanoi, Y.; Nishihara, H. *Chem. Commun.* ***2013***, *49*, 134.
[1428] Murata, M.; Watanabe, S.; Masuda, Y. *Tetrahedron Lett.* ***1999***, *40*, 9255.

10-55 Preparation of Alkyl and Alkenyl Organometallics

$$RX + M \text{ or } MX_n \longrightarrow R—M$$

A variety of aliphatic organometallic reagents have been prepared.[1429] For the most part, the organometallic is prepared in situ for use in myriad reactions. New solvents for organometallic reactions have been discussed.[1430] Site selectivity in reactions is often controlled by the choice of catalyst.[1431] In some cases the organometallic is readily isolable, and in others the organometallic is used as a catalyst or part of a catalytic system.

The reaction of alkyl or aryl halides with magnesium for the formation of the classical Grignard reagent, RMgX, is well known (**16-22**).[1432] Grignard reagents have been prepared using flow conditions (Sec. 7.D).[1433] Alkylmagnesium reagents have been prepared by the hydroboration of alkenes (**15-11**) followed by B–Mg exchange.[1434] For homocoupling reactions of organolithium reagents, organohalides react with lithium metal.[1435] The aggregation behavior of butyllithium has been discussed,[1436] as well as the aggregation states of other organolithium reagents.[1437] Secondary alkyllithium reagents bearing an OTBS group at the 3 position have been prepared by an I/Li exchange from secondary alkyl iodides.[1438] A reductive lithiation reaction has been developed in a flow reactor (Sec. 7.D).[1439] Mixed aggregates of an alkyllithium reagent have been reported.[1440] Functionalized lithium, magnesium, aluminum, zinc,[1441] manganese, and indium[1442] organometallics have been prepared from functionalized organic halides.[1443] Organopalladium-catalyzed reactions have been reviewed.[1444] The role of cyclocarbopalladation in cascade reactions has been reviewed,[1445] as has σ-arylpalladium intermediates in cyclization reactions.[1446]

[1429] Bochmann, M. *Organometallics and Catalysis. An Introduction*, Oxford University Press, Oxford, ***2014***. For a discussion of organometallic reaction mechanisms, see *Understanding Organometallic Reaction Mechanisms and Catalysis: Computational and Experimental Tools*, Ananikov, V.P. (ed.), Wiley-VCH, Weinheim ***2014***.

[1430] Pace, V. *Aust. J. Chem.* ***2012***, *65*, 301.

[1431] Hartwig, J.F. *Acc. Chem. Res.* ***2017***, *50*, 549.

[1432] See Gutmann, B.; Schwan, A.M.; Reichart, B.; Gspan, C.; Hofer, F.; Kappe, C.O. *Angew. Chem. Int. Ed.* ***2011***, *50*, 7636. Read, J.A.; Woerpel, K.A. *J. Org. Chem.* ***2017***, *82*, 2300.

[1433] Goldbach, M.; Danieli, E.; Perlo, J.; Kaptein, B.; Litvinov, V.M.; Blümich, B.; Casanova, F.; Duchateau, A.L.L. *Tetrahedron Lett.* ***2016***, *57*, 122; Huck, L.; de la Hoz, A.; Díaz-Ortiz, A.; Alcázar, J. *Org. Lett.* ***2017***, *19*, 3747.

[1434] Reichle, M.A.; Breit, B. *Angew. Chem. Int. Ed.* ***2012***, *51*, 5730.

[1435] Fyfe, A.A.; Kennedy, A.R.; Klett J.; Mulvey, R.E. *Angew. Chem. Int. Ed.* ***2011***, *50*, 7776. For a modeling study of organolithium reagent equilibrium, see Streitwieser, A.; Leong, Y.H. *Helv. Chim. Acta* ***2012***, *95*, 1976.

[1436] Böhler, B.; Günther, H. *Helv. Chim. Acta* ***2015***, *98*, 427.

[1437] Reich, H.J. *Chem. Rev.* ***2013***, *113*, 7130. See Hevia, E.; Mulvey, R.E. *Angew. Chem. Int. Ed.* ***2011***, *50*, 6448; Tai, O.; Hopson, R.; Williard, P.G. *Org. Lett.* ***2017***, *19*, 3966.

[1438] Moriya, K.; Didier, D.; Simon, M.; Hammann, J.M.; Berionni, G.; Karaghiosoff, K.; Zipse, H.; Mayr, H.; Knochel, P. *Angew. Chem. Int. Ed.* ***2015***, *54*, 2754.

[1439] Umezu, S.; Yoshiiwa, T.; Tokeshi, M.; Shindo, M. *Tetrahedron Lett.* ***2014***, *55*, 1822.

[1440] Su, C.; Hopson, R.; Williard. P.G. *J. Am. Chem. Soc.* ***2013***, *135*, 14637.

[1441] Jung, H.-S.; Kim, S.-H. *Synlett* ***2015***, *26*, 666.

[1442] See Schneider, U.; Kobayashi, S. *Acc. Chem. Res.* ***2012***, *45*, 1331.

[1443] Dagousset, G.; François, C.; León, T.; Blanc, R.; Sansiaume-Dagousset, E.; Knochel, P. *Synthesis* ***2014***, *46*, 3133.

[1444] He, J.; Wasa, M.; Chan, K.S.L.; Shao, Q.; Yu, J.-Q. *Chem. Rev.* ***2017***, *117*, 8754.

[1445] Blouin, S.; Blond, G.; Donnard, M.; Gulea, M.; Suffert, J. *Synthesis* ***2017***, *49*, 1767.

[1446] Solé, D.; Fernández, I. *Acc. Chem. Res.* ***2014***, *47*, 168.

Benzylic chlorides react with Al powder and $InCl_3$ to give functionalized benzylic aluminum sesquichlorides with minimal homocoupling.[1447] Alkynylaluminum reagents have been prepared using continuous flow techniques (Sec. 7.D).[1448] The role of LiCl in generating organozinc reagents has been discussed.[1449] Alkynylzinc pivalates with enhanced air and moisture stability have been prepared.[1450] The preparation of 5-bromo-2-pyridylzinc iodide used the reaction of 5-bromo-2-iodopyridine with active zinc.[1451] A radical pathway has been proposed for the preparation of allenylzinc compounds from propargyl iodides and dialkylzinc reagents.[1452]

Gold-mediated C—H activation processes are increasingly important.[1453] Organobismuth reagents are known.[1454] Benzylic manganese chlorides have been prepared by treatment of benzylic chlorides with magnesium in the presence of $MnCl_2$•2LiCl.[1455] Iron catalysts facilitated the reaction of 2-substituted oxetanes with Grignard reagents to give 3-oxidopropylmagnesium compounds.[1456]

10-56 Coupling of Alkyl Halides: The Wurtz Reaction

$$2\ RX + Na \longrightarrow RR$$

The coupling of alkyl halides by treatment with sodium metal to give a symmetrical product is called the *Wurtz reaction*. Side reactions (elimination and rearrangement) are so common that the reaction is seldom used. Mixed Wurtz reactions of two alkyl halides are even less feasible because of the number of products obtained. A somewhat more useful reaction (but still not very good) takes place when a mixture of an alkyl halide and an aryl halide is treated with sodium to give an alkylated aromatic compound (the *Wurtz-Fittig reaction*).[1457] However, the coupling of two aryl halides with sodium is impractical (but see **13-10**). The reaction can be performed intramolecularly; large (11–20-membered) rings can be made in good yields (60–80%) by the use of high dilution.[1458]

It seems likely that the mechanism of the Wurtz reaction consists of two basic steps. The first is halogen–metal exchange to give an organometallic compound:

$$RX + M \rightarrow RM$$

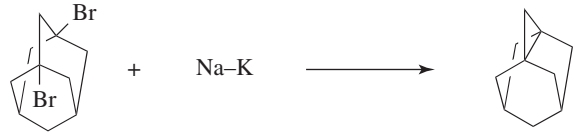
which in many cases can be isolated (**12-37**). In a subsequent reaction, the organometallic compound reacts with a second molecule of alkyl halide:

$$RX + RM \rightarrow RR$$

See **10-57**.

[1447] Blümke, T.D.; Groll, K.; Karaghiosoff, K.; Knochel, P. *Org. Lett.* ***2011***, *13*, 6440.
[1448] Piccardi, R.; Coffinet, A.; Benedetti, E.; Turcaud, S.; Micouin, L. *Synthesis* ***2016***, *48*, 3272.
[1449] Feng, C.; Cunningham, D.W.; Easter, Q.T.; Blum, S.A. *J. Am. Chem. Soc.* ***2016***, *138*, 11156.
[1450] Chen, Y.-H.; Tüllmann, C.P.; Ellwart, M.; Knochel, P. *Angew. Chem. Int. Ed.* ***2017***, *56*, 9236.
[1451] Rieke, R.D.; Kim, S.-H. *Tetrahedron Lett.* ***2011***, *52*, 244.
[1452] Jammi, S.; Mouysset, D.; Siri, D.; Bertrand, M.P.; Feray, L. *J. Org. Chem.* ***2013***, *78*, 1589.
[1453] De Haro, T.; Nevado, C. *Synthesis* ***2011***, *43*, 2530.
[1454] Gagnon, A.; Dansereau, J.; Le Roch, A. *Synthesis* ***2017***, *49*, 1707. Condon, S.; Pichon, C.; Davi, M. *Org. Prep. Proceed. Int.* ***2014***, *46*, 89.
[1455] Quinio, P.; Benischke, A.D.; Moyeux, A.; Cahiez, G.; Knochel, P. *Synlett* ***2015***, *26*, 514. See Peng, Z.; Li, N.; Sun, X.; Wang, F.; Xu, L.; Jiang, C.; Song, L.; Ya, Z.-F. *Org. Biomol. Chem.* ***2014***, *12*, 7800.
[1456] Sugiyama,Y.-k.; Heigozono, S.; Okamoto, S. *Org. Lett.* ***2014***, *16*, 6278.
[1457] For an example, see Kwa, T.L.; Boelhouwer, C. *Tetrahedron* ***1970***, *25*, 5771.
[1458] Corey, E.J.; Wat, E.K.W. *J. Am. Chem. Soc.* ***1967***, *89*, 2757. See also, Reijnders, P.J.M.; Blankert, J.F.; Buck, H.M. *Recl. Trav. Chim. Pays-Bas* ***1978***, *97*, 30.

One type of Wurtz reaction that is quite useful is the closing of small rings, especially three-membered rings.[1459] For example, 1,3-dibromopropane can be converted to cyclopropane by Zn and NaI.[1460] Two highly strained molecules prepared this way are bicyclobutane[1461] and tetracyclo[3.3.1.1^{3,7}.0^{1,3}]decane.[1462] Three- and four-membered rings can also be closed in this manner with certain other reagents,[1463] including *t*-BuLi[1464] and lithium amalgam,[1465] as well as electrochemically.[1466]



Tetracyclo[3.3.1.1^{3,7}.0^{1,3}]decane

OS **III**, 157; **V**, 328, 1058; **VI**, 133, 153.
OS **III**, 121; **IV**, 748; **VI**, 722.

10-57 The Reaction of Alkyl Halides and Sulfonate Esters with Group 1 and 2 Organometallic Reagents[1467]

$$\text{R—Na(K)(Li)(Mg)} + \text{R}'\text{X} \longrightarrow \text{R—R}'$$

A variety of Group 1 and 2 organometallic compounds[1468] couple with alkyl halides.[1469] Organosodium and organopotassium compounds are more reactive than *Grignard reagents*, and couple even with less reactive halides. *Grignard reagents* are generally unreactive with alkyl halides unless allylic and benzylic reagents and substrates are used,[1470] although allylic rearrangements are common. These organometallc compounds also couple with tertiary alkyl halides, but generally in low or moderate yields.[1471] Grignard reagents react with allylic substrates, but if there is steric hindrance at the carbon bearing the leaving group,

[1459] See Freidlina, R.Kh.; Kamyshova, A.A.; Chukovskaya, E.Ts. *Russ. Chem. Rev.* ***1982***, *51*, 368; in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1, Wiley, NY, ***1987***, see the reviews by Tsuji, T.; Nishida, S. pp. 307–373 and by Verhé, R.; De Kimpe, N. pp. 445–564.
[1460] See Applequist, D.E.; Pfohl, W.F. *J. Org. Chem.* ***1978***, *43*, 867.
[1461] See Lampman, G.M.; Aumiller, J.C. *Org. Synth.* ***VI***, 133.
[1462] Pincock, R.E.; Schmidt, J.; Scott, W.B.; Torupka, E.J. *Can. J. Chem.* ***1972***, *50*, 3958.
[1463] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 175–184.
[1464] Bailey, W.F.; Gagnier, R.P. *Tetrahedron Lett.* ***1982***, *23*, 5123.
[1465] Connor, D.S.; Wilson, E.R. *Tetrahedron Lett.* ***1967***, 4925.
[1466] Rifi, M.R. *J. Am. Chem. Soc.* ***1967***, *89*, 4442; *Org. Synth.* ***VI***, 153.
[1467] See Naso, F.; Marchese, G. in Patai, S.; Rappoport, Z. *The Chemstry of Functional Groups, Supplement D*, pt. 2, Wiley, NY, ***1983***, pp. 1353–1449.
[1468] For lists of reagents and substrates, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 101–127.
[1469] See Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 249–262.
[1470] See Raston, C.L.; Salem, G. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 161–306, 269–283; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 1046–1165.
[1471] See Ohno, M.; Shimizu, K.; Ishizaki, K.; Sasaki, T.; Eguchi, S. *J. Org. Chem.* ***1988***, *53*, 729.

the reaction may proceed by an S_N2' pathway (Sec. 10.E).[1472] It is noted that Cu salts have been used to facilitate coupling with Grignard reagents.[1473]

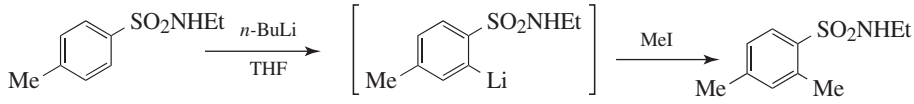
Symmetrical coupling of allylic halides occurs by heating with magnesium in ether.[1474] The coupling of two different allylic groups has been achieved by treatment of an allylic bromide with an allylic Grignard reagent in THF containing HMPA.[1475] Alkyl triflates have been used rather than alkyl halides.[1476] Chiral Cu complexes have been used with allylic halides to give rearranged alkylated products, with high enantioselectivity.[1477] A similar reaction was reported using a Grignard reagent and a chiral imidazolium carbene complex.[1478]

Coupling of organolithium compounds with alkyl halides[1479] or aryl halides[1480] is possible.[1481] Unactivated aryl halides couple with alkyllithium reagents in THF.[1482] The reaction of *n*-butyllithium/TMEDA with a homoallylic alcohol [CH_2=C(Me)CH_2CH_2OH] leads to the allyllithium reagent, and subsequent reaction with an alkyl halide gives the substituted homoallylic alcohol [CH_2=C(CH_2R)CH_2CH_2OH].[1483] Organolithium reagents exhibit an important side reaction: they react with ether solvents via deprotonation to form the corresponding organolithium reagent, and their half-life in such solvents is known.[1484] With highly reactive organolithium reagents, such as tertiary organolithium derivatives, preparing and keeping them long enough for the alkyl halide to be added is sometimes a problem. α-Lithioepoxides can also be formed, and reaction with an alkyl halide gives the substituted epoxide.[1485] Exchange of organotin compounds with organolithium reagents generates a new organolithium, and in one case intramolecular coupling in the presence of (−)-sparteine led to chiral pyrrolidine derivatives.[1486] It is noted that 1-lithioalkynes were coupled to alkyl halides in the presence of a Pd catalyst.[1487]

Because Grignard and organolithium reagents react with the C=O group (**16-22**, **16-29**), they cannot be used to couple with halides containing ketone, CO_2R, or amide functions. It is noted that small amounts of symmetrical coupling product are commonly formed while Grignard reagents are being prepared (**10-56**).

[1472] Kar, A.; Argade, N.P. *Synthesis* ***2005***, 2995. For an example, see Sen, S.; Singh, S.; Sieburth, S.McN. *J. Org. Chem.* ***2009***, *74*, 2884.
[1473] Tissot-Croset, K.; Alexakis, A. *Tetrahedron Lett.* ***2004***, *45*, 7375; Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 2426; van der Molen, N.C.; Tiemersma-Wegman, T.D.; Fañanás-Mastral, M.; Feringa, B.L. *J. Org. Chem.* ***2015***, *80*, 4981.
[1474] Turk, A.; Chanan, H. *Org. Synth.* ***III***, 121.
[1475] Stork, G.; Grieco, P.A.; Gregson, M. *Tetrahedron Lett.* ***1969***, 1393; Grieco, P.A. *J. Am. Chem. Soc.* ***1969***, *91*, 5660.
[1476] Wang, S.; Zhang, A. *Org. Prep. Proceed. Int.* ***2008***, *40*, 293.
[1477] Geurts, K.; Fletcher, S.P.; Feringa, B.L. *J. Am. Chem. Soc.* ***2006***, *128*, 15572.
[1478] Lee, Y.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2006***, *128*, 15604.
[1479] Snieckus, V.; Rogers-Evans, M.; Beak, P.; Lee, W.K.; Yum, E.K.; Freskos, J. *Tetrahedron Lett.* ***1994***, *35*, 4067; Nguyen, M.H.; O'Brien, K.T.; Smith III, A.B. *J. Org. Chem.* ***2017***, *82*, 11056.
[1480] Dieter, R.K.; Li, S.J. *J. Org. Chem.* ***1997***, *62*, 7726. Also see Beak, P.; Wu, S.; Yum, E.K.; Jun, Y.M. *J. Org. Chem.* ***1994***, *59*, 276.
[1481] For example, see Brimble, M.A.; Gorsuch, S. *Aust. J. Chem.* ***1999***, *52*, 965.
[1482] Merrill, R.E.; Negishi, E. *J. Org. Chem.*, ***1974***, *39*, 3452. For another method, see Hallberg, A.; Westerlund, C. *Chem. Lett.*, ***1982***, 1993.
[1483] Yong, K.H.; Lotoski, J.A.; Chong, J.M. *J. Org. Chem.* ***2001***, *66*, 8248.
[1484] Stanetty, P.; Mihovilovic, M.D. *J. Org. Chem.* ***1997***, *62*, 1514.
[1485] Marié, J.-C.; Curillon, C.; Malacria, M. *Synlett* ***2002***, 553.
[1486] Serino, C.; Stehle, N.; Park, Y.S.; Florio, S.; Beak, P. *J. Org. Chem.* ***1999***, *64*,1160.
[1487] Yang, L.-M.; Huang, L.-F.; Luh, T.-Y. *Org. Lett.* ***2004***, *6*, 1461.

Lithium, under the influence of ultrasound, has been used to couple alkyl, aryl, and benzylic halides.[1488] Aryllithium reagents are formed by metal–halogen exchange with aryl halides or H–metal exchange with various aromatic compounds, and they react with alkyl halides. The reaction of **117** with *n*-butyllithium, for example, generated the aryllithium (**118**), which reacted with iodomethane to give **119**.[1489]



117 **118** **119**

When an aromatic ring has an attached heteroatom or an heteroatom-containing substituent, reaction with a strong base, such as an organolithium reagent, usually leads to an *ortho*-lithiated species.[1490] Subsequent reaction with an electrophilic species gives the *ortho*-substituted product. This phenomenon is known as *directed ortho metalation* (see **13-12**). This selectivity was discovered independently by Gilman and by Wittig in 1939–1940, when anisole was found to give *ortho* deprotonation in the presence of butyllithium.[1491] Alkylation *ortho* to a carbonyl is possible, and treatment of the acyl hydrazide $PhC(=O)NHNMe_2$ with *sec*-butyllithium and then iodoethane gave the *ortho* ethyl derivative.[1492]

Propargyl derivatives can be prepared by treating propynyllithium with Me_3SiCl to give $MeC{\equiv}CSiMe_3$, reacted with BuLi to remove a proton, and subsequently reacted with an alkyl halide to give the coupling product, as shown in the reaction:[1493]

$$RX + LiCH_2{-}C{\equiv}C{-}SiMe_3 \longrightarrow RCH_2{-}C{\equiv}C{-}SiMe_3$$

Allylic halides reacted with organolithium reagents, in the presence of $CuBr{\bullet}SMe_2$ as a catalyst, plus a *N*-heterocyclic carbene catalyst at − 80 °C to give the hydrocarbon coupling product.[1494] Allylic bromides or chlorides react with organolithium reagents in the presence of a Cu(I) complex and a chiral ligand to give the alkylated terminal alkene.[1495] A Cu-catalyzed, enantioselective allylic alkylation of allyl bromides with organolithium reagents has been reported.[1496]

Alkyl sulfates and sulfonates generally make better substrates in reactions with Grignard reagents than the corresponding halides. The method is useful for compounds with

[1488] Han, B.H.; Boudjouk, P. *Tetrahedron Lett.* ***1981***, *22*, 2757.
[1489] MacNeil, S.L.; Familoni, O.B.; Snieckus, V. *J. Org. Chem.* ***2001***, *66*, 3662.
[1490] See Snieckus, V. *Chem. Rev.* ***1990***, *90*, 879; Gschwend, H.W.; Rodriguez, H.R. *Org. React.* ***1979***, *26*, 1. See also, Green, L.; Chauder, B.; Snieckus, V. *J. Heterocyclic Chem.* ***1999***, *36*, 1453.
[1491] Gilman, H.; Bebb, R.L. *J. Am. Chem. Soc.* ***1939***, *61*, 109; Wittig, G.; Fuhrman, G. *Chem. Ber.* ***1940***, *73*, 1197.
[1492] McCombie, S.W.; Lin, S.-I.; Vice, S.F. *Tetrahedron Lett.* ***1999***, *40*, 8767.
[1493] See Ireland, R.E.; Dawson, M.I.; Lipinski, C.A. *Tetrahedron Lett.* ***1970***, 2247.
[1494] Pizzalato, S.F.; Giannerini, M.; Bos, P.H.; Fañanás-Mastral, M.; Feringa, B.L. *Chem. Commun.* ***2015***, *51*, 8142.
[1495] Guduguntla, S.; Fañanás-Mastral, M.; Feringa, B.L. *J. Org. Chem.* ***2013***, *78*, 8274.
[1496] Mastral, M.F.; Vitale, R.; Pérez, M.; Feringa, B.L. *Chem. Eur. J.* ***2015***, *21*, 4209.

primary and secondary alkyl groups. Tosylates and other sulfonates and sulfates couple with Grignard reagents,[1497] most often those prepared from aryl or benzylic halides.[1498]

The reaction with Grignard reagents proceeds better when OR can be the leaving group, providing that activating groups are present in the ring. Aryl halides, even when activated, generally do not couple with Grignard reagents, although certain transition metal catalysts do effect this reaction in variable yields,[1499] including V compounds.[1500] Aryl triflates couple with arylmagnesium halides in the presence of a Pd catalyst,[1501] as do vinyl halides with RMgX with a Pd[1502] or Ni catalyst.[1503] Alkyl halides are coupled to arylmagnesium bromides in the presence of a Co catalyst.[1504] It is also possible to couple alkynylmagnesium halides with aryl iodides in the presence of Pd catalysts.[1505] A silica-supported phosphine–Pd complex was used to couple arylmagnesium halides with aryl iodides.[1506] Aryl Grignard reagents couple with alkyl halides, including neopentyl iodide, in the presence of $ZnCl_2$ and a Ni catalyst.[1507] The cross-coupling reaction of alkyl halides with alkylmagnesium halides was catalyzed by nickel catalysts[1508]

Vinyl halides[1509] and aryl halides[1510] also couple with alkyl Grignard reagents in the presence of a catalytic amount of an iron catalyst,[1511] as do vinyl triflates with CuI[1512] or vinyl halides with a Co catalyst.[1513] Grignard reagents prepared from primary or secondary[1514] alkyl or aryl halides can be coupled with vinylic or aryl halides (see **13-9**) in high yields in the presence of a Ni catalyst.[1515] When a chiral Ni catalyst is used, optically active hydrocarbons can be prepared from achiral reagents.[1516] The Pd-catalyzed coupling of arylmagnesium halides and vinyl bromides has also been reported.[1517]

The mechanisms of these reactions have been studied extensively,[1518] but firm conclusions are still lacking, in part because the mechanisms vary depending on the metal, the R

[1497] See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 1277–1286.
[1498] See Danheiser, R.L.; Tsai, Y.; Fink, D.M. *Org. Synth. 66*, 1.
[1499] See Bell, T.W.; Hu, L.; Patel, S.V. *J. Org. Chem*., ***1987***, *52*, 3847; Ozawa, F.; Kurihara, K.; Fujimori, M.; Hidaka, T.; Toyoshima, T.; Yamamoto, A. *Organometallics* ***1989***, *8*, 180.
[1500] Yasuda, S.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* ***2008***, *81*, 287.
[1501] Kamikawa, T.; Hayashi, T. *Synlett*, ***1997***, 163.
[1502] Hoffmann, R.W.; Gieson, V.; Fuest, M. *Liebigs Ann. Chem.* ***1993***, 629.
[1503] Babudri, F.; Fiandanese, V.; Mazzone, L.; Naso, F. *Tetrahedron Lett.* ***1994***, *35*, 8847.
[1504] Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* ***2006***, *128*, 1886.
[1505] Negishi, E.; Kotora, M.; Xu, C. *J. Org. Chem.* ***1997***, *62*, 8957.
[1506] Cai, M.-Z.; Song, C.-S.; Huang, X. *J. Chem. Res. (S)* ***1998***, 264.
[1507] Kondo, S.; Ohira, M.; Kawasoe, S.; Kunisada, H.; Yuki, Y. *J. Org. Chem.* ***1993***, *58*, 5003.
[1508] Garcia, P.M.P.; Di Franco, T.; Orsino, A.; Ren, P.; Hu, X. *Org. Lett.* ***2012***, *14*, 4286.
[1509] Nagano, T.; Hayashi, T. *Org. Lett.* ***2004***, *6*, 1297; Terao, J.; Watanabe, H.; Kambe, N. *J. Am. Chem. Soc.* ***2005***, *127*, 3656.
[1510] Martin, R.; Fürstner, A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 3955.
[1511] Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* ***2001***, 1901. See Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* ***2004***, *69*, 3943.
[1512] Karlström, A.S.E.; Rönn, M.; Thorarensen, A.; Bäckvall, J.-E. *J. Org. Chem.* ***1998***, *63*, 2517.
[1513] Cahiez, G.; Avedissian, H. *Tetrahedron Lett.* ***1998***, *39*, 6159.
[1514] Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* ***1984***, *106*, 158.
[1515] See Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* ***2002***, *124*, 4222. See Kumada, M. *Pure Appl. Chem.* ***1980***, *52*, 669.
[1516] See Hayashi, T.; Kumada, M. in Morrison, J.D. *Asymmetic Synthesis* Vol. 5, Academic Press, NY, ***1985***, pp. 147–169. See also, Iida, A.; Yamashita, M. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 2365.
[1517] Rathore, R.; Deselnicu, M.I.; Burns, C.L. *J. Am. Chem. Soc.* ***2002***, *124*, 14832.
[1518] See Beletskaya, I.P.; Artamkina, G.A.; Reutov, O.A. *Russ. Chem. Rev.* ***1976***, *45*, 330.

group, the catalyst, if any, and the reaction conditions. Two basic pathways can be envisioned: a nucleophilic substitution process (which might be S_N1 or S_N2) and a free-radical mechanism, although an SET pathway, or some other route that provides radicals, are possible. For SET pathways, the two radicals R• and R′• would be in a solvent cage, as shown.

$$RX + R'M \longrightarrow \underset{\text{Solvent cage}}{[R\bullet + R'\bullet]} \xrightarrow{+MX} RR'$$

It is necessary to postulate the solvent cage because, if the radicals were "free," the products would be about 50% RR′, 25% RR, and 25% R′R′. This distribution is generally not the case, and in most of these reactions RR′ is the predominant or exclusive product.[1519] An example where an S_N2 mechanism has been demonstrated (by the finding of inversion of configuration at R) is the reaction between allylic or benzylic lithium reagents with secondary halides.[1520] The fact that in some of these cases the reaction can be successfully applied to aryl and vinylic substrates indicates that a simple S_N2 process cannot be the only mechanism. One possibility is that the reagents first undergo an exchange reaction:

$$ArX + RM \rightarrow RX + ArM$$

and then a nucleophilic substitution takes place. On the other hand, there is evidence that many coupling reactions involving organometallic reagents with simple alkyl groups occur by free-radical mechanisms. Among the evidence[1521] is the observation of CIDNP in reactions of alkyl halides with simple organolithium reagents[1522] and detection of free radicals by ESR spectroscopy[1523] (Sec. 5.C.i). The formation of 2,3-dimethyl-2,3-diphenylbutane when the reaction was carried out in the presence of cumene[1524] (this product is formed when a free radical abstracts a hydrogen from cumene to give $PhCMe_2$, which dimerizes). Evidence for free-radical mechanisms has also been found for the coupling of alkyl halides with simple organosodium compounds (*Wurtz*),[1525] with *Grignard reagents*,[1526] and with lithium dialkylcopper reagents (see **10-58**).[1527] Free radicals have also been implicated in the metal ion-catalyzed coupling of alkyl and aryl halides with Grignard reagents.[1528]

For symmetrical coupling of organometallic reagents (2RM → RR), see **14-19** and **14-20**.

OS **I**, 186; **III**, 121; **IV**, 748; **VI**, 407; **VII**, 77, 172, 326, 485; **VIII**, 226, 396; **IX**, 530; **X**, 332, 396.

[1519] When a symmetrical distribution of products *is* found, this is evidence for a free-radical mechanism: the solvent cage is not efficient and breaks down.

[1520] Sommer, L.H.; Korte, W.D. *J. Org. Chem.* ***1970***, *35*, 22; Korte, W.D.; Kinner, L.; Kaska, W.C. *Tetrahedron Lett.* ***1970***, 603. See also, Schlosser, M.; Fouquet, G. *Chem. Ber.* ***1974***, *107*, 1162, 1171.

[1521] See Muraoka, K.; Nojima, M.; Kusabayashi, S.; Nagase, S. *J. Chem. Soc., Perkin Trans. 2* ***1986***, 761.

[1522] Podoplelov, A.V.; Leshina, T.V.; Sagdeev, R.Z.; Kamkha, M.A.; Shein, S.M. *J. Org. Chem. USSR* ***1976***, *12*, 488; Ward, H.R.; Lawler, R.G.; Cooper, R.A. in Lepley, A.R.; Closs, G.L. *Chemically Induced Magnetic Polarization*, Wiley, NY, ***1973***, pp. 281–322.

[1523] Russell, G.A.; Lamson, D.W. *J. Am. Chem. Soc.* ***1969***, *91*, 3967.

[1524] Bryce-Smith, D. *Bull. Soc. Chim. Fr.* ***1963***, 1418.

[1525] Garst, J.F.; Hart, P.W. *J. Chem. Soc., Chem. Commun.* ***1975***, 215.

[1526] Singh, P.R.; Tayal, S.R.; Nigam, A. *J. Organomet. Chem.* ***1972***, *42*, C9.

[1527] Bertz, S.H.; Dabbagh, G.; Mujsce, A.M. *J. Am. Chem. Soc.* ***1991***, *113*, 631.

[1528] Lehr, G.F.; Lawler, R.G. *J. Am. Chem. Soc.* ***1984***, *106*, 4048.

10-58 Reaction of Alkyl Halides and Sulfonate Esters with Organocopper Reagents

$$RX + R_2'CuLi \longrightarrow R{-}R'$$

Gilman et al. first observed that reaction of cuprous salts with 2 molar equivalents of an organolithium reagent generated an organocuprate such as lithium dibutylcuprate (Bu_2CuLi).[1529] These reagents are now called *Gilman reagents*[1530] and they react with alkyl bromides, chlorides, and iodides in ether or THF to give good yields of the cross-coupling products.[1531] As noted, they are prepared by the reaction of an organolithium compound with CuI or CuBr, but other Cu(I) compounds can be used.[1532] They are usually generated at temperatures < 0 °C due to the thermal instability of any dialkyl cuprate that has a hydrogen atom on a carbon that is β to the Cu.[1533] The reaction with alkyl halides is of wide scope[1534] and R in R_2CuLi may be primary alkyl, allylic, benzylic, aryl, vinylic, or allenic, and may contain keto, CO_2H, CO_2R, or $CONR_2$ groups.[1535] Reaction with allylic substrates usually proceeds with high selectivity for the γ position[1536] in S_N2'-type reactions.[1537] When treated with organocopper compounds and Lewis acids (e.g., *n*-BuCu•BF_3), allylic halides give substitution with almost complete allylic rearrangement, independently of the degree of substitution at the two ends of the allylic system.[1538] The mechanism of these reactions probably involves formation of a Cu(II) intermediate.[1539] Rapid injection NMR has shown the presence of η^3-π-allyl Cu(III) intermediates.[1540]

The R′ in R'_2CuLi may be primary alkyl, vinylic, allylic, or aryl. With simple Gilman reagents, secondary or tertiary alkyl groups on the organocuprate or the alkyl halide give

[1529] Gilman, H.; Jones, R.G.; Woods, L.A. *J. Org. Chem.* ***1952***, *17*, 1630; Gilman, H.; Straley, J.M. *Recl. Trav. Chim. Pays-Bas* ***1936***, *55*, 821. See Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA, ***1987***, pp. 682–698.

[1530] See Stemmler, T.L.; Barnhart, T.M.; Penner-Hahn, J.E.; Tucker, C.E.; Knochel, P.; Böhme, M.; Frenking, G. *J. Am. Chem. Soc.* ***1995***, *117*, 12489. Solution compositions of Gilman reagents have also been studied: see Lipshutz, B.H.; Kayser, F.; Siegmann, K. *Tetrahedron Lett.* ***1993***, *34*, 6693.

[1531] Bergbreiter, D.E.; Whitesides, G.M. *J. Org. Chem.* ***1975***, *40*, 779. See Bertz, S.H.; Eriksson, M.; Miao, G.; Snyder, J.P. *J. Am. Chem. Soc.* ***1998***, *118*, 10906 for the reactivity of β-silyl organocuprates.

[1532] For an example using a Cu(II) salt, see Nguyen, T.T.; Chevallier, F.; Jouikov, V.; Mongin, F. *Tetrahedron Lett.* ***2009***, *50*, 6787.

[1533] Whitesides, G.M.; Fischer Jr., W.F.; San Filippo, Jr., J.; Bashe, R.W.; House, H.O. *J. Am. Chem. Soc.* ***1969***, *91*, 4871.

[1534] See Posner, G.H. *Org. React.* ***1975***, *22*, 253; Lipshutz, B.H. *Accts. Chem. Res*. ***1997***, *30*, 277; Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, ***1980***. For lists of substrates and reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 392–399, 599–604, 1564.

[1535] See Mori, S.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc.* ***2000***, *122*, 7294.

[1536] Yoshikai, N.; Zhang, S.-L.; Nakamura, E. *J. Am. Chem. Soc.* ***2008***, *130*, 12862.

[1537] Some intermediates in this reaction have been prepared, see Bartholomew, E.R.; Bertz, S.H.; Cope, S.; Murphy, M.; Ogle, C.A. *J. Am. Chem. Soc.* ***2008***, *130*, 11244. For a review, see Falciola, C.A.; Alexakis, A. *Eur. J. Org. Chem.* ***2008***, 3765.

[1538] Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* ***1980***, *102*, 2318. See also, Lipshutz, B.H.; Ellsworth, E.L.; Dimock, S.H. *J. Am. Chem. Soc.* ***1990***, *112*, 5869.

[1539] See Mori, S.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc.* ***2000***, *122*, 7294; Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, ***1980***. See Bertz, S.H.; Cope, S.; Dorton, D.; Murphy, M.; Ogle, C.A. *Angew. Chem. Int. Ed.* ***2007***, *46*, 7082.

[1540] Bertz, S.H.; Hardin, R.A.; Murphy, M.D.; Ogle, C.A.; Richter, J.D.; Thomas, A.A. *J. Am. Chem. Soc.* ***2012***, *134*, 9557. π-Complexes have also been observed, see Bertz, S.H.; Hardin, R.A.; Ogle, C.A. *J. Am. Chem. Soc.* ***2013***, *135*, 9656.

poor results. However, secondary and tertiary alkyl coupling can be achieved (on primary RX) by the use of $R'_2CuLi{\bullet}PBu_2$,[1541] although this procedure has a problematic workup. The use of PhS(R′)CuLi[1542] selectively couples a secondary or tertiary R′ with a primary iodide RI to give RR′.[1543] With such mixed cuprates, one ligand is tightly bound to the copper, allowing the other ligand to be transferred in a coupling reaction. Other examples are known, including the common example that adds a 2-thienyl group to the cuprate to give R(Th)CuLi, where the R group is transferred in lieu of the thienyl unit.[1544] A lithium neopentyl aryl cuprate selectively transferred an aryl group to an allylic halide.[1545] When α,α‘-dibromo ketones are treated with Me_2CuLi in ether at − 78 °C and the mixture quenched with methanol, monomethylation takes place[1546] (no dimethylation is observed). It has been suggested that the reaction involves cyclization (**10-56**) to a cyclopropanone followed by nucleophilic attack to give the enolate anion, which is protonated by the methanol. If iodomethane is added rather than methanol, an α,α′-dimethyl ketone is obtained, presumably from S_N2 attack (**10-68**). Cyclic allylic picolinates react with TMS—C≡CMgBr/$Cu(acac)_2$ and give the S_N2' product.[1547] Alkenyl organocuprates formed from alkenyl halides react with allylic halides to give highly substituted symmetrical 1,3-dienes.[1548]

Lithium dialkylcopper reagents couple with alkyl tosylates.[1549] High yields are obtained with primary tosylates; secondary tosylates give lower yields[1550] but aryl tosylates do not react. Vinylic triflates[1551] couple very well to give alkenes,[1552] and they also couple with allylic cuprates to give 1,4-dienes.[1553] The fact that R'_2CuLi do not react with ketones provides a method for the alkylation of ketones via the organocuprate coupling with α-halo ketones.[1554] (see also **10-68** and **10-73**). Note that halogen–metal exchange (**12-38**) is a side reaction and can become the main reaction.[1555]

Coupling to a secondary alkyl halide (R in RX above = secondary) can be achieved in high yield with the reagents $R'_2Cu(CN)Li_2$,[1556] where R′ is primary alkyl or vinylic (but not aryl).[1557] This modified reagent is commonly known as a *higher order mixed cuprate*. The

[1541] Whitesides, G.M.; Fischer Jr., W.F.; San Filippo Jr., J.; Bashe, R.W.; House, H.O., *J. Am. Chem. Soc.* ***1969***, *91*, 4871.
[1542] See Posner, G.H.; Brunelle, D.J.; Sinoway, L. *Synthesis* ***1974***, 662.
[1543] Posner, G.H.; Whitten, C.E.; Sterling, J.J. *J. Am. Chem. Soc.* ***1973***, *95*, 7788.
[1544] See Lipshutz, B.H.; Kozlowski, J.A.; Parker, D.A.; Nguyen, S.L.; McCarthy, K.E. *J. Organomet. Chem.* ***1985***, *285*, 437.
[1545] Piazza, C.; Knochel, P. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3263.
[1546] Posner, G.H.; Sterling, J.J. *J. Am. Chem. Soc.* ***1973***, *95*, 3076. See also, Posner, G.H.; Sterling, J.J.; Whitten, C.E.; Lentz, C.M.; Brunelle, D.J. *J. Am. Chem. Soc.* ***1975***, *97*, 107; Doubleday Jr., C.; Turro, N.J. *Tetrahedron Lett.* ***1986***, *27*, 4671.
[1547] Wang, Q.; Kobayashi, Y. *Org. Lett.* ***2011***, *13*, 6252.
[1548] Aves, S.J.; O'Connell, K.M.G.; Pike, K.G.; Spring, D.R. *Synlett* ***2012***, *23*, 298.
[1549] Johnson, C.R.; Dutra, G.A. *J. Am. Chem. Soc.* ***1973***, *95*, 7777, 7783. See Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents* Wiley, NY, ***1980***, pp. 85–90.
[1550] Secondary tosylates give higher yields when they contain an O or S atom: Hanessian, S.; Thavonekham, B.; DeHoff, B. *J. Org. Chem.* ***1989***, *54*, 5831.
[1551] See Scott, W.J.; McMurry, J.E. *Acc. Chem. Res.* ***1988***, *21*, 47.
[1552] Tsushima, K.; Araki, K.; Murai, A. *Chem. Lett.* ***1989***, 1313.
[1553] Lipshutz, B.H.; Elworthy, T.R. *J. Org. Chem.* ***1990***, *55*, 1695.
[1554] Dubois, J.E.; Fournier, P.; Lion, C. *Bull. Soc. Chim. Fr.* ***1976***, 1871.
[1555] See Wakselman, C.; Mondon, M. *Tetrahedron Lett.* ***1973***, 4285.
[1556] See Lipshutz, B.H. *Synthesis* ***1987***, 325; *Synlett* ***1990***, 119. See also, Bertz, S.H. *J. Am. Chem. Soc.* ***1990***, *112*, 4031; Lipshutz, B.H.; Sharma, S.; Ellsworth, E.L. *J. Am. Chem. Soc.* ***1990***, *112*, 4032.
[1557] Lipshutz, B.H.; Wilhelm, R.S.; Floyd, D.M. *J. Am. Chem. Soc.* ***1981***, *103*, 7672.

reagents $RCu(PPh_2)Li$, $RCu(NR'_2)Li$, and $RCu(PR'_2)Li$ (R′ = cyclohexyl) are more stable than R_2CuLi and can be used at higher temperatures,[1558] but they are rather reactive. Unactivated aryl triflates[1559] $ArOSO_2CF_3$ react to give ArR in good yields when treated with $R_2Cu(CN)Li_2$.[1560] Both OTf units in $RCH(OTf)_2$ can be replaced with $Me_2(CN)CuLi_2$.[1561] With an allenic substrate, reaction with R(CN)CuLi can give ordinary displacement (with retention of configuration)[1562] or an S_N2' reaction to produce an alkyne.[1563] In the latter case, a chiral allene (Sec. 4.C, category 5) gave a chiral alkyne. The structures of "higher order mixed" cuprates has been called into question[1564] by Bertz, who suggested the reagent actually existed as $R_2CuLi{\bullet}LiCN$ in THF.[1565] This conclusion was contradicted by Lipshutz.[1566]

Grignard reagents may react with alkyl halides in the presence of certain metal catalysts,[1567] and stereocontrol is possible in these reactions.[1568] The reaction of CuI with Grignard reagents gives magnesium cuprates,[1569] and CuCN has been used to generate the cuprate.[1570] Magnesium cuprates give conjugate addition reactions (**15-21**), similar to Gilman reagents.[1569,1570,1571] Other metals used include Ag,[1572] Pd,[1573] Co,[1574] Fe,[1575] and an Fe–amine complex.[1576] Iron nanoparticles have also been employed to facilitate this type of coupling.[1577] Prochiral enyne chlorides reacted with Grignard reagents and CuTC [copper(I) thiophenecarboxylate] to give a chiral allylic enyne.[1578] Allenes were prepared by the cross coupling of propargylic bromides with Grignard reagents, using a Ni catalyst.[1579]

[1558] Bertz, S.H.; Dabbagh, G. *J. Org. Chem.* ***1984***, *49*, 1119.
[1559] See Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.*, ***1988***, *110*, 3296.
[1560] McMurry, J.E.; Mohanraj, S. *Tetrahedron Lett.*, ***1983***, *24*, 2723.
[1561] Martínez, A.G.; Barcina, J.O.; Díez, B.R.; Subramanian, L.R. *Tetrahedron* ***1994***, *50*, 13231.
[1562] Mooiweer, H.H.; Elsevier, C.J.; Wijkens, P.; Vermeer, P. *Tetrahedron Lett.* ***1985***, *26*, 65.
[1563] Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* ***1984***, *25*, 3059, 3063. For the reaction of these reagents with haloalkynes, see Yeh, M.C.P.; Knochel, P. *Tetrahedron Lett.* ***1989***, *30*, 4799.
[1564] Bertz, S.H.; Miao, G.; Eriksson, M. *Chem. Commun.* ***1996***, 815; Snyder, J.P.; Bertz, S.H. *J. Org. Chem.* ***1995***, *60*, 4312. Also see, Snyder, J.P.; Tipsword, G.E.; Spangler, D.P. *J. Am. Chem. Soc.* ***1992***, *114*, 1507.
[1565] Bertz, S.H. *J. Am. Chem. Soc.* ***1990***, *112*, 4031.
[1566] Lipshutz, B.H.; James, B. *J. Org. Chem.* ***1994***, *59*, 7585 and references therein.
[1567] See Erdik, E. *Tetrahedron* ***1984***, *40*, 641; Kochi, J.K. *Organometallic Mechanisms and Catalysis*, Academic Press, NY, ***1978***, pp. 374–398.
[1568] Bäckvall, J.-E.; Persson, E.S.M.; Bombrun, A. *J. Org. Chem.* ***1994***, *59*, 4126.
[1569] Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* ***2003***, *125*, 5646. See also, Cahiez, G.; Gager, O.; Buendia, J. *Synlett* ***2010***, 299. Kabir, S.M.H.; Rahman, M.T. *J. Organomet. Chem.* ***2001***, *619*, 31.
[1570] Kanai, M.; Tomioka, K. *Tetrahedron Lett.* ***1995***, *36*, 4273.
[1571] For an asymmetric allyl–allyl cross-coupling, see Hornillos, V.; Pérez, M.; Fañanás-Mastral, M.; Feringa, B.L. *J. Am. Chem. Soc.* ***2013***, *135*, 2140.
[1572] Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2008***, *10*, 969.
[1573] López-Pérez, A.; Adrio, J.; Carretero, J.C. *Org. Lett.* ***2009***, *11*, 5514. For other references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 386–392.
[1574] Frlan, R.; Sova, M.; Gobec, S.; Stavber, G.; Časar, Z. *J. Org. Chem.* ***2015***, *80*, 7803.
[1575] Cahiez, G.; Habiak, V.; Duplais, C.; Moyeux, A. *Angew. Chem. Int. Ed.* ***2007***, *46*, 4364. See Bedford, R.B.; Bruce, D.W.; Frost, R.M.; Goodby, J.W.; Hird, M. *Chem. Commun.* ***2004***, 2822.
[1576] Bedford, R.B.; Bruce, D.W.; Frost, R.M.; Hird, M. *Chem. Commun.* ***2005***, 4161.
[1577] Bedford, R.B.; Betham, M.; Bruce, D.W.; Davis, S.A.; Frost, R.M.; Hird, M. *Chem. Commun.* ***2006***, 1398.
[1578] Li, H.; Alexakis, A. *Angew. Chem. Int. Ed.* ***2012***, *51*, 1055.
[1579] Li, Q.; Gau, H. *Synlett* ***2012***, *23*, 747.

Inversion of configuration has been shown in the reaction of 2-bromobutane with Ph_2CuLi,[1580] but the same reaction with 2-iodobutane was reported to proceed with racemization.[1581] The reaction at a vinylic substrate occurs stereospecifically, with retention of configuration.[1582] Many *gem*-dihalides do not react, but when the two halogens are on a carbon α to an aromatic ring,[1583] or on a cyclopropane ring,[1584] both halogens can be replaced by R, for example, $PhCHCl_2 \rightarrow PhCHMe_2$. However, 1,2-dibromides give exclusive elimination (**17-22**).[1585] Vinylmagnesium halides, upon addition of a catalytic amount of Li_2CuCl_4, couple to alkyl halides.[1585]

When dialkylcopperzinc reagents ($R_2CuZnCl$) couple with allylic halides, allylic rearrangement occurs (S_N2') almost completely, and the reaction is diastereoselective if the allylic halide contains a δ-alkoxy group.[1586] Another type of Cu reagent was prepared from RZnI/CuCN, and was shown to couple with alkenyl halides.[1587] Diethylzinc in the presence of a catalytic amount of CuBr coupled to allylic chlorides.[1588]

OS **IX**, 502.

10-59 Reaction of Alkyl Halides and Sulfonate Esters With Other Organometallic Reagents

$$RX + R'—M \longrightarrow R—R'$$

A variation of the Wurtz coupling uses other metals to mediate or facilitate the coupling.[1589] Other metals include Ag, Zn,[1590] Fe,[1591] activated Cu,[1592] In,[1593] La,[1594] and Mn compounds.[1595] Other metals are commonly used for coupling reaction, often with an organic ligand.[1596] Organoaluminum compounds couple very well with tertiary halides (to give products containing a quaternary carbon) and benzylic halides at – 78 °C.[1597] This reaction can also be applied to allylic, secondary, and some primary halides, but the reaction may

[1580] Posner, G.H.; Ting, J. *Synth. Commun.* ***1973***, *3*, 281.
[1581] Lipshutz, B.H.; Wilhelm, R.S.; Nugent, S.T.; Little, R.D.; Baizer, M.M. *J. Org. Chem.* ***1983***, *48*, 3306.
[1582] Klein, J.; Levene, R. *J. Am. Chem. Soc.* ***1972***, *94*, 2520. For a discussion of the mechanism, see Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* ***2004***, *126*, 12264.
[1583] Posner, G.H.; Brunelle, D.J. *Tetrahedron Lett.* ***1972***, 293.
[1584] See Kitatani, K.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 1600.
[1585] Cahiez, G.; Chaboche, C.; Jézéquel, M. *Tetrahedron* ***2000***, *56*, 2733.
[1586] Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* ***1989***, *111*, 3091.
[1587] Marquais, S.; Cahiez, G.; Knochel, P. *Synlett*, ***1994***, 849.
[1588] Malda, H.; van Zijl, A.W.; Arnold, L.A.; Feringa, B.L. *Org. Lett.* ***2001***, *3*, 1169.
[1589] For a list of reagents, including metals and other reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 83–84.
[1590] See, for example, Nosek, J. *Collect. Czech. Chem. Commun.* ***1964***, *29*, 597.
[1591] Onsager, O. *Acta Chem. Scand. Ser. B* ***1978***, *32*, 15.
[1592] Ginah, F.O.; Donovan, T.A.; Suchan, S.D.; Pfennig, D.R.; Ebert, G.W. *J. Org. Chem.* ***1990***, *55*, 584.
[1593] Ranu, B.C.; Dutta, P.; Sarkar, A. *Tetrahedron Lett.* ***1998***, *39*, 9557.
[1594] Nishino, T.; Watanabe, T.; Okada, M.; Nishiyama, Y.; Sonoda, N. *J. Org. Chem.* ***2002***, *67*, 966.
[1595] See Gilbert, B.C.; Lindsay, C.I.; McGrail, P.T.; Parsons, A.F.; Whittaker, D.T.E. *Synth. Commun.* ***1999***, *29*, 2711.
[1596] Ardolino, M.J.; Morken, J.P. *Tetrahedron* ***2015***, *71*, 6409. Philipova, I.; Stavrakov, G.; Chimov, A.; Nikolova, R.; Shivachev, B.; Dimitrov, V. *Tetrahedron: Asymmetry* ***2011***, *22*, 970. Magre, M.; Mazuela, J.; Diéguez, M.; Pàmies, O.; Alexakis, A. *Tetrahedron: Asymmetry* ***2012***, *23*, 67. Philipova, I.; Stavrakov, G.; Dimitrov, V. *Tetrahedron: Asymmetry* ***2012***, *23*, 927.
[1597] Kennedy, J.P. *J. Org. Chem.* ***1970***, *35*, 532. See also, Sato, F.; Kodama, H.; Sato, M. *J. Organomet. Chem.* ***1978***, *157*, C30.

be slow. Alkynylaluminum reagents react with alkyl halides using a copper catalyst.[1598] Organoaluminum reagents react with secondary benzylic bromides in a cross-coupling reaction.[1599] Vinylic aluminum compounds (in the presence of a suitable transition metal catalyst) couple with allylic halides, acetates, and alcohol derivatives to give 1,4-dienes,[1600] and with vinylic and benzylic halides to give 1,3-dienes and allylic arenes, respectively.[1601] Alkenylaluminum reagents have been coupled with benzylic halides using a Ni catalyst.[1602]

Diarylmanganese reagents react with a Co catalyst to give the cross-coupling product.[1603] Coupling that involves the C–F bond using main group elements has been reviewed.[1604] The Ir-catalyzed cross-coupling of allylic carbonates with 1,3-diarylpropenes has been reported.[1605] Allylic halides have been coupled with triarylindium reagents in the presence of rhodium catalysts.[1606] A nickel-catalyzed cross-coupling of alkyl aziridines has been reported.[1607]

The mechanism of many of these reactions differs with the metal catalyst. Aryl tin compounds couple with vinyl halides[1608] or vinyl triflates when a Pd catalyst is present.[1609] Homocoupling of benzylic halides was also effected by alumina-supported Ni nanoparticles in aqueous media.[1610] The ultrasound homocoupling of benzylic halides in the presence of Mg has been reported.[1611]

Vinylic halides can be coupled to give buta-1,3-dienes by treatment with activated Cu powder in a reaction analogous to the *Ullmann reaction* (**13-10**).[1612] This reaction is stereospecific, with retention of configuration at both carbons, and with *n*-BuLi in ether in the presence of $MnCl_2$.[1613] Alkyl and allylic halides are coupled under electrochemical conditions, in aqueous media under air, catalyzed by $Pd(OAc)_2$ and $Cu(OAc)_2 \bullet H_2O$, and mediated by Pt–Zn.[1614] The polymeric phosphine-mediated coupling of alkyl halides has been reported using flow conditions (Sec. 7.D).[1615] The photoreductive coupling of 2-arylallyl bromides with visible light, in the presence of a Ru catalyst, a Hantzsch ester, and *i*-Pr_2NEt gave 2,5-diaryl-1,5-dienes.[1616]

[1598] Shrestha, B.; Thapa, S.; Gurung, S.K.; Pike, R.A.S.; Giri, R. *J. Org. Chem.* ***2016***, *81*, 787.
[1599] Fang, H.; Yang, Z.; Zhang, L.; Wang, W.; Li, Y.; Xu, X.; Zhou, S. *Org. Lett.* ***2016***, *18*, 6022.
[1600] See Lee, Y.; Akiyama, K.; Gillingham, D.G.; Brown, M.K.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2008***, *130*, 446.
[1601] Negishi, E.; Takahashi, T.; Baba, S.; van Horn, D.E.; Okukado, N. *J. Am. Chem. Soc.* ***1987***, *109*, 2393.
[1602] Biradar, D.B.; Gau, H.-M. *Org. Biomol. Chem.* ***2012***, *10*, 4243.
[1603] Hofmayer, M.S.; Hammann, J.M.; Haas, D.; Knochel, P. *Org. Lett.* ***2016***, *18*, 6456.
[1604] Chen, W.; Bakewell, C.; Crimmin, M.R. *Synthesis* ***2017***, *49*, 810.
[1605] Yuan, Q.; Yao, K.; Liu, D.; Zhang, W. *Chem. Commun.* ***2015***, *51*, 11834.
[1606] Riveiros, R.; Tato, R.; Sestelo, J.P.; Sarandeses, L.A. *Eur. J. Org. Chem.* ***2012***, 3018.
[1607] Nielsen, D.K.; Huang, C.-Y.; Doyle, A.G. *J. Am. Chem. Soc.* ***2013***, *135*, 13605; Do, H.-Q.; Chandrashekar, E.R.R.; Fu, G.C. *J. Am. Chem. Soc.* ***2013***, *135*, 16288.
[1608] Shen, W.; Wang, L. *J. Org. Chem.* ***1999***, *64*, 8873.
[1609] Fouquet, E.; Rodriguez, A.L. *Synlett* ***1998***, 1323.
[1610] Khan, S.; Ghatak, A.; Bhar, S. *Tetrahedron Lett.* ***2015***, *56*, 2480.
[1611] Gorhina, O.V.; Thomassen, I.K.; Lejn, T. *Synth. Commun.* ***2013***, *43*, 1867.
[1612] Cohen, T.; Poeth, T. *J. Am. Chem. Soc.* ***1972***, *94*, 4363. See Vanderesse, R.; Fort, Y.; Becker, S.; Caubere, P. *Tetrahedron Lett.* ***1986***, *27*, 3517.
[1613] Cahiez, G.; Bernard, D.; Normant, J.F. *J. Organomet. Chem.* ***1976***, *113*, 99.
[1614] Lai, Y.-L.; Huang, J.-M. *Org. Lett.* ***2017***, *19*, 2022.
[1615] Tran, U.P.N.; Hock, K.J.; Gordon, C.P.; Koenigs, R.M.; Nguyen, T.V. *Chem. Commun.* ***2017***, *53*, 4950.
[1616] Pratsch, G.; Overman, L.E. *J. Org. Chem.* ***2015***, *80*, 11388.

The coupling reaction with vinyltin reagents and vinyl halides occurs with a Pd catalyst.[1617] When the vinyltin reagent is coupled with a vinyl triflate in the presence of a Pd catalyst, the reaction is known as the *Stille reaction* (**12-15**). In the Stille reaction, vinylic triflates, in the presence of a Pd catalyst and LiCl, couple with organotin compounds $R'SnMe_3$, where R′ can be alkyl, allylic, vinylic, or alkynyl.[1618] The reaction has been performed intramolecularly, to prepare large-ring lactones.[1619] Allyltributylstannane compounds react with benzyl chlorides using Pd nanoparticles as a catalyst.[1620]

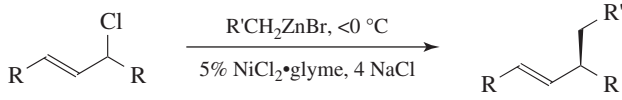
Products containing a quaternary carbon can also be obtained by treatment of tertiary halides with dialkyl or diaryl zinc reagents in CH_2Cl_2.[1621] Diarylzinc reagents reacted with benzylic bromides to give the coupling product.[1622] This organozinc coupling reaction has been done in ionic liquids.[1623] Palladium-catalyzed variations are also known for alkyl or vinyl halides with organozinc compounds.[1624] Dimethylzinc was coupled to aryl halides with a Pd catalyst,[1625] and *Reformatsky-type* zinc derivatives (see **16-27**; **16-31**) have been coupled to aryl halides using a Pd catalyst and microwave irradiation.[1626]

Alkyl or aryl triflates (halides) couple with alkyl or ArZn(halide) reagents in the presence of a Pd catalyst.[1627] Alkenylzinc iodides have been coupled to allylic halides in the presence of a Cu catalyst to give 1,4-dienes.[1628] Aryl ketones have been prepared by the coupling of aryl acid chlorides with alkylzinc chlorides, in the presence of Pd nanoparticles.[1629] Aryl iodides and benzyl chlorides or benzoyl chlorides were coupled, with CO and Zn powder and a Pd catalyst, to give 1,2-diarylethanones.[1630] Vinyl halides have been coupled to benzylic halides in the presence of Zn dust, in water, with a Pd catalyst.[1631] An alkyl halide with a CF_3 group was coupled with arylzinc compounds in the presence of a Ni catalyst.[1632] Ruthenium catalysts have been used for the allylic alkylation of disubstituted allylic esters.[1633] Cross-coupling reactions with achiral alkylzinc reagents have been reported.[1634] Secondary alkylzinc halides have been coupled with aryl or heteroaryl halides using Pd-PEPPSI-IPent, where PEPPSI is pyridine-**e**nhanced **p**recatalyst **p**reparation **s**tabilization

[1617] Paley, R.S.; de Dios, A.; de la Pradilla, R.F. *Tetrahedron Lett.* ***1993***, *34*, 2429.
[1618] Kwon, H.B.; McKee, B.H.; Stille, J.K. *J. Org. Chem.* ***1990***, *55*, 3114. See Stang, P.J.; Kowalski, M.H. *J. Am. Chem. Soc.* ***1989***, *111*, 3356.
[1619] Stille, J.K.; Tanaka, M. *J. Am. Chem. Soc.* ***1987***, *109*, 3785.
[1620] Feng, X.; Sun, A.; Zhang, S.; Yu, X.; Bao, M. *Org. Lett.* ***2013***, *15*, 108.
[1621] Reetz, M.T.; Wenderoth, B.; Peter, R.; Steinbach, R.; Westermann, J. *J. Chem. Soc., Chem. Commun.* ***1980***, 1202. See also, Klingstedt, T.; Frejd, T. *Organometallics* ***1983***, *2*, 598.
[1622] Dunsford, J.J.; Clark, E.R.; Ingleson, M.J. *Angew. Chem. Int. Ed.* ***2015***, *54*, 5688.
[1623] Sirieix, J.; Oßberger, M.; Betzemeier, B.; Knochel, P. *Synlett* ***2000***, 1613.
[1624] See Andrei, D.; Wnuk, S.F. *J. Org. Chem.* ***2006***, *71*, 405. For a variation using Pd-nanoparticles, see Liu, J.; Deng, Y.; Wang, H.; Zhang, H.; Yu, G.; Wu, B.; Zhang, H.; Li, Q.; Marder, T.B.; Yang, Z.; Lei, A. *Org. Lett.* ***2008***, *10*, 2661.
[1625] Herbert, J.M. *Tetrahedron Lett.* ***2004***, *45*, 817.
[1626] Bentz, E.; Moloney, M.G.; Westaway, S.M. *Tetrahedron Lett.* ***2004***, *45*, 7395.
[1627] Takahashi, H.; Hossain, K.M.; Nishihara, Y.; Shibata, T.; Takagi, K. *J. Org. Chem.* ***2006***, *71*, 671. See also Sase, S.; Jaric, M.; Metzger, A.; Malakhov, V.; Knochel, P. *J. Org. Chem.* ***2008***, *73*, 7380.
[1628] Zhurkin, F.E.; Hu, X. *J. Org. Chem.* ***2016***, *81*, 5795.
[1629] Yu, L.; Ren, L.; Chen, T.; Yi, R.; Wu, Y.; Guo, R. *Org. Prep. Proceed. Int.* ***2012***, *44*, 169.
[1630] Wu, X.-F.; Schranck, J.; Neumann, H.; Beller, M. *Chem. Asian J.* ***2012***, *7*, 40.
[1631] Krasovskaya, V.; Krasovskiy, A.; Bhattacharjya, A.; Lipshutz, B.H. *Chem. Commun.* ***2011***, *47*, 5717.
[1632] Liang, Y.; Fu, G.C. *J. Am. Chem. Soc.* ***2015***, *137*, 9523. See Chu, C.K.; Liang, Y.; Fu, G.C. *J. Am. Chem. Soc.* ***2016***, *138*, 6404.
[1633] Kawatsura, M.; Sato, M.; Tsuji, H.; Ata, F.; Itoh, T. *J. Org. Chem.* ***2011***, *76*, 5485.
[1634] Binder, J.T.; Cordier, C.J.; Fu, G.C. *J. Am. Chem. Soc.* ***2012***, *134*, 17003.

and initiation(a group of Pd catalysts), and IPent is the 3-pentyl substituent attached at the *ortho* positions of the aromatic rings.[1635] Alkenyl halides have been coupled with alkylzinc halides with a Pd catalyst.[1636] Organozinc reagents have been coupled with heteroaryl iodides using a Cu catalyst.[1637]

The coupling of alkyl or alkenyl halides and organozinc compound with a Ni complex has come to be known as *Negishi coupling*.[1638] The Ni-catalyzed reaction of an allylic halide and an organozinc reagent to give the coupling product is a generalized example,[1639]



although geminal diiodo compounds can be coupled without a catalyst.[1640] Arylzinc compounds[1641] have been used, as have arylvinyl iodides.[1642] The structure of bis(iodozincio)methane in THF solution has been reported.[1643] Pyridylzinc compounds have been used in Negishi coupling.[1644] Arylzinc bromides have been coupled to acid chlorides with a Ni catalyst to give aryl ketones.[1645] Pyridylzinc reagents have been used in the Negishi reaction.[1646] Organozinc compounds add to α-chloroaldimines.[1647]

Carbonylative cross-coupling reactions have been reported.[1648] Asymmetric variations are known using various chiral additives or chiral catalysts,[1649] including reactions of allylic chlorides.[1650] Coupling with propargylic substrates has also been reported.[1651] Aminoalkylation of arenes and alkenes has been reported using a Ni catalyst.[1652] The cross-coupling reaction of organotellurium compounds has been used for the preparation of biaryls and aryl acetylenes.[1653] The Co-catalyzed cross coupling of heteroarylzinc or arylzinc reagents

[1635] Çalimsiz, S.; Organ, M.G. *Chem. Commun.* ***2011***, *47*, 5181.
[1636] Krasovskiy, A.; Lipshutz, B.H. *Org. Lett.* ***2011***, *13*, 3822.
[1637] Thapa, S.; Kafle, A.; Gurung, S.K.; Montoya, A.; Riedel, P.; Giri, R. *Angew. Chem. Int. Ed.* ***2015***, *54*, 8236.
[1638] Negishi, E. *Acc. Chem. Res.* ***1982***, *15*, 340; Negishi, E.; Okukado, N.; King, A.O.; van Horn, D. E.; Spiegel, B.I. *J. Am. Chem. Soc.* ***1978***, *100*, 2254; Dong, Z.-B.; Manolikakes, G.; Shi, L.; Knochel, P.; Mayr, H. *Chem. Eur. J.* ***2010***, *16*, 248. For insights into the mechanism, see Schley, N.D.; Fu, G.C. *J. Am. Chem. Soc.* ***2014***, *136*, 16588. Also see Glorius, F. *Angew. Chem. Int. Ed.* ***2008***, *47*, 8347.
[1639] Zhou, J.; Fu, G.C. *J. Am. Chem. Soc.* ***2003***, *125*, 14726; Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N. *Angew. Chem. Int. Ed.* ***2004***, *43*, 6180.
[1640] Shibli, A.; Varghese, J.P.; Knochel, P.; Marek, I. *Synlett* ***2001***, 818.
[1641] Mutule, I.; Suna, E. *Tetrahedron* ***2005***, *61*, 11168. For a Cu-catalyzed reaction, see Thapa, S.; Vangala, A.S.; Giri, R. *Synthesis* ***2016***, *48*, 504.
[1642] Kabir, M.S.; Monte, A.; Cook, J.M. *Tetrahedron Lett.* ***2007***, *48*, 7269.
[1643] Matsubara, S.; Oshima, K.; Matsuoka, H.; Matsumoto, K.; Ishikawa, K.; Matsubara, E. *Chem. Lett.* ***2005***, *34*, 952.
[1644] Coleridge, B.M.; Bello, C.S.; Ellenberger, D.H.; Leitner, A. *Tetrahedron Lett.* ***2010***, *51*, 357.
[1645] Kim, S.-H.; Rieke, R.D. *Tetrahedron Lett.* ***2011***, *52*, 1523.
[1646] Colombe, J.R.; Bernhardt, S.; Stathakis, C.; Buchwald, S.L.; Knochel, P. *Org. Lett.* ***2013***, *15*, 5754.
[1647] Stanton, G.R.; Norrby, P.-O.; Carroll, P.J.; Walsh, P.J. *J. Am. Chem. Soc.* ***2012***, *134*, 17599.
[1648] Wang, Q.; Chen, C. *Tetrahedron Lett.* ***2008***, *49*, 2916.
[1649] See Fischer, C.; Fu, G.C. *J. Am. Chem. Soc.* ***2005***, *127*, 4594; Arp, F.O.; Fu, G.C. *J. Am. Chem. Soc.* ***2005***, *127*, 10482.
[1650] Son, S.; Fu, G.C. *J. Am. Chem. Soc.* ***2008***, *130*, 2756.
[1651] Smith, S.W.; Fu, G.C. *Angew. Chem. Int. Ed.* ***2008***, *47*, 9334.
[1652] Melzig, L.; Dennenwaldt, T.; Gavryushin, A.; Knochel, P. *J. Org. Chem.* ***2011***, *76*, 8891.
[1653] Stefani, A.; Pena, J.M.; Manarin, F.; Ando, R.A.; Leal, D.M.; Petragnani, N. *Tetrahedron Lett.* ***2011***, *52*, 4398.

with heteroaryl or aryl halides has been reported.[1654] An Fe-catalyzed cross-coupling reaction has been reported.[1655] The homocoupling of benzylic halides to give diarylethanes was effected with Me_2Zn and $RhCl(PPh_3)_3$.[1656] A Ni-catalyzed reductive approach to the cross-coupling of two unactivated alkyl halides, of which at least one must be a bromide, has been reported using a Ni catalyst with 3 equivalents of zinc.[1657]

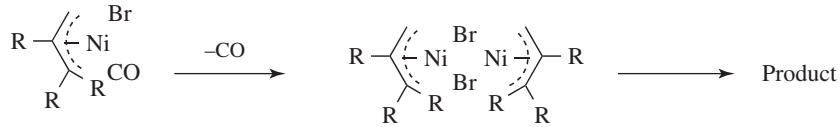
There have been mechanistic studies of the Cu-catalyzed coupling reactions.[1658] Vinyl halides can be coupled with vinyltin reagents in the presence of CuI.[1659] Copper compounds can also be used as catalysts with dialkylzinc reagents.[1660] Alkyl halides can be treated with SmI_2 and then CuBr to give a reactive species that couples with other alkyl halides.[1661] Trialkylindium compounds couple to allylic bromides in the presence of $Cu(OTf)_2$•$P(OEt)_3$[1662] and vinyl indium compounds are coupled to α-halo esters with a BEt_3 catalyst.[1663] Vinylzirconium reagents can be coupled to allylic halides in the presence of Cu(I) compounds.[1664] A S_N2' reaction of allylic phosphates with alkylaluminum reagents, in the presence of a Cu–NMC catalyst, gave the corresponding enyne.[1665]

Allylic, benzylic, vinylic, and aryl halides or triflates (trifluoromethylsulfonates) couple with organotin reagents in a reaction catalyzed by Pd complexes.[1666] The advantage of this procedure is that the aryl group may contain nitro, ester, or aldehyde groups, and so on, which cannot be present in a *Grignard reagent*. Functional groups such as CO_2R, CN, OH, and CHO may be present in either reagent, but the substrate may not bear a β hydrogen on an sp^3 carbon, because that results in elimination. Indium metal has been used to mediate the coupling of an allylic halide and an arylpalladium complex,[1667] and organoindium compounds were coupled to 1-iodonaphthalene with a Pd catalyst.[1668] Aryl halides have been coupled to allylic silanes in the presence of a Pd catalyst.[1669] Alkyl halides couple with ArMnCl or RMnCl in the presence of a Pd catalyst.[1670] Cobalt-catalyzed coupling reactions are known.[1671] The conversion of an aryllithium to an arylzirconium reagent was followed by coupling to a aryl halide in the presence of a Pd catalyst.[1672] Vinyl iodides couple

[1654] Haas, D.; Hammann, J.M.; Lutter, F.H.; Knochel, P. *Angew. Chem. Int. Ed.* ***2016***, *55*, 3809.
[1655] Harvey, M.H.; Cartes, M.Á.; Mansell, S.M.; Mendoza, C.; Murphy, D.M.; Neeve, E.C.; Nunn, J. *J. Am. Chem. Soc.* ***2012***, *134*, 10333.
[1656] Sato, K.; Inoue, Y.; Mori, T.; Sakaue, A.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *Org. Lett.* ***2014***, *16*, 3756.
[1657] Yu, X.; Yang, T.; Wang, S.; Xu, H.; Gong, H. *Org. Lett.* ***2011***, *13*, 2138.
[1658] Rideau, E.; You, H.; Sidera, M.; Claridge, T.D.W.; Fletcher, S.P. *J. Am. Chem. Soc.* ***2017***, *139*, 5614.
[1659] Kang, S.-K.; Kim, J.-S.; Choi, S.-C. *J. Org. Chem.* ***1997***, *62*, 4208.
[1660] Shi, W.J.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Zhou, Q.-L. *Tetrahedron: Asymmetry* ***2003***, *14*, 3867.
[1661] Berkowitz, W.F.; Wu, Y. *Tetrahedron Lett.* ***1997***, *38*, 3171.
[1662] Rodríguez, D.; Sestelo, J.P.; Sarandeses, L.A. *J. Org. Chem.* ***2003***, *68*, 2518.
[1663] Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2004***, *6*, 4555.
[1664] Sato, A.; Ito, H.; Taguchi, T. *J. Org. Chem.* ***2005***, *70*, 709.
[1665] Dabrowski, J.A.; Gao, F.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2011***, *133*, 4778.
[1666] See Stille, J.K. *Angew. Chem. Int. Ed.* ***1986***, *25*, 508; Bumagin, N.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1990***, *59*, 1174. See Martínez, A.G.; Barcina, J.O.; Heras, Md.R.C.; Cerezo, A.d.F. *Org. Lett.* ***2000***, *2*, 1377.
[1667] Lee, P.H.; Sung, S.-y.; Lee, K. *Org. Lett.* ***2001***, *3*, 3201.
[1668] Rodríguez, D.; Sestelo, J.P.; Sarandeses, L.A. *J. Org. Chem.* ***2004***, *69*, 8136.
[1669] Denmark, S.E.; Werner, N.S. *J. Am. Chem. Soc.* ***2008***, *130*, 16382.
[1670] Riquet, E.; Alami, M.; Cahiez, G. *Tetrahedron Lett.* ***1997***, *38*, 4397.
[1671] Czaplik, W.M.; Mayer, M.; von Wangelin, A.J. *Synlett* ***2009***, 2931.
[1672] Frid, M.; Pérez, D.; Peat, A.J.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1999***, *121*, 9469. See also, Villiers, P.; Vicart, N.; Ramondenc, Y.; Plé, G. *Tetrahedron Lett.* ***1999***, *40*, 8781.

with RMnCl with an iron catalyst[1673] and $Bu_3MnMgBr$ reacted with a geminal dibromocyclopropane to give a dialkylated cyclopropane.[1674] α-Haloketones are coupled with aryl halides using a Ni catalyst.[1675] Allylgallium reagents have been coupled to α-bromo esters in the presence of BEt_3/O_2.[1676]

Because of the presence of the 1,5-diene moiety in many naturally occurring compounds, methods that couple[1677] allylic groups are quite important. In one of these methods, allylic halides, tosylates, and acetates can be symmetrically coupled by treatment with nickel carbonyl[1678] to give 1,5-dienes.[1679] The order of halide reactivity is I > Br > Cl. With unsymmetrical allylic substrates, coupling nearly always takes place at the less-substituted end. The mechanism of coupling likely involves reaction of the allylic compound with $Ni(CO)_4$ to give one or more π allyl complexes, one of which may be the η^3 complex **120**. Loss of CO to give a π-allylnickel bromide (**121**) and ligand transfer leads to coupling and the final product. In some cases, the η^3 complexes **121** can be isolated from the solution and crystallized as stable solids.



120 **121**

Unsymmetrical coupling can be achieved by treating an alkyl halide directly with **121**, in a polar aprotic solvent,[1680] and coupling occurs at the less substituted end. There is evidence that free radicals are involved in such couplings.[1681] Hydroxy or carbonyl groups in the alkyl halide do not interfere. When **121** reacts with an allylic halide, a mixture of three products is obtained because of halogen–metal interchange.

OS **VII**, 245; **VIII**, 295; **X**, 391.

10-60 Coupling of Organometallic Reagents With Carboxylic Esters

Several organometallic reagents react with allylic esters and carbonates to give the coupling product. Lithium dialkylcopper reagents couple with allylic acetates to give normal

[1673] Cahiez, G.; Marquais, S. *Tetrahedron Lett.* ***1996***, *37*, 1773.
[1674] Kakiya, H.; Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron* ***2000***, *56*, 2131.
[1675] Durandetti, M.; Sibille, S.; Nédélec, J.-Y.; Périchon, J. *Synth. Commun.* ***1994***, *24*, 145.
[1676] Usugi, S.-i.; Yorimitsu, H.; Oshima, K. *Tetrahedron Lett.* ***2001***, *42*, 4535.
[1677] See Magid, R.M. *Tetrahedron* ***1980***, *36*, 1901 (pp. 1910–1924).
[1678] See Tamao, K.; Kumada, M. in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 819–887.
[1679] Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R. *Principles and Applications of Organotransition Metal Chemsitry*, 2nd ed., University Science Books, Mill Valley, CA, ***1987***, pp. 739–748; Billington, D.C. *Chem. Soc. Rev.* ***1985***, *14*, 93.
[1680] See Semmelhack, M.F. *Org. React.* ***1972***, *19*, 115 (pp. 147–162); Semmelhack, M.F. *Org. React.* ***1972***,*199*, 115 (pp. 144–146).
[1681] Hegedus, L.S.; Thompson, D.H.P. *J. Am. Chem. Soc.* ***1985***, *107*, 5663.

coupling products or those resulting from allylic rearrangement, depending on the substrate.[1682] A mechanism involving a σ-allylic copper(III) complex has been suggested.[1683] Propargylic acetates reacted with cuprates to give an allene. Silyl cuprates have also been used with benzoate esters, to give allylsilanes.[1684] Interestingly, allylic silanes have been coupled to acetates using $B(C_6F_5)_3$[1685] or BF_3.[1686]

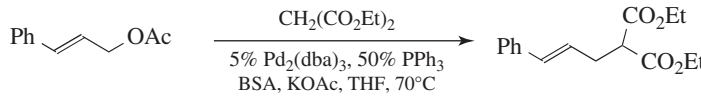
Lithium dialkylcopper reagents give normal coupling products with enol acetates of β-dicarbonyl compounds.[1687] It is also possible to carry out the coupling of allylic acetates with Grignard reagents, if catalytic amounts of cuprous salts are present.[1688] Yields are better with this method, and regioselectivity can be controlled by the choice of cuprous salts.

Several metal-catalyzed coupling reactions are known. Allylic, benzylic, and cyclopropylmethyl acetates couple with trialkylaluminums,[1689] and allylic acetates couple with aryl and vinylic tin reagents, in the presence of a Pd catalyst.[1690] Many Ni(0) coupling reactions are known.[1691] Titanium-mediated,[1692] Ir-catalyzed,[1693] and Fe-catalyzed[1694] reactions are also known. Allylic phosphonates have been used as substrates for displacement by higher order cuprates[1695] (see **10-58**) or dialkylzinc reagents.[1696]

A now common coupling reaction is the reaction of η^3-π-allyl Pd complexes[1697] (Sec. 3.C.i) with various nucleophiles,[1698] where the complex is obtained from allylic esters (acetate is the most common) or allylic carbonates (also see **10-30**). This coupling reaction is often called the *Tsuji-Trost* reaction.[1699] The mechanism of such π-allyl palladium reactions has been discussed.[1700] The structure and nature of the ligands associated with the

[1682] Purpura, M.; Krause, N. *Eur. J. Org. Chem.* ***1999***, 267.
[1683] Goering, H.L.; Kantner, S.S.; Seitz Jr., E.P. *J. Org. Chem.* ***1985***, *50*, 5495.
[1684] Fleming, I.; Higgins, D.; Lawrence, N.J.; Thomas, A.P. *J. Chem. Soc., Perkin Trans. 1* ***1992***, 3331.
[1685] Rubin, M.; Gevorgyan, V. *Org. Lett.* ***2001***, *3*, 2705. See Schwier, T.; Rubin, M.; Gevorgyan, V. *Org. Lett.* ***2004***, *6*, 1999.
[1686] Smith, D.M.; Tran, M.B.; Woerpel, K.A. *J. Am. Chem. Soc.* ***2003***, *125*, 14149; Ayala, L.; Lucero, C.G.; Romero, J.A.C.; Tabacco, S.A.; Woerpel, K.A. *J. Am. Chem. Soc.* ***2003***, *125*, 15521.
[1687] Casey, C.P.; Marten, D.F. *Tetrahedron Lett.* ***1974***, 925. See also Kobayashi, S.; Takei, H.; Mukaiyama, T. *Chem. Lett.* ***1973***, 1097.
[1688] Karlström, A.S.E.; Huerta, F.F.; Muezelaar, G.J.; Bäckvall, J.-E. *Synlett* ***2001***, 923; Alexakis, A.; Malan, C.; Lea, L.; Benhaim, C.; Fournioux, X. *Synlett* ***2001***, 927.
[1689] van Klaveren, M.; Persson, E.S.M.; del Villar, A.; Grove, D.M.; Bäckvall, J.-E.; van Koten, G. *Tetrahedron Lett.* ***1995***, *36*, 3059.
[1690] Del Valle, L.; Stille, J.K.; Hegedus, L.S. *J. Org. Chem.* ***1990***, *55*, 3019. For another method, see Legros, J.; Fiaud, J. *Tetrahedron Lett.* ***1990***, *31*, 7453.
[1691] Yatsumonji, Y.; Ishida, Y.; Tsubouchi, A.; Takeda, T. *Org. Lett.* ***2007***, *9*, 4603; Sasaoka, S.; Yamamoto, T.; Kinoshita, H.; Inomata, K.; Kotake, H. *Chem. Lett.* ***1985***, 315.
[1692] Mandal, S.K.; Paira, M.; Roy, S.C. *J. Org. Chem.* ***2008***, *73*, 3823.
[1693] Spiess, S.; Welter, C.; Franck, G.; Taquet, J.-P.; Helmchen, G. *Angew. Chem. Int. Ed.* ***2008***, *47*, 7652.
[1694] Plietker, B. *Angew. Chem. Int. Ed.* ***2006***, *45*, *6053*.
[1695] Belelie, J.L.; Chong, J.M. *J. Org. Chem.* ***2001***, *66*, 5552.
[1696] Kacprzynski, M.A.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2004***, *126*, 10676.
[1697] See Tsuji, J. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 3, Wiley, NY, ***1985***, pp. 163–199.
[1698] See Trost, B.M.; Crawley, M.L. *Chem. Rev.* ***2003***, *103*, 2921. For a discussion of the mechanism, see Tsurugi, K.; Nomura, N.; Aoi, K. *Tetrahedron Lett.* ***2002***, *43*, 469.
[1699] For a review, see Trost, B.M. *Tetrahedron* ***2015***, *71*, 5708. See Mohr, J.T.; Stoltz, B.M. *Chem. Asian J.* ***2007***, *2*, 1476; Trost, B.M. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1173; Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 130–166.
[1700] Trost, B.M.; Toste, F.D. *J. Am. Chem. Soc.* ***1999***, *121*, 4545; de Jong, G.Th.; Bickelhaupt, F.M. *ChemPhysChem* ***2007***, *8*, 1170; de Jong, G.T.; Bickelhaupt, F.M. *J. Chem. Theory Comput.* ***2007***, *3*, 514.

metal are important to the reaction, particularly with respect to stereoselectivity of a given reaction.[1701] A typical transformation is shown for the reaction of an allylic acetate with diethyl malonate, BSA (*N*,*O*-bis(trimethylsilyl)acetamide) and potassium acetate, which gives a coupling product in the presence of the Pd catalyst.[1702]



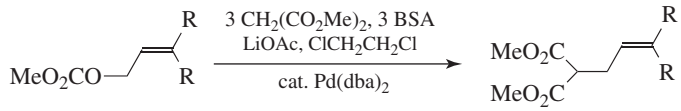
This reaction is a variation of the basic transformation reported several years ago by Trost.[1703]

Enolate anions of active methylene compounds[1704] and also sulfone anions[1705] have been used as nucleophiles much of the time. In most reported cases, the R'M species is the anion of an active methylene compound (such as sodium, potassium, or lithium dimethylmalonate), or *Knoevenagel-type* carbanions (see **16-38**), or amino acid surrogates.[1706] Enolate anions (see **10-67**) have also been used.[1707] The Pd catalyst used, the reaction conditions, and the nature of the organometallic compounds varies widely. Although two allylic coupling products are possible via the π-allyl intermediate, attack at the less-substituted position is generally favored. This transformation has been done in ionic liquids[1708] and ionic liquids have been used as additives in catalytic amounts in other solvents.[1709] The reaction has been done in water, using a Pd catalyst and micellar catalysts that use a photochromic surfactant.[1710] S_N2' reactions with allylic substrates have been reported.[1711] Benzoate esters have been used successfully in lieu of the acetate.[1712] Catalyst metals other than Pd have been used for this reaction with allylic acetates.[1713] The Ni-catalyzed reaction is known for the coupling of allylic acetates with alkyl halides.[1714] The reaction has been done using continuous flow techniques (Sec. 7.D) using a Pd–C catalyst.[1715] The use of chiral

[1701] See Wang, Q.-F.; He, W.; Liu, X.-Y.; Chen, H.; Qin, X.-Y.; Zhang, S.-Y. *Tetrahedron: Asymmetry* ***2008***, *19*, 2447; Jin, Y.; Du, D.M. *Tetrahedron* ***2012***, *68*, 3633.
[1702] Poli, G.; Giambastiani, G.; Mordini, A. *J. Org. Chem.* ***1999***, *64*, 2962.
[1703] Trost, B.M.; Weber, L.; Strege, P.E.; Fullerton, T.J.; Dietsche, T.J. *J. Am. Chem. Soc.* ***1978***, *100*, 3416, 3426. These papers include a discussion of the mechanism of this reaction.
[1704] Braun, M.; Meier, T. *Angew. Chem. Int. Ed.* ***2006***, *45*, 6952.
[1705] Manchand, P.S.; Wong, H.S.; Blount, J.F. *J. Org. Chem.* ***1978***, *43*, 4769.
[1706] Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *Org. Lett.* ***2001***, *3*, 3329.
[1707] Braun, M.; Laicher, F.; Meier, T. *Angew. Chem. Int. Ed.* ***2000***, *39*, 3494.
[1708] See Chen, W.; Xu, L.; Chatterton, C.; Xiao, J. *Chem. Commun.* ***1999***, 1247.
[1709] Sato, Y.; Yoshino, T.; Mori, M. *Org. Lett.* ***2003***, *5*, 31.
[1710] Billamboz, M.; Mangin, F.; Drillaud, N.; Chevrin-Villette, C.; Banaszak-Léonard, E.; Len, C. *J. Org. Chem.* ***2014***, *79*, 493.
[1711] Falciola, C.A.; Tissot-Croset, K.; Alexakis, A. *Angew. Chem. Int. Ed.* ***2006***, *45*, 5995.
[1712] Krafft, M.E.; Sugiura, M.; Abboud, K.A. *J. Am. Chem. Soc.* ***2001***, *123*, 9174.
[1713] **Ir**: Kinoshita, N.; Marx, K.H.; Tanaka, K.; Tsubaki, K.; Kawabata, T.; Yoshikai, N.; Nakamura, E.; Fuji, K. *J. Org. Chem.* ***2004***, *69*, 7960. **Pt**: Blacker, A.J.; Clarke, M.L.; Loft, M.S.; Mahon, M.F.; Humphries, M.E.; Williams, J.M.J. *Chem. Eur. J.* ***2000***, *6*, 353. **Ru**: Renaud, J.-L.; Bruneau, C.; Demerseman, B. *Synlett* ***2003***, 408.
[1714] Anka-Lufford, L.L.; Prinsell, M.R.; Weix, D.J. *J. Org. Chem.* ***2012***, *77*, 9989. See Cazorla, C.; Billamboz, M.; Bricout, H.; Monflier, E.; Len, C. *Eur. J. Org. Chem.* ***2017***, 1078.
[1715] Vaddula, B.R.; Saha, A.; Varma, R.S.; Leazer, J. *Eur. J. Org. Chem.* ***2012***, 6707.

ligands[1716] or chiral additives that may act as ligands[1717] leads to asymmetric induction in the coupling product.[1718]

As mentioned above, a common variation is to replace the acetate leaving group with a carbonate (—OCO_2R), where methyl carbonate (—OCO_2Me) is most common.[1719] A generalized reaction is the transformation of an allylic carbonate to the malonate derivative:[1720]



As with allylic acetates, chiral ligands and chiral additives lead to asymmetric induction.[1721] A variety of active methylene compounds can be used as nucleophiles,[1722] including enolate anions.[1723] Other nucleophiles can be used to displace allylic carbonates,[1724] often in conjunction with chiral ligands to give the product with enantioselectivity. Polymer-supported phosphine ligands have been used successfully,[1725] and catalyst systems other than Pd have been used for this reaction with allylic carbonates.[1726]. Potassium vinyltrifluoroborates (**10-72**) have also been used in Pd-catalyzed coupling reactions with allylic acetates.[1727]

Intramolecular cyclization is possible when the active methylene compound and an allylic acetate or carbonate is incorporated into the same molecule.[1728] Propargylic esters have been used in Pd-catalyzed coupling reactions, including a reaction with trialkylindium reagents.[1729]

[1716] See Boaz, N.W.; Ponaskik Jr., J.A.; Large, S.E.; Debenham, S.D. *Tetrahedron: Asymmetry* ***2004***, *15*, 2151.

[1717] Molander, G.A.; Burke, J.P.; Carroll, P.J. *J. Org. Chem.* ***2004***, *69*, 8062; Kloetzing, R.J.; Lotz, M.; Knochel, P. *Tetrahedron: Asymmetry* ***2003***, *14*, 255; Nakano, H.; Yokayama, J.-i.; Koiyama, Y.; Fjita, R.; Hongo, H. *Tetrahedron: Asymmetry* ***2003***, *14*, 2361; Mercier, F.; Brebion, F.; Dupont, R.; Mathey, F. *Tetrahedron: Asymmetry* ***2003***, *14*, 3137.

[1718] See Consiglio, G.; Waymouth, R.M. *Chem. Rev.* ***1989***, *89*, 257.

[1719] See Ito, K.; Kashiwagi, R.; Hayashi, S.; Uchida, T.; Katsuki, T. *Synlett* ***2001***, 284.

[1720] Hamada, Y.; Sakaguchi, K.-e.; Hatano, K.; Hara, O. *Tetrahedron Lett.* ***2001***, *42*, 1297.

[1721] Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* ***2003***, *125*, 12104; Faller, J.W.; Wilt, J.C. *Tetrahedron Lett.* ***2004***, *45*, 7613.

[1722] See Kazmaieer, U.; Zumpe, F.L. *Angew. Chem. Int. Ed.* ***1999***, *38*, 1468.

[1723] Evans, P.A.; Lawler, M.J. *J. Am. Chem. Soc.* ***2004***, *126*, 8642. For a reaction of a silyl enol ether, see Muraoka, T.; Matsuda, I.; Itoh, K. *Tetrahedron Lett.* ***2000***, *41*, 8807.

[1724] **Aryllithium reagents**: Evans, P.A.; Uraguchi, D. *J. Am. Chem. Soc.* ***2003***, *125*, 7158. **Alkoxides**: Evans, P.A.; Leahy, D.K.; Slieker, L.M. *Tetrahedron: Asymmetry* ***2003***, *14*, 3613. **Phenoxide anions**: Evans, P.A.; Leahy, D.K. *J. Am. Chem. Soc.* ***2000***, *122*, 5012; López, F.; Ohmura, T.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2003***, *125*, 3426. **Secondary amines**: Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.-a.; Takahashi, S. *J. Am. Chem. Soc.* ***2001***, *123*, 10405. **Primary amines**: Ohmura, T.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2002***, *124*, 15164. ***N*-Lithio-sulfonamides**: Evans, P.A.; Robinson, J.E.; Baum, E.W.; Fazal, A.N. *J. Am. Chem. Soc.* ***2002***, *124*, 8782. ***C*-Alkylation with an indole**: Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Org. Lett.* ***2004***, *6*, 3199. **Michael addition of conjugated esters**: Muraoka, T.; Matsuda, I.; Itoh, K. *J. Am. Chem. Soc.* ***2000***, *12*, 9552.

[1725] Uozumi, Y.; Shibatmoi, K. *J. Am. Chem. Soc.* ***2001***, *123*, 2919.

[1726] **Ru**: Trost, B.M.; Fraisse, P.L.; Ball, Z.T. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1059. **Mo**: Glorius, F.; Pfaltz, A. *Org. Lett.* ***1999***, *1*, 141; Malkov, A.V.; Spoor, P.; Vinader, V.; Kocovsky, P. *Tetrahedron Lett.* ***2001***, *42*, 509. **Ir**: Alexakis, A.; Polet, D. *Org. Lett.* ***2004***, *6*, 3529; Lee, P.H.; Sung, S.-y.; Lee, K.; Chang, S. *Synlett* ***2002***, 146.

[1727] Kabalka, G.W.; Al-Masum, M. *Org. Lett.* ***2006***, *8*, 11.

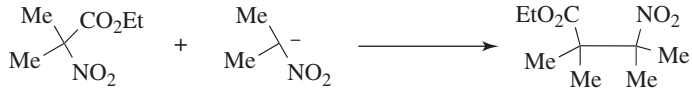
[1728] Castaño, A.M.; Méndez, M.; Ruano, M.; Echavarren, A.M. *J. Org. Chem.* ***2001***, *66*, 589. See also, Zhang, Q.; Lu, X.; Han, X. *J. Org. Chem.* ***2001***, *66*, 7676.

[1729] Riveiros, R.; Rodríguez, D.; Sestelo, J.P.; Sarandeses, L.A. *Org. Lett.* ***2006***, *8*, 1403.

10-61 Coupling of Organometallic Reagents With Miscellaneous Substrates

$$RSO_2X + R'M \longrightarrow R{-}R'$$

Leaving groups other than halide, esters or carbonates, or sulfonate esters are sometimes used. Sulfates, sulfonates, and epoxides give the expected products. The reactions of sodium sulfonates and alkyl halides in ionic liquids have been reported.[1730] The NR_2 group from *Mannich bases* such as $RCOCH_2CH_2NR_2$ can also act as a leaving group in this reaction (elimination–addition mechanism, Sec. 10.F). A nitro group can be displaced[1731] from α-nitro esters, ketones, nitriles, and α,α-dinitro compounds,[1732] and even from simple tertiary nitro compounds of the form R_3CNO_2[1733] or ArR_2CNO_2[1734] by salts of nitroalkanes, for example:



These reactions take place by SET mechanisms.[1735] However, with α-nitro sulfones it is the sulfone group that is displaced, rather than the nitro group.[1736] The SO_2R group of allylic sulfones can be replaced by CHZZ'

$$C{=}CCH_2{-}SO_2R \rightarrow C{=}CCH_2{-}CHZZ'$$

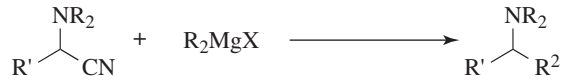
if a $Mo(CO)_6$ catalyst is used.[1737]

tert-Butyl sulfones react with organolithium reagents, in the presence of a catalytic amount of an Fe complex, to give coupling.[1738] Treatment with phenyliodonium bis(trifluoroacetate) gave the five-membered ring lactone.[1739] Similar displacement of $TolSO_2$ was observed with tolylsulfones and diethylzinc.[1740] Phosphonic esters, $ROPO(OR)_2$, react with allylic Grignard reagents to give the coupling product.[1741]

OS **I**, 471; **II**, 47, 360; **VII**, 351; **VIII**, 97, 471.

[1730] Hu, Y.; Chen, Z.-C.; Le, Z.-G.; Zheng, Q.G. *Synth. Commun.* ***2004***, *34*, 4031.
[1731] See Kornblum, N. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 361–393; Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* ***1991***, 423; Kornblum, N. in Feuer, H.; Nielsen, A.T. *Nitro Compounds: Recent Advances in Synthesis and Chemisry*, VCH, NY, ***1990***, pp. 46–85.
[1732] Kornblum, N.; Kelly, W.J.; Kestner, M.M. *J. Org. Chem.* ***1985***, *50*, 4720.
[1733] Kornblum, N.; Erickson, A.S. *J. Org. Chem.* ***1981***, *46*, 1037.
[1734] Kornblum, N.; Carlson, S.C.; Widmer, J.; Fifolt, M.J.; Newton, B.N.; Smith, R.G. *J. Org. Chem.* ***1978***, *43*, 1394.
[1735] For a review of the mechanism, see Beletskaya, I.P.; Drozd, V.N. *Russ. Chem. Rev.* ***1979***, *48*, 431. See also, Kornblum, N.; Wade, P.A. *J. Org. Chem.* ***1987***, *52*, 5301; Bowman, W.R. *Chem. Soc. Rev.* ***1988***, *17*, 283.
[1736] Kornblum, N.; Boyd, S.D.; Ono, N. *J. Am. Chem. Soc.* ***1974***, *96*, 2580.
[1737] Trost, B.M.; Merlic, C.A. *J. Org. Chem.* ***1990***, *55*, 1127.
[1738] Jin, L.; Julia, M.; Verpeaux, J.N. *Synlett* ***1994***, 215.
[1739] Casey, M.; Manage, A.C.; Murphy, P.J. *Tetrahedron Lett.* ***1992***, *33*, 965.
[1740] Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* ***2002***, *124*, 5940.
[1741] Yanagisawa, A.; Hibino, H.; Nomura, N.; Yamamoto, H. *J. Am. Chem. Soc.* ***1993***, *115*, 5879.

10-62 The Bruylants Reaction



The *Bruylants reaction* is the reaction of an amino nitrile with a *Grignard reagent* to give a substituted amine.[1742] This reaction is most often used for the preparation of aliphatic amines via aliphatic Grignard reagents. In a few cases, vinylic Grignard reagents can be used to prepare allylic amines.[1743] The use of $AgBF_4$ to convert amino nitriles to the corresponding iminium ion facilitates the Bruylants reaction with vinylic Grignard reagents.[1744] Replacement of the cyano group in a tertiary nitrile is also possible.[1745]

10-63 Coupling Involving Alcohols

In some cases, it is possible to couple an alcohol in the presence of an organometallic compound.[1746] Allylic alcohols are coupled with alkylmagnesium bromides in the presence of Ti(O*i*-Pr)$_4$, for example.[1747] Benzylic alcohols have been coupled to Grignard reagents as an alkyl or aryl source, in the presence of a Ni catalyst.[1748] Benzylic alcohols have been converted to benzylic Grignard reagents using hexylmagnesium chloride using an Fe, Ni, or Co catalyst.[1748] Using an Ir catalyst, the enantioselective reaction of secondary allylic alcohols with potassium alkynyltrifluoroborates, a chiral ligand, trifluoroacetic acid, and KHF_2 give the corresponding enyne.[1749] The Pd-catalyzed reaction of active methylene compounds with allylic alcohols[1750] or benzylic alcohols[1751] is also known. The coupling of an alcohol to the α carbon of a ketone to give a β-substituted alcohol is possible in the presence of a Ru catalyst.[1752] Alcohols are coupled to allenes in the presence of an Ir catalyst.[1753] Allylic carbonates are coupled to allylic alcohols with a Ni catalyst.[1754]

[1742] Bruylants, P. *Bull. Soc. Chem. Belg.* ***1924***, *33*, 467.
[1743] Trost, B.M.; Spagnol, M.D. *J. Chem. Soc., Perkin Trans. 1* ***1995***, 2083.
[1744] Agami, C.; Couty, F.; Evano, G. *Org. Lett.* ***2000***, *2*, 2085.
[1745] Katritzky, A.R.; Yang, H.; Singh, S.K. *J. Org. Chem.* ***2005***, *70*, 286.
[1746] For general reviews, see Huy, P.H.; Hauch, T.; Filbrich, I. *Synlett* ***2016***, *27*, 2631; Bandini, M.; Cera, G.; Chiarucci, M. *Synthesis* ***2012***, *44*, 504. For a review of Pd-catalyzed reactions, see Muzart, J. *Tetrahedron* ***2005***, *61*, 4179. For a review of Ru catalysts, see Roy, B.C.; Chakrabarti, K.; Shee, S.; Paul, S.; Kundu, S. *Chem. Eur. J.* ***2016***, *22*, 18147. See Nikolaev, A.; Orellana, A. *Synthesis* ***2016***, *48*, 1749. See Dryzhakov, M.; Richmond, E.; Moran, J. *Synthesis* ***2016***, *48*, 935.
[1747] Kulinkovich, O.G.; Epstein, O.L.; Isakov, V.E.; Khmel'nitskaya, E.A. *Synlett* ***2001***, 49.
[1748] Yu, D.-G.; Wang, X.; Zhu, R.-Y.; Luo, S.; Zhang, X.-B.; Wang, B.-Q.; Wang, L.; Shi, Z.-J. *J. Am. Chem. Soc.* ***2012***, *134*, 14638.
[1749] Hamilton, J.; Sarlah, D.; Carreira, E.M. *Angew. Chem. Int. Ed.* ***2013***, *52*, 7532.
[1750] Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* ***2004***, *6*, 4085.
[1751] Bisaro, F.; Prestat, G.; Vitale, M.; Poli, G. *Synlett* ***2002***, 1823.
[1752] Cho, C.S.; Kim, B.T.; Kim. T.-J.; Shim. S.C. *J. Org. Chem.* ***2001***, *66*, 9020. See also, Morita, M.; Obora, Y.; Ishii, Y. *Chem. Commun.* ***2007***, 2850.
[1753] Bower, J.F.; Skucas, E.; Patman, R.L.; Krische, M.J. *J. Am. Chem. Soc.* ***2007***, *129*, 15134.
[1754] Sumida, Y.; Hayashi, S.; Hirano, K.; Hideki, H.; Oshima, K. *Org. Lett.* ***2008***, *10*, 1629.

Allylic or benzylic alcohols can be symmetrically coupled[1755] by treatment with methyllithium and titanium trichloride at −78 °C[1756] or by heating with $TiCl_3$ and $LiAlH_4$.[1757] When the substrate is an allylic alcohol, the reaction is not regiospecific, but a mixture of normal coupling and allylic rearranged products is found. A free-radical mechanism is involved.[1758] The $TiCl_3$–$LiAlH_4$ reagent can also convert 1,3-diols to cyclopropanes, provided that at least one phenyl group is present.[1759]

A catalyst has been developed with magnetite impregnated with Ir that catalyzes the cross-alkylation of primary alcohols; the catalyst can be removed from the reaction medium by magnetic sequestering.[1760] The Ru-catalyzed coupling of two alcohols with KOH gave the ketone, whereas reaction with Mg_3N_2 gave the corresponding ester.[1761] Alcohols reacted with $CH_2{=}CHCH_2SiMe_3$ in the presence of 15% iodine and an iodoimidazolium catalyst to give the allyl coupling product.[1762] The $Al(OTf)_3$-catalyzed reaction of propargylic alcohols with molecules such as alcohols, aromatic compounds, amides, and thiols to give replacement of the hydroxyl unit with the nucleophile has been conducted.[1763] The cross coupling of alcohols in the presence of $NaHSO_4/SiO_2$ gave the corresponding substituted alkenes.[1764] The stereospecific coupling of alkenes with alcohols to give the corresponding substituted (*E*)-alkenes was reported with an Fe catalyst.[1765] Me_2TiCl_2 reacts with tertiary alcohols in the same way.[1766] β-Alkylation of secondary alcohols has been reported using alcohol substrates in the presence of an Ir complex.[1767] Allylic alcohols couple with a reagent prepared from MeLi, CuI, or R'Li in the presence of $(Ph_3PNMePh)^+ I^-$ to give alkenes that are products of allylic rearrangement.[1768] Allylic alcohols also couple with certain Grignard reagents[1769] in the presence of a Ni complex to give both normal products and the products of allylic rearrangement. Allylic alcohols reacted with 3 equivalents of EtMgBr via a S_N2' alkylation in the presence of $ClTi(O\textit{i}\text{-}Pr)_3$, then treated with iodomethane, to give the corresponding alkene.[1770]

The reaction gives good yields with primary, secondary, and tertiary alcohols, and with alkyl and aryllithium reagents.[1771] The Co-catalyzed coupling of secondary alcohols and

[1755] See Lai, Y. *Org. Prep. Proceed. Int.* ***1980***, *12*, 363 (pp. 377–388).
[1756] Sharpless, K.B.; Hanzlik, R.P.; van Tamelen, E.E. *J. Am. Chem. Soc.* ***1968***, *90*, 209.
[1757] McMurry, J.E.; Silvestri, M.G.; Fleming, M.P.; Hoz, T.; Grayston, M.W. *J. Org. Chem.* ***1978***, *43*, 3249. See Nakanishi, S.; Shundo, T.; Nishibuchi, T.; Otsuji, Y. *Chem. Lett.* ***1979***, 955.
[1758] van Tamelen, E.E.; Åkermark, B.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1969***, *91*, 1552.
[1759] Walborsky, H.M.; Murati, M.P. *J. Am. Chem. Soc.* ***1980***, *102*, 426.
[1760] Cano, R.; Yus, M.; Ramón, J. *Chem. Commun.* ***2012***, *48*, 7628.
[1761] Makarov, I.S.; Madsen, R. *J. Org. Chem.* ***2013***, *78*, 6593.
[1762] Saito, M.; Tsuji, N.; Kobayashi, Y.; Takemoto, Y. *Org. Lett.* ***2015***, *17*, 3000.
[1763] Gohain, M.; Marais, C.; Bezuidenhoudt, B.C.B. *Tetrahedron Lett.* ***2012***, *53*, 1048. For a similar reaction, catalyzed by 4-nitrobenzenesulfonic acid, see Savarimuthu, S.A.; Prakash, D.G.L.; Thomas, S.A. *Tetrahedron Lett.* ***2014***, *55*, 3213. For reviews, see Nishibayashi, Y. *Synthesis* ***2012***, *44*, 489; Bauer, E.B. *Synthesis* ***2012***, *44*, 1131.
[1764] Aoyama, T.; Koda, S.; Takeyoshi, Y.; Ito, T.; Takido, T.; Kodomari, M. *Chem. Commun.* ***2013***, *49*, 6605.
[1765] Liu, Z.-Q.; Zhang, Y.; Zhao, L.; Li, Z.; Wang, J.; Li, H.; Wu, L.-M. *Org. Lett.* ***2011***, *13*, 2208.
[1766] Reetz, M.T.; Westermann, J.; Steinbach, R. *J. Chem. Soc., Chem. Commun.* ***1981***, 237.
[1767] Fujita, K.; Asai, C.; Yamaguchi, T.; Hanasaka, F.; Yamaguchi, R. *Org. Lett.* ***2005***, *7*, 4017.
[1768] Goering, H.L.; Tseng, C.C. *J. Org. Chem.* ***1985***, *50*, 1597. For another procedure, see Yamamoto, Y.; Maruyama, K. *J. Organomet. Chem.* ***1978***, *156*, C9.
[1769] Consiglio, G.; Morandini, F.; Piccolo, O. *J. Am. Chem. Soc.* ***1981***, *103*, 1846 and references cited therein. See Fujisawa, T.; Iida, S.; Yukizaki, H.; Sato, T. *Tetrahedron Lett.* ***1983***, *24*, 5745.
[1770] Das, P.P.; Lysenko, I.L.; Cha, J.K. *Angew. Chem. Int. Ed.* ***2011***, *50*, 9459.
[1771] See Cella, J.A. *J. Org. Chem.* ***1982***, *47*, 2125.

primary alcohols gave the alkylated mono alcohol.[1772] Allenic alcohols couple with allyl indium reagents at 140 °C to give allylic alcohol products.[1773] Secondary benzylic alcohols have been coupled to primary benzylic alcohols with a ruthenacycle catalyst, in the presence of base, to give the coupling product, an alcohol.[1774] Alcohols react with 1,3-ketones in the presence of a sulfuric acid catalyst at 101 °C.[1775] Alcohols react with acetonitrile to give the corresponding nitrile in the presence of Cs_2CO_3 and an Ir catalyst, under microwave irradiation.[1776] The Pd-catalyzed coupling of allylic alcohols with cyclic 1,3-diones, in water, gave the corresponding allylated products.[1777] Alcohols react with allylsilanes, in the presence of an $InCl_3$[1778] or $InBr_3$[1779] catalyst, to give the corresponding coupling product. Propargylic alcohols have been coupled to allylic silanes using an Au catalyst[1780] or a Rh catalyst.[1781]

10-64 Coupling of Organometallic Reagents With Compounds Containing the Ether Linkage[1782]

$$R_2C(OR')_2 + R''MgX \longrightarrow R_2CR''(OR') + R'OMgX$$
$$RC(OR')_3 + R''MgX \longrightarrow RCR''(OR')_2 + R'OMgX$$

Acetals,[1783] ketals, and ortho esters[1784] react with Grignard reagents to give, respectively, ethers and acetals (or ketals). The latter can be hydrolyzed to aldehydes or ketones (**10-6**). This procedure is a way of converting a halide R″X (which may be alkyl, aryl, vinylic, or alkynyl) to an aldehyde R″CHO, increasing the length of the carbon chain by one carbon (see also **10-77**). The ketone synthesis generally gives lower yields. Acetals, including allylic acetals, also give this reaction with organocopper compounds and BF_3.[1785] Dihydropyrans react with Grignard reagents in the presence of a Ni catalyst.[1786] Acetals also undergo substitution when treated with silyl enol ethers or allylic silanes, with a Lewis acid catalyst,[1787] to give a β-alkoxy ketone. ω-Ethoxy lactams react with Grignard regents to give ω-substituted lactams.[1788]

[1772] Freitag, F.; Irrgang, T.; Kempe, R. *Chem. Eur. J.* ***2017***, *23*, 12110.
[1773] Araki, S.; Usui, H.; Kato, M.; Butsugan, Y. *J. Am. Chem. Soc.* ***1996***, *118*, 4699.
[1774] Chang, X.; Chuan, L.W.; Yongxin, L.; Pullarkat, S.A. *Tetrahedron Lett.* ***2012***, *53*, 1450. For catalysis with bimetallic Pt–Sn/γ-A_2O_3, see Wu, K.; He, W.; Sun, C.; Yu, Z. *Tetrahedron Lett.* ***2016***, *57*, 4017. For catalysis by imidizoium hydrogen sulfates, see Chu, X.-Q.; Jiang, R.; Fang,Y.; Gu, Z.-Y.; Meng, H.; Wang, S.-Y.; Ji, S.-J. *Tetrahedron* ***2013***, *69*, 1166.
[1775] Xia, F.; Zhao, Z.L.; Liu, P.N. *Tetrahedron Lett.* ***2012***, *53*, 2828.
[1776] Anxionnat, B.; Pardo, D.G.; Ricci, G.; Cossy, J. *Org. Lett.* ***2011***, *13*, 4084.
[1777] Shue, Y.-J.; Yang, S.-C. *Tetrahedron Lett.* ***2012***, *53*, 1380.
[1778] Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* ***2006***, *71*, 8516; Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem. Int. Ed.* ***2006***, *45*, 793.
[1779] Kim, S.H.; Shin, C.; Pae, A.N.; Koh, H.Y.; Chang, M.H.; Chung, B.Y.; Cho, Y.S. *Synthesis* ***2004***, 1581.
[1780] Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* ***2005***, *127*, 14180.
[1781] Funayama, A.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* ***2005***, *127*, 15354.
[1782] See Trofimov, B.A.; Korostova, S.E. *Russ. Chem. Rev.* ***1975***, *44*, 41.
[1783] See Mukaiyama, T.; Murakami, M. *Synthesis* ***1987***, 1043; For a list of substrates and reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 934–942.
[1784] See DeWolfe, R.H. *Carboxylic Ortho Acid Derivatives*, Academic Press, NY, ***1970***, pp. 44–45, 224–230.
[1785] Normant, J.F.; Alexakis, A.; Ghribi, A.; Mangeney, P. *Tetrahedron* ***1989***, *45*, 507; Alexakis, A.; Mangeney, P.; Ghribi, A.; Marek, I.; Sedrani, R.; Guir, C.; Normant, J.F. *Pure Appl. Chem.* ***1988***, *60*, 49.
[1786] Ducoux, J.-P.; LeMénez, P.; Kunesch, N.; Wenkert, E. *J. Org. Chem.* ***1993***, *58*, 1290.
[1787] See Mori, I.; Ishihara, K.; Flippin, L.A.; Nozaki, K.; Yamamoto, H.; Bartlett, P.A.; Heathcock, C.H. *J. Org. Chem.* ***1990***, *55*, 6107, and references cited therein.
[1788] Wei, Z.Y.; Knaus, E.E. *Org. Prep. Proceed. Int.* ***1993***, *25*, 255.

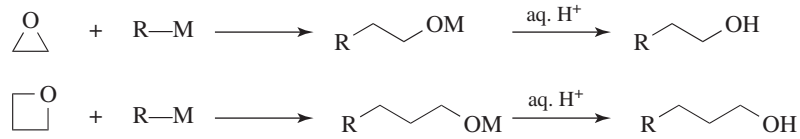
Ordinary ethers are not cleaved by Grignard reagents (in fact, diethyl ether and THF are the most common solvents for Grignard reagents), although more active organometallic compounds can cleave ethers.[1789] However, a Ni-catalyzed coupling reaction of ROMe with MeMgBr led to replacement of the OMe group with a methyl group from the Grignard reagent:[1790]

$$\text{MeMgX} + \text{ROMe} \rightarrow \text{R—Me}$$

Oxetanes have been opened with organolithium reagents and BF_3•OEt_2[1791] and also with excess Li metal with a biphenyl catalyst.[1792] Allylic ethers can be cleaved by Grignard reagents in THF if CuBr is present.[1793] The reaction can take place either with or without allylic rearrangement.[1794] Vinylic ethers can also be cleaved by Grignard reagents in the presence of a Ni catalyst.[1795] Silyl enol ethers $R_2C{=}CROSiMe_3$ behave similarly.[1796] Bicyclic benzofurans can be opened by dialkylzinc reagents in the presence of a Pd catalyst.[1797] Benzylic methoxy compounds are converted to the methyl derivative by reaction with methylmagnesium iodide and a Ni catalyst.[1798]

OS **II**, 323; **III**, 701. Also see OS **V**, 431.

10-65 The Reaction of Organometallic Reagents With Epoxides (Oxiranes) or Oxetanes



The reaction between *Grignard reagents* or organolithium reagents and epoxides is very valuable and is often used to increase the length of a carbon chain by two carbons.[1799] The Grignard reagent may be aromatic or aliphatic, although tertiary Grignard reagents give low yields. As expected for an S_N2 process, attack is at the less substituted carbon. With allylic Grignard reagents, the addition of a catalytic amount of $Yb(OTf)_3$ facilitated

[1789] See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 1013–1045.
[1790] Guan, B.-T.; Xiang, S.-K.; Wang, B.-Q.; Sun, Z.-P.; Wang, Y.; Zhao, K.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* ***2008***, *130*, 3268.
[1791] Bach, T.; Eilers, F. *Eur. J. Org. Chem.* ***1998***, 2161.
[1792] Rama, K.; Pasha, M.A. *Tetrahedron Lett.* ***2000***, *41*, 1073.
[1793] Commercon, A.; Bourgain, M.; Delaumeny, M.; Normant, J.F.; Villieras, J. *Tetrahedron Lett.* ***1975***, 3837; Claesson, A.; Olsson, L. *J. Chem. Soc., Chem. Commun.* ***1987***, 621.
[1794] Calo, V.; Lopez, L.; Pesce, G. *J. Chem. Soc., Perkin Trans. 1* ***1988***, 1301. See also, Valverde, S.; Bernabé, M.; Garcia-Ochoa, S.; Gómez, A.M. *J. Org. Chem.* ***1990***, *55*, 2294.
[1795] Kocienski, P.; Dixon, N.J.; Wadman, S. *Tetrahedron Lett.* ***1988***, *29*, 2353.
[1796] Hayashi, T.; Katsuro, Y.; Kumada, M. *Tetrahedron Lett.* ***1980***, *21*, 3915.
[1797] Lauens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* ***2000***, *122*, 1804.
[1798] Taylor, B.L.H.; Swift, E.C.; Waetzig, J.D.; Jarvo, E.R. *J. Am. Chem. Soc.* ***2011***, *133*, 389.
[1799] See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 961–1012; Schaap, A.; Arens, J.F. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 1249. Also see Schrumpf, G.; Grätz, W.; Meinecke, A.; Fellenberger, K. *J. Chem. Res. (S)* ***1982***, 162.

alkylation.[1800] Organolithium reagents,[1801] in the presence of chiral additives, lead to the 2-substituted alcohol with good enantioselectivity. Similar reaction with a chiral *Schiff base* gave the same type of product, with excellent enantioselectivity.[1802]

Lithium dialkylcopper reagents also give the reaction[1803] as do higher order cuprates,[1804] which often give higher yields. Organocuprates have the additional advantage that they do not react with ester, ketone, or carboxyl groups so that the epoxide ring of epoxy esters, ketones, and carboxylic acids can be selectively attacked, often in a regioselective manner.[1805] The use of BF_3 increases the reactivity of R_2CuLi, enabling the use with thermally unstable epoxides.[1806] Lithium diaminocyano cuprates have also been used.[1807]

The reaction has also been performed with other organometallic compounds,[1808] and epoxides or oxetanes are ring opened by reaction with various reagents in the presence of transition metal catalysts.[1809] Terminal epoxides react with aryl halides using a $NiI_2 \bullet xH_2O$/2,2′-bipyridine catalyst, with 20% pyridine, 25% NaI, 2 equivalents of Zn, and $Et_3H^+ Cl^-$ to give the corresponding alcohol.[1810] Arenes react with terminal epoxides in the presence of a Pd catalyst to give the alcohol.[1811] Aryl iodides ring-open terminal epoxides in the presence of selenium and CuCl as a catalyst to give a β-arylselenyl alcohol.[1812] Styryl epoxides reacted with butyllithium and $LiCH_2CN$ to give 1-hydroxymethylstyrene derivatives in an α-methenylation reaction.[1813] 2,3-Epoxyamines reacted with $TMSN_3$ in the presence of a Lewis acid to give 3-azido-2-hydroxyamines or 2-azido-3-hydroxyamines.[1814] Catalysis with $BF_3 \bullet OEt_2$ or $ZnCl_2$ gives the 3-azido-2-hydroxyamines whereas Ti(O-*i*-Pr)$_4$ gave the 2-azido-3-hydroxyamines.[1814] The reaction of anisole derivatives with butyllithium in the presence of a catalytic amount of TMEDA, for 16 h at 0 °C, followed by reaction with terminal epoxides at – 78 °C gave the *ortho*-2-hydroxyalkylanisole derivative with high regioselectivity.[1815]

[1800] Likhar, P.R.; Kumar, M.P.; Bandyopadhyay, A.K. *Tetrahedron Lett.* ***2002***, *43*, 3333.

[1801] Hodgson, D.M.; Stent, M.A.H.; Stefane, B.; Wilson, F.X. *Org. Biomol. Chem.* ***2003***, *1*, 1139; Hodgson, D.M.; Maxwell, C.R.; Miles, T.J.; Paruch, E.; Matthews, I.R.; Witherington, J. *Tetrahedron* ***2004***, *60*, 3611.

[1802] Oguni, N.; Miyagi, Y.; Itoh, K. *Tetrahedron Lett.* ***1998***, *39*, 9023.

[1803] See Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, ***1980***, pp. 103–113. See also, Lipshutz, B.H.; Kozlowski, J.; Wilhelm, R.S. *J. Am. Chem. Soc.* ***1982***, *104*, 2305; Blanchot-Courtois, V.; Hanna, I. *Tetrahedron Lett.* ***1992***, *33*, 8087.

[1804] Chauret, D.C.; Chong, J.M. *Tetrahedron Lett.* ***1993***, *34*, 3695.

[1805] Chong, J.M.; Cyr, D.R.; Mar, E.K. *Tetrahedron Lett.* ***1987***, *28*, 5009; Larchevêque, M.; Petit, Y. *Tetrahedron Lett.* ***1987***, *28*, 1993.

[1806] See Alexakis, A.; Jachiet, D.; Normant, J.F. *Tetrahedron* ***1986***, *42*, 5607.

[1807] Yamamoto, Y.; Asao, N.; Meguro, M.; Tsukada, N.; Nemoto, H.; Sadayori, N.; Wilson, J.G.; Nakamura, H. *J. Chem. Soc., Chem. Commun.* ***1993***, 1201.

[1808] See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1045–1063. **Ba**: Yasue, K.; Yanagisawa, A.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* ***1997***, *70*, 493. **Mn**: Tang, J.; Yorimitsu, H.; Kakiya, H.; Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* ***1997***, *38*, 9019**. Sn**: Yadav, J.S.; Reddy, B.V.S.; Satheesh, G. *Tetrahedron Lett.* ***2003***, *44*, 6501**. Zn**: Equey, O.; Vrancken, E.; Alexakis, A. *Eur. J. Org. Chem.* ***2004***, 2151.

[1809] For a review, see Wang, C.; Luo, L.; Yamamoto, H. *Acc. Chem. Res.* ***2016***, *49*, 193.

[1810] Zhao, Y.; Weix, D.J. *J. Am. Chem. Soc.* ***2014***, *136*, 48.

[1811] Wang, Z.; Kuninobu, Y.; Kanai, M. *J. Am. Chem. Soc.* ***2015***, *137*, 6140.

[1812] Min, L.; Wu, G.; Liu, M.; Gao, W.; Ding, J.; Chen, J.; Huang, X.; Wu, H. *J. Org. Chem.* ***2016***, *81*, 7584.

[1813] Tomioka, T.; Sankranti, R.; Yamada, T.; Clark, C. *Org. Lett.* ***2013***, *15*, 5099; Tomioka, T.; Sankranti, R.; James, A.M.; Mattern, D.L. *Tetrahedron Lett.* ***2014***, *55*, 3443.

[1814] Righi, G.; Antonioletti, R.; Pelagalli, R. *Tetrahedron Lett.* ***2012***, *53*, 5582.

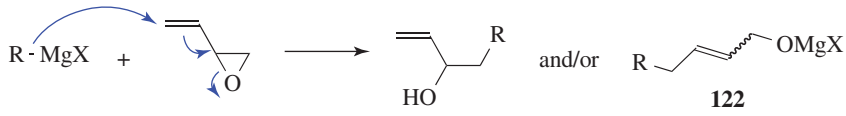
[1815] Ertürk, E.; Tezeren, M.A.; Atalar, T.; Tilki, T. *Tetrahedron* ***2012***, *68*, 6463.

Epoxides are opened to give the corresponding alcohols by treatment with $Ti(O\text{-}i\text{-}Pr)_4$, Me_3SiCl, and Mg.[1816] Epoxides reacted with potassium alkyltrifluoroborates in the presence of TFAA to give ring opening and the corresponding alcohols.[1817] Epoxides reacted with 3 equivalents of trimethylsulfoxonium iodide and 3 equivalents of KO-*t*-Bu, in the presence of a cobalt catalyst, to give a homoallylic alcohol.[1818] A symmetric ring opening of 3-substituted oxetanes with nucleophiles leads to ring opening and the alcohol.[1819] The epoxides of dihydrofurans and dihydropyrans reacted with organolithium reagents to give unsaturated diols.[1820]

Trialkylaluminum reagents open epoxides with delivery of the alkyl group to carbon.[1821] In the presence of a Lewis acid catalyst such as BF_3, alkylation can occur at the more substituted carbon.[1822] *Friedel-Crafts-type alkylation* (see **11-11**) is possible when an aromatic compound reacts with an epoxide and $AlCl_3$.[1823] Epoxides react with allyl bromide in the presence of In metal with the expected delivery of allyl to the less-substituted carbon.[1824] When a substituted epoxide was treated with CO, $BF_3{\bullet}OEt_2$, and a Co catalyst, carbonylation occurred and the final product was a β-lactone.[1825] Similar β-lactone-forming reactions were reported using substituted epoxides, CO, and a metal compound–BF_3 complex.[1826] Five-membered ring lactams were formed from substituted epoxides using $BF_3{\bullet}OEt_2$ followed by treatment with KHF_2.[1827] Ring opening of epoxides with Ti compounds has been shown to be selective for the more substituted carbon.[1828] Epoxides react with Ag salts of alkynes, in the presence of Zr compounds, to give the rearrangement product, a propargylic alcohol.[1829] A Ga/Sm-induced ring opening with alkyl halides has been reported.[1830] In the presence of a Sc catalyst, chiral allylic boranes open epoxides at the less-substituted position to generate chiral, homoallylic alcohols.[1831]

When the substrate is a vinylic epoxide,[1832] Grignard reagents generally give a mixture of the normal product of attack at the less substituted carbon atom and the product of allylic rearrangement (**122**).[1833]

[1816] Kawaji, T.; Shohji, N.; Miyashita, K.; Okamoto, S. *Chem. Commun.* ***2011***, *47*, 7857.
[1817] Roscales, S. Csákÿ, A.G. *Chem. Commun.* ***2014***, *50*, 454.
[1818] Jamieson, M.L.; Hume, P.A.; Furkert, D.P.; Brimble, M.A. *Org. Lett.* ***2016***, *18*, 468.
[1819] Wang, Z.; Chen, Z.; Sun, J. *Org. Biomol. Chem.* ***2014***, *12*, 6028.
[1820] Odgson, D.M.; Stent, M.A.H.; Wilson, F.X. *Synthesis* ***2002***, 1445.
[1821] Schneider, C.; Brauner, J. *Eur. J. Org. Chem.* ***2001***, 4445; Sasaki, M.; Tanino, K.; Miyashita, M. *J. Org. Chem.* ***2001***, *66*, 5388; Shanmugam, P.; Miyashita, M. *Org. Lett.* ***2003***, *5*, 3265 (formation of *O*-silyl ether product). For the reaction in an ionic liquid, see Zhou, H.; Campbell, E.J.; Nguyen, S.T. *Org. Lett.* ***2001***, *3*, 2229.
[1822] See Zhao, H.; Pagenkopf, B.L. *Chem. Commun.* ***2003***, 2592.
[1823] Lin, J.; Kanazaki, S.; Kashino, S.; Tsuboi, S. *Synlett* ***2002***, 899.
[1824] Hirashita, T.; Mitsui, K.; Hayashi, Y.; Araki, S. *Tetrahedron Lett.* ***2004***, *45*, 9189. For a reaction using Pd nanoparticles, see Jiang, N.; Hu, Q.; Reid, C.S.; Ou, Y.; Li, C.J. *Chem. Commun.* ***2003***, 2318.
[1825] Lee, J.T.; Thomas, P.J.; Apler, H. *J. Org. Chem.* ***2001***, *66*, 5424.
[1826] Schmidt, J.A.R.; Mahadevan, V.; Getzler, Y.D.Y.L.; Coates, G.W. *Org. Lett.* ***2004***, *6*, 373.
[1827] Movassaghi, M.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2002***, *124*, 2456.
[1828] Tanaka, T.; Hiramatsu, K.; Kobayashi, Y.; Ohno, H. *Tetrahedron* ***2005***, *61*, 6726.
[1829] Albert, B.J.; Koide, K. *J. Org. Chem.* ***2008***, *73*, 1093.
[1830] Gohain, M.; Prajapati, D. *Chem. Lett.* ***2005***, *34*, 90.
[1831] Lautens, M.; Maddess, M.L.; Sauer, E.L.O.; Ouellet, S.G. *Org. Lett.* ***2002***, *4*, 83.
[1832] For a list of organometallic reagents that react with vinylic epoxides, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 244–250.
[1833] Marshall, J.A.; Trometer, J.D.; Cleary, D.G. *Tetrahedron* ***1989***, *45*, 391.

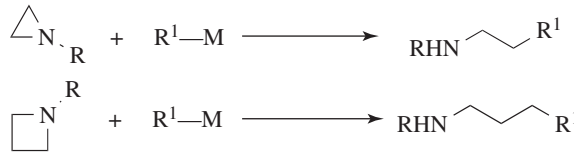


122

Butyllithium reacted with a *gem*-difluoroalkylidene epoxide (F_2C=CR–epoxide) and S_N2' displacement gave alkylation at the difluoro carbon and opened the epoxide.[1834] The S_N2' product (e.g., **122**) often predominates. In the case of R_2CuLi,[1835] acyclic substrates give mostly allylic rearrangement (S_N2').[1835]

OS **I**, 306; **VII**, 501; **VIII**, 33, 516; **X**, 297.

10-66 Reaction of Organometallics With Aziridines or Azetidines



Aziridines have been opened by organometallic reagents to give amines.[1836] It is also possible to open aziridines, with organometallic reagents particularly, when there is a *N*-sulfonyl group such as tosyl (formally making it a sulfonamide), although they are less reactive than epoxides.[1837] Transition metals have been used with three-membered ring heterocycles.[1838] Grignard reagents react with *N*-tosyl 2-phenylaziridine to give the corresponding *N*-tosyl amine.[1839] Organocuprates (**10-58**) reaction with *N*-alkyl aziridines to give the corresponding amine.[1840] Aziridines react with benzene, in the presence of $In(OTf)_3$, to give the β-aryl amine.[1841]

N-Tosyl aziridines have also been opened with enolate anions, which led to a pyrroline derivative.[1842] Allylic alcohols open *N*-tosyl aziridines with KSF-Montmorillonite clay.[1843] *C*-Arylation is possible, giving e a ring-opened amine derivative with a Ag(I) catalyst.[1844] *N*-Sulfonyl aziridines react with the enolate anions of β-keto esters under phase-transfer conditions.[1845] *N*-Tosyl aziridines react with $InCl_3$ to give the chloro *N*-tosylamine.[1846] *N*-Sulfonyl aziridines react with aromatic or heteroaromatic compounds with a catalytic amount $Zn(OT)_2$ and $Sc(OTf)_3$, leading to ring opening and formation of the sulfonamide derivative.[1847] A similar reaction has been reported using TMSNCS to give the thiocyanate

[1834] Ueki, H.; Chiba, T.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* ***2004***, *69*, 7616.
[1835] See Marshall, J.A. *Chem. Rev.* ***1989***, *89*, 1503.
[1836] See Onistschenko, A.; Buchholz, B.; Stamm, H. *Tetrahedron* ***1987***, *43*, 565.
[1837] Crotti, P.; Favero, L.; Gardelli, C.; Macchia, F.; Pineschi, M. *J. Org. Chem.* ***1995***, *60*, 2514.
[1838] Huang, C.-Y.; Doyle, A.G. *Chem. Rev.* ***2014***, *114*, 8153.
[1839] Müller, P.; Nury, P. *Org. Lett.* ***1999***, *1*, 439; Müller, P.; Nury, P. *Helv. Chim. Acta* ***2001***, *84*, 662.
[1840] Penkett, C.S.; Simpson, I.D. *Tetrahedron Lett.* ***2001***, *42*, 1179.
[1841] Saidi, M.R.; Azizi, N.; Naimi-Jamal, M.R. *Tetrahedron Lett.* ***2001***, *42*, 8111.
[1842] Lygo, B. *Synlett* ***1993***, 764.
[1843] Yadav, J.S.; Reddy, B.V.S.; Balanarsaiah, E.; Raghavendra, S. *Tetrahedron Lett.* ***2002***, *43*, 5105.
[1844] Bera, M.; Roy, S. *Tetrahedron Lett.* ***2007***, *48*, 7144.
[1845] Moss, T.A.; Fenwick, D.R.; Dixon, D.J. *J. Am. Chem. Soc.* ***2008***, *130*, 10076.
[1846] Yadav, J.S.; Subba Reddy, B.V.; Kumar, G.M. *Synlett* ***2001***, 1417.
[1847] Ghorai, M.K.; Tiwari, D.P.; Jain, N. *J. Org. Chem.* ***2013***, *78*, 7121.

product.[1848] Aziridines react with alkyl diselenides in the presence of zinc and HCl, to give the β-alkylseleno amine.[1849]

Aziridines react with nucleophiles other than carbon nucleophiles. *N*-Benzylic aziridines are opened by trimethylsilyl azide in the presence of a Cr catalyst.[1850] Mediated by Lewis bases, aziridines react with silylated nucleophiles.[1851] *N*-Protected azetidines reacted with aryl thiols in the presence of a chiral phosphoric acid catalyst to give the protected amine derivative.[1852] Azetidines containing a basic ring nitrogen atom reacted with alkyl bromides and acyl chlorides to give 3-halo-1-amino propane derivatives.[1853]

10-67 Alkylation and Arylation at a Carbon Bearing an Active Hydrogen

This section will focus on the general reaction of a suitable base with active methylene compounds such as malonate derivatives,[1854] acetoacetic ester derivatives, and 1,3-diketone derivatives, and with substrates bearing a leaving group, not necessarily allylic substrates or metal catalyzed. Both Z and Z′ may be COOR′, CHO, COR′,[1855] $CONR'_2$, COO^-, CN,[1856] NO_2, SOR′, SO_2R',[1857] SO_2OR', $SO_2NR'_2$, or similar groups.[1858] When compounds contain two or three strong electron-withdrawing groups on a carbon atom bearing a proton (the so-called α proton), that proton is more acidic than in compounds without such groups (Sec. 5.B.i, category 1). Treatment with *a base that has a conjugate acid with a* pK_a *greater than the* α *proton* removes the α proton and generates the corresponding *enolate anion* (**10-68**). These enolate anions react as carbon nucleophiles and attack alkyl halides, resulting in their alkylation.[1859] Some commonly used bases are sodium ethoxide and potassium *tert*-butoxide, each in its respective alcohol as solvent. With particularly acidic compounds (e.g., β-diketones, Z, Z′ = COR′), sodium hydroxide (in water, aqueous alcohol or acetone), or even sodium carbonate,[1860] are strong enough bases for the reaction. If at least one Z group

[1848] Nakamura, S.; Ohara, M.; Koyari, M.; Hayashi, M.; Hyodo, K.; Nabisaheb, N.R.; Funahashi, Y. *Org. Lett.* ***2014***, *16*, 4452.

[1849] Salman, S.M.; Schwab, R.S.; Alberto, E.E.; Vargas, J.; Dornelles, L.; Rodrigues, O.E.D.; Braga, A.L. *Synlett* ***2011***, *22*, 69.

[1850] Li, Z.; Fernández, M.; Jacobsen, E.N. *Org. Lett.* ***1999***, *1*, 1611.

[1851] Minakata, S.; Okada, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* ***2005***, *7*, 3509. See also Matsukawa, S.; Tsukamoto, K. *Org. Biomol. Chem.* ***2009***, ***7***, 3792.

[1852] Wang, Z.; Sheong, F.K.; Sung, H.H.Y.; Williams, I.D.; Lin Z.; Sun, J. *J. Am. Chem. Soc.* ***2015***, *137*, 5895. Also see Hodgson, D.M.; Mortimer, C.L.; McKenna, J.M. *Org. Lett.* ***2015***, *17*, 330.

[1853] Xiao, J.; Wright, S.W. *Tetrahedron Lett.* ***2013***, *54*, 2502.

[1854] For a discussion of the nucleophilic reactivities of 2-substituted malonates, see Puente, Á.; He, S.; Bautista, F.-C.; Ofial, A.R.; Mayr, H. *Eur. J. Org. Chem.* ***2016***, 1841.

[1855] See Christoffers, J. *Synth. Commun.* ***1999***, *29*, 117.

[1856] See Fatiadi, A.J. *Synthesis* ***1978***, 165, 241; Freeman, F. *Chem. Rev.* ***1969***, *69*, 591.

[1857] See Neplyuev, V.M.; Bazarova, I.M.; Lozinskii, M.O. *Russ. Chem. Rev.* ***1986***, *55*, 883.

[1858] For lists of examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1522–1527 *ff*, 1765–1769.

[1859] For dicussions of reactions **10-67** and **10-68**, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 492–570, 586–595; Carruthers, W. *Some Modern Methods of Organic Synthesis*, 3rd ed., Cambridge University Press, Cambridge, ***1986***, pp. 1–26.

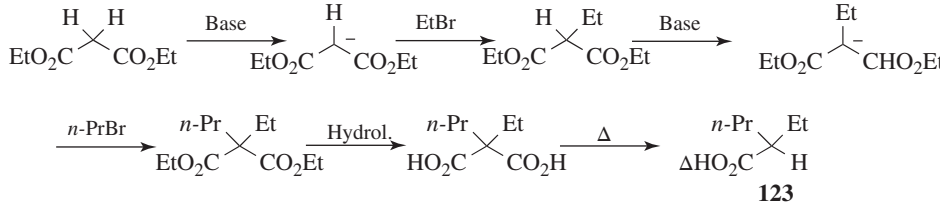
[1860] See Fedorynski, M.; Wojciechowski, K.; Matacz, Z.; Makosza, M. *J. Org. Chem.* ***1978***, *43*, 4682.

is COOR′, saponification is a possible side reaction. In addition to the groups listed above, Z may also be phenyl, but if two phenyl groups are on the same carbon, the acidity is less than in the other cases and a stronger base must be used. Diphenylmethane was deprotonated using $NaNH_2$ as the base.[1861]

If the solvent used in the reaction is a stronger acid than the substrate that reacts with the base, it is acidic enough to protonate either the enolate anion or the base. In such a case, an equilibrium will be established leading to only small amounts of the enolate anion (thermodynamic conditions). Such solvents are usually protic solvents that include water, alcohols, or amines. Aprotic solvents can be used in some cases to avoid this reaction. The use of polar aprotic solvents (e.g., DMF or DMSO) markedly increases the rate of alkylation[1862] but also increases the extent of alkylation at the oxygen rather than the carbon with highly reactive species such as iodomethane (Sec. 10.G.viii). In general, enolate anions such as those described here react with alkyl halides via *C*-alkylation, although *trialkylsilyl halides and anhydrides tend to react via O-alkylation*. Phase-transfer catalysis has also been used,[1863] and the use of chiral phase-transfer catalysts led to enantioselectivity in the alkylated product.[1864] Various functional groups may be present in RX as long as they are not sensitive to base. Side reactions that may cause problems are the above-mentioned competing *O*-alkylations, elimination (if the enolate anion is a strong enough base), and dialkylation.

With substrates such as ZCH_2Z' it is possible to alkylate twice. Initial removal of the proton with a base followed by alkylation of the resulting enolate anion with RX, can be followed by subsequent removal of the proton from ZCHRZ' and then alkylation with the same or a different RX. When ω,ω'-dihalides are used, ring closures can be effected:[1865] This method has been used to close rings of from three ($n = 0$) to seven members, although five-membered ring closures proceed in highest yields. Another ring-closing method involves internal alkylation.[1866] This method has been shown to be applicable to medium rings (10 to 14 members) without the use of high-dilution techniques.[1867]

An important example of this reaction is the *malonic ester synthesis*, in which both Z groups are COOEt. The product can be hydrolyzed and decarboxylated (**12-40**) to give a carboxylic acid. An illustration is the preparation of 2-ethylpentanoic acid (**123**) from malonic ester.

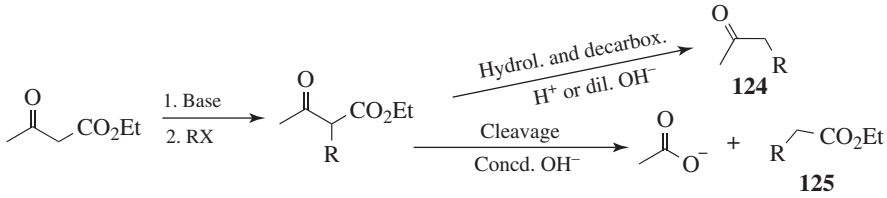


123

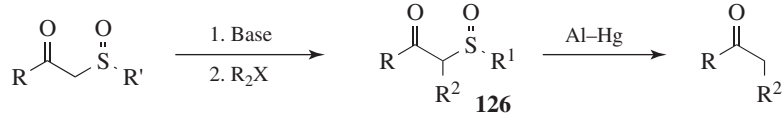
[1861] Murphy, W.S.; Hamrick Jr., P.J.; Hauser, C.R. *Org. Synth.* ***V***. 523.
[1862] Johnstone, R.A.W.; Tuli, D.; Rose, M.E. *J. Chem. Res. (S)* ***1980***, 283.
[1863] See Tundo, P.; Venturello, P.; Angeletti, E. *J. Chem. Soc., Perkin Trans. 1* ***1987***, 2159.
[1864] Park, E.J.; Kim, M.H.; Kim, D.Y. *J. Org. Chem.* ***2004***, *69*, 6897.
[1865] Zefirov, N.S.; Kuznetsova, T.S.; Kozhushkov, S.I.; Surmina, L.S.; Rashchupkina, Z.A. *J. Org. Chem. USSR* ***1983***, *19*, 474.
[1866] See Walborsky, H.M.; Murari, M.P. *Can. J. Chem.* ***1984***, *62*, 2464. For a list of examples, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 156–157, 165–166.
[1867] See Deslongchamps, P.; Lamothe, S.; Lin, H. *Can. J. Chem.* ***1987***, *65*, 1298.

A variation of this alkylation sequence employs 1,2-dibromoethane as the alkylating agent, and subsequent treatment with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) leads to incorporation of a vinyl group on the α carbon.[1868] Another variation involved coupling of a dimalonate with an allylic carbonate (see **10-60**), using a polymer-supported Pd catalyst.[1869]

Another important example is the *acetoacetic ester synthesis*, in which Z is CO_2Et and Z′ is $COCH_3$. In this case, the product can be decarboxylated with acid or dilute base (**12-39**) to give a ketone (**124**) or cleaved with concentrated base (**12-42**) to give a carboxylic ester (**125**) and a salt of acetic acid. This reaction has been done in *tert*-butanol in the presence of alumina, *in vacuo*, to give the alkylated keto acid directly from the keto ester.[1870]

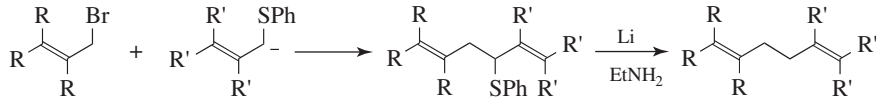


Another way of preparing ketones involves alkylation[1871] of β-keto sulfoxides[1872] or sulfones,[1873] to give **126**. The sulfoxide group in the product (**126**) is easily reduced (desulfurized, see **19-70**) to give the ketone in high yields using aluminum amalgam or by electrolysis.[1874] β-Keto sulfoxides such as **126** or sulfones (—SO_2—) are easily prepared (**16-82**). When one group attached to the sulfur atom is chiral, the alkylation proceeds with reasonable enantioselectivity.[1875]



In another method for the coupling of two different allylic groups,[1876] a carbanion derived from a β,γ-unsaturated thioether couples with an allylic halide to give **127**.[1877] The product **127** contains an SPh group that must be removed (with Li in ethylamine) to give the 1,5-diene. Unlike most of the methods previously discussed, this method has the advantage that the coupling preserves the original positions and configurations of the two double bonds; no allylic rearrangements take place.

[1868] Bunce, R.A.; Burns, S.E. *Org. Prep. Proceed. Int.* ***1999***, *31*, 99.
[1869] Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* ***2003***, *125*, 3412.
[1870] Bhar, S.; Chaudhuri, S.K.; Sahu, S.G.; Panja, C. *Tetrahedron* ***2001***, *57*, 9011.
[1871] See Trost, B.M. *Chem. Rev.* ***1978***, *78*, 363; Solladié, G. *Synthesis* ***1981***, 185.
[1872] See Kuwajima, I.; Iwasawa, H. *Tetrahedron Lett.* ***1974***, 107.
[1873] Kurth, M.J.; O'Brien, M.J. *J. Org. Chem.* ***1985***, 3846.
[1874] Lamm, B.; Samuelsson, B. *Acta Chem. Scand.* ***1969***, *23*, 691.
[1875] Enders, D.; Harnying, W.; Vignola, N. *Eur. J. Org. Chem.* ***2003***, 3939.
[1876] See Axelrod, E.H.; Milne, G.M.; van Tamelen, E.E. *J. Am. Chem. Soc.* ***1970***, *92*, 2139; Morizawa, Y.; Kanemoto, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* ***1982***, *23*, 2953.
[1877] Biellmann, J.F.; Ducep, J.B. *Tetrahedron Lett.* ***1969***, 3707.



127

Alkylation takes place at the most acidic position of a reagent molecule. For example, acetoacetic ester (CH_3COCH_2COOEt) is alkylated at the methylene and not at the methyl group; this is because the former is more acidic than the latter and hence gives up its proton to the base. However, if 2 molar equivalents of base are used, then not only is the most acidic proton removed but also the second most acidic. Alkylation of this doubly charged anion (a dianion) occurs at the less acidic position, in this case the second most acidic position[1878] (Sec. 10.G.vii). The first and second ion pair acidities of β-diketones has been studied.[1879]

The reaction is not limited to Z—CH_2—Z′ compounds. Other compounds have acidic C—H hydrogen atoms. Some examples are the methyl hydrogen atoms of α-aminopyridines, the methyl hydrogen atoms of ynamines of the form $CH_3C{\equiv}CNR_2$[1880] (the product in this case can be hydrolyzed to an amide $RCH_2CH_2CONR_2$), the CH_2 hydrogen atoms of cyclopentadiene and its derivatives (Sec. 2.I.ii), hydrogen atoms connected to a triple-bond carbon (**10-74**), and the hydrogen of HCN (**10-76**), which can also be removed with a base and the resulting ion alkylated (see also **10-68** to **10-72**). α-Imino esters have been used since treatment with a strong base with a Ti catalyst followed by an aldehyde leads to hydroxy amino esters.[1881]

The mechanism of these reactions is usually S_N2 with inversion taking place at a chiral RX, although an SET[1882] mechanism may be involved in certain cases,[1883] especially where the nucleophile is an α-nitro carbanion[1884] and/or the substrate contains a nitro or cyano[1885] group. Alkylation α to a nitro group can be achieved with the *Katritzky pyrylium–pyridinium reagents*.[1886] This reaction probably has a free-radical mechanism.[1887] Tertiary alkyl groups can be introduced by an S_N1 mechanism if the ZCH_2Z' compound (not the enolate anion) is treated with a tertiary carbocation generated *in situ* from an alcohol or alkyl halide and BF_3 or $AlCl_3$,[1888] or with a tertiary alkyl perchlorate.[1889]

Cyclohexa-1,3-diones reacted with a Cu catalyst and diisopropylethylamine in the presence of a chiral tridentate *P*,*P*,*N*-ketimine ligand to give the α-alkylated product.[1890] Propargylic pivalates reacted with $HC(CO_2Et)_3$ in the presence of a Cu catalysts and a chiral

[1878] For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1540–1541. Also see, Lu, Y.-Q.; Li, C.-J. *Tetrahedron Lett.* ***1996***, *37*, 471.

[1879] Facchetti, A.; Streitwieser, A. *J. Org. Chem.* ***2004***, *69*, 8345.

[1880] Corey, E.J.; Cane, D.E. *J. Org. Chem.* ***1970***, *35*, 3405.

[1881] Kanemasa, S.; Mori, T.; Wada, E.; Tatsukawa, A. *Tetrahedron Lett.* ***1993***, *34*, 677. See Kotha, S.; Kuki, A. *Tetrahedron Lett.* ***1992***, *33*, 1565 for a related reaction.

[1882] These SET mechanisms are often called SRN1 mechanisms. See also, Ref. 107.

[1883] Bordwell, F.G.; Harrelson Jr., J.A. *J. Am. Chem. Soc.* ***1989***, *111*, 1052.

[1884] For a review of mechanisms with these nucleophiles, see Bowman, W.R. *Chem. Soc. Rev.* ***1988***, *17*, 283.

[1885] Kornblum, N.; Fifolt, M. *Tetrahedron* ***1989***, *45*, 1311.

[1886] Katritzky, A.R.; Kashmiri, M.A.; Wittmann, D.K. *Tetrahedron* ***1984***, *40*, 1501.

[1887] Katritzky, A.R.; Chen, J.; Marson, C.M.; Maia, A.; Kashmiri, M.A. *Tetrahedron* ***1986***, *42*, 101.

[1888] See Crimmins, T.F.; Hauser, C.R. *J. Org. Chem.* ***1967***, *32*, 2615; Boldt, P.; Militzer, H.; Thielecke, W.; Schulz, L. *Liebigs Ann. Chem.* ***1968***, *718*, 101.

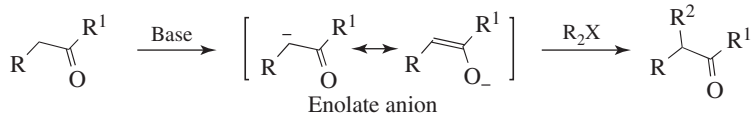
[1889] Boldt, P.; Ludwieg, A.; Militzer, H. *Chem. Ber.* ***1970***, *103*, 1312.

[1890] Han, F.Z.; Zhu, F.-L.; Wang, Y.-H.; Zou, Y.; Hu, X.-H.; Chen, S.; Hu, X.-P. *Org. Lett.* ***2014***, *16*, 588.

Pybox ligand, and 2 equivalents of DIPEA, giving the trialkyl methanetricaboxylate.[1891] α-Diazomalonates reacted with potassium trifluoroborates in the presence of a Rh catalyst to give the α-alkylated malonate derivative.[1892] 1,3-Diketones are methylated by reaction with 3 equivalents of *tert*-butyl peroxybenzoate with a CuCl catalyst, in air, in acetic acid, at 120 °C.[1893] 1,3-Diketones are benzylated or allylated using Bi catalysts.[1894]

OS **I**, 248, 250; **II**, 262, 279, 384, 474; **III**, 213, 219, 397, 405, 495, 705; **IV**, 10, 55, 288, 291, 623, 641, 962; **V**, 76, 187, 514, 523, 559, 743, 767, 785, 848, 1013; **VI**, 223, 320, 361, 482, 503, 587, 781, 991; **VII**, 339, 411; **VIII**, 5, 312, 381. See also OS **VIII**, 235.

10-68 Alkylation of Ketones, Aldehydes, Nitriles, and Carboxylic Esters, etc.



Enolate anion

Ketones,[1895] nitriles,[1896] and carboxylic esters[1897] can be alkylated in the α position in a reaction similar to **10-67**.[1898] Current literature contains several hundred examples of work in this area, and only a handful can be presented here. The chosen new literature citations are simply meant to show some of the newer research in this area. The pK_a of the proton α to the carbonyl or CN is in the range of 19–25, depending on the number of substituents (see Chapter 8, Table 8.1), and a base that has a conjugate acid with a pK_a greater than that proton must be employed. Note that since only one activating group is present, compared with two activating groups for the substrates in **10-67**, the pK_a of the α proton is higher (a weaker acid) and so a stronger base is required. The mechanism for this deprotonation reaction has been studied,[1899] as has the rate of deprotonation.[1900] Reaction of the α proton with the base generates the key nucleophilic intermediate, a *resonance-stabilized enolate anion*.[1901] The most common bases[1902] are lithium diethylamide (Et_2NLi), lithium diisopropylamide [$(Me_2CH)_2NLi$, LDA],[1903] lithium hexamethyldisilazide [$LiN(SiMe_3)_2$], *t*-BuOK, $NaNH_2$,

[1891] Huang, G.; Cheng, C.; Ge, L.; Guo, B.; Zhao, L.; Wu, X. *Org. Lett.* ***2015***, *17*, 4894.
[1892] Lu, Y.-S.; Yu, W.-Y. *Org. Lett.* ***2016***, *18*, 1350.
[1893] Zhou, Z.-H.; Li, C.-K.; Zhou, S.F.; Shoberu, A.; Zou, J.-P. *Tetrahedron* ***2017***, *73*, 2740.
[1894] Rueping, M.; Nachtsheim, B.J.; Kuenkel, A. *Org. Lett.* ***2007***, *9*, 825.
[1895] See Caine, D. in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1; Marcel Dekker, NY, ***1979***, pp. 85–352. See Cano, R.; Zakarian, A.; McGlacken, G.P. *Angew. Chem. Int. Ed.* ***2017***, *56*, 9278.
[1896] See Arseniyadis, S.; Kyler, K.S.; Watt, D.S. *Org. React.* ***1984***, *31*, 1. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1801–1808. See Rojas, G.; Baughman, T.W.; Wagener, K.B. *Synth. Commun.* ***2007***, *37*, 3923.
[1897] See Petragnani, N.; Yonashiro, M. *Synthesis* ***1982***, 521. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1724–1758 *ff*.
[1898] Nadir, U.K.; Arora, A. *J. Chem. Soc., Perkin Trans. 1* ***1995***, 2605.
[1899] Sun, X.; Kenkre, S.L.; Remenar, J.F.; Gilchrist, J.H. *J. Am. Chem. Soc.* ***1997***, *119*, 4765.
[1900] Majewski, M.; Nowak, P. *Tetrahedron Lett.* ***1998***, *39*, 1661.
[1901] For alternative approaches to enolate chemistry, see Sheppard, T.D. *Synlett* ***2011***, *22*, 1340.
[1902] For a list of some bases, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1476–1479.
[1903] See Klusener, P.A.A.; Brandsma, L.; Verkruijsse, H.D.; Schleyer, P.v.R.; Friedl, T.; Pi, R. *Angew. Chem. Int. Ed.* ***1986***, *25*, 465. See Algera, R.F.; Gupta, L.; Hoepker, A.C.; Liang, J.; Ma, Y.; Singh, K.J.; Collum. D.B. *J. Org. Chem.* ***2017***, *82*, 4513.

and KH. The base lithium *N*-isopropyl-*N*-cyclohexylamide (LICA) is particularly successful for carboxylic esters[1904] and nitriles.[1905] Lithium enolate anions exist as aggregates in solution.[1906] The structure of lithium enolates has been reviewed.[1907] Short-lived chiral enolate anions with a chiral C—O axis have been reported.[1908] The solution structures of Evan's enolates has been examined.[1909] Lithium enolates derived from Weinreb amides have been discussed.[1910] Enolate anion formation with lithium amides can also be regioselective (see **12-22**).[1911]

Solid KOH in DMSO has been used to methylate ketones, in high yields.[1912] Some bases are strong enough to convert the ketone, nitrile, or ester completely to its enolate anion conjugate base in an effectively irreversible manner, while others (especially *t*-BuOK) leads to an equilibrium that favors a significant fraction of the molecules. In the latter case, the *aldol reaction* (**16-34**) or *Claisen condensation* (**16-81**) may be side reactions, since under the thermodynamic (equilibrium) conditions associated with this base, both the free molecule and its conjugate base are present at the same time. Protic solvents generally favor the equilibrium or thermodynamic conditions because they protonate the base. Some common aprotic solvents are 1,2-dimethoxyethane, THF, and DMF, while protic solvents include water, alcohols, and liquid NH_3. Phase-transfer catalysis has been used to alkylate many nitriles, as well as some esters and ketones.[1913]

Aldehydes bearing only one α hydrogen have been alkylated with allylic and benzylic halides in good yields using the base KH to prepare the potassium enolate,[1914] or alkylated in moderate yields by the use of a phase-transfer catalyst.[1915] Even the use of amide bases (such as lithium diisopropylamide, LDA, lithium hexamethyldisilazide, LHMDS, or lithium tetramethylpiperidide, LTMP) to generate the enolate anion in an aprotic solvent (such as ether or THF) cannot completely suppress rapid aldol side reactions, although with modern techniques the side reactions are usually not a problem.

As in **10-67**, the alkyl halide that reacts with the enolate anion may be primary or secondary, while tertiary halides give elimination. If the enolate anion is a strong enough base (e.g., the enolate anion from Me_3CCOMe), even primary and secondary halides may give predominant elimination,[1916] but this is unusual. If the reaction is performed on a silyl enol

[1904] Bos, W.; Pabon, H.J.J. *Recl. Trav. Chim. Pays-Bas* ***1980***, *99*, 141. See also, Cregge, R.J.; Herrmann, J.L.; Lee, C.S.; Richman, J.E.; Schlessinger, R.H. *Tetrahedron Lett.* ***1973***, 2425.

[1905] Watt, D.S. *Tetrahedron Lett.* ***1974***, 707.

[1906] Liou, L.R.; McNeil, A.J.; Toombes, G.E.S.; Collum, D.B. *J. Am. Chem. Soc.* ***2008***, *130*, 17334; Khartabil, H.K.; Gros, P.C.; Fort, Y.; Ruiz-López, M.F. *J. Org. Chem.* ***2008***, *73*, 9393. See also Pratt, L.M.; Nguyen, S.C.; Thanh, B.T. *J. Org. Chem.* ***2008***, *73*, 6086.

[1907] Braun, M. *Helv. Chim. Acta* ***2015***, *98*, 1.

[1908] Yoshimura, T.; Tomohara, K.; Kawabata, T. *J. Am. Chem. Soc.* ***2013***, *135*, 7102.

[1909] Tallmadge, E.H.; Collum, D.B. *J. Am. Chem. Soc.* ***2015***, *137*, 13087. Also see Reyes-Rodríguez, G.J.; Algera, R.F.; Collum, D.B. *J. Am. Chem. Soc.* ***2017***, *139*, 1233.

[1910] Houghton, M.J.; Collum, D.B. *J. Org. Chem.* ***2016***, *81*, 11057.

[1911] See Comins, D.L.; Killpack, M.O. *J. Org. Chem.* ***1987***, *52*, 104. See Xie, L.; Isenberger, K.M.; Held, G.; Dahl, M. *J. Org. Chem.* ***1997***, *62*, 7516 for steric versus electronic effects.

[1912] Langhals, E.; Langhals, H. *Tetrahedron Lett.* ***1990***, *31*, 859.

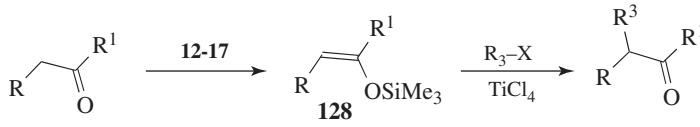
[1913] See Makosza, M. *Russ. Chem. Rev.* ***1977***, *46*, 1151; *Pure Appl. Chem.* ***1975***, *43*, 439; Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Acaemic Press, NY, ***1978***, pp. 170–217; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 136–204.

[1914] Artaud, I.; Torossian, G.; Viout, P. *Tetrahedron* ***1985***, *41*, 5031.

[1915] Buschmann, E.; Zeeh, B. *Liebigs Ann. Chem.* ***1979***, 1585.

[1916] Zook, H.D.; Kelly, W.L.; Posey, I.Y. *J. Org. Chem.* ***1968***, *33*, 3477.

ether (see **128**)[1917] of a ketone, aldehyde, or ester with a Lewis acid catalyst, tertiary alkyl as well as other groups that normally give S_N1 reactions can be introduced.[1918]



Tertiary alkyl fluorides were coupled to silyl enol ethers with BF_3•etherate.[1919] Silyl enol ethers can be converted to the enolate anion, which can then be alkylated in the usual manner.[1920] Metal-catalyzed alkylation reactions are known with silyl enol ethers, including an In-catalyzed[1921] reaction. An Ir-catalyzed regioselective and enantioselective alkylation of silyl enol ethers using allylic carbonates as a substrate has been reported.[1922] Enol acetates react with alcohols with a Re-complex catalyst.[1923] Enol ethers react with allylic bromides in water using $SnCl_2$ and KI.[1924] Enol acetates undergo direct alkylation with an InI_3/Me_3SiI catalyst.[1925] Zinc enolates were allylated using an Fe catalyst.[1926] Enol carbonates react with alkylating agents in the presence of a Pd catalyst.[1927]

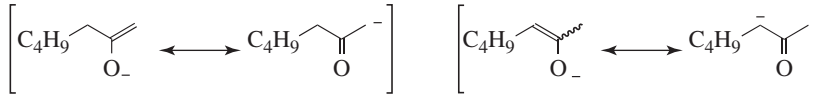
Efficient enantioselective alkylations are known,[1928] including the use of a chiral base to form the enolate anion.[1929] Alternatively, a chiral auxiliary can be attached. Many auxiliaries are based on the use of chiral amides[1930] or esters.[1931] Subsequent formation of the enolate anion allows alkylation to proceed with high enantioselectivity. A subsequent step is required to convert the chiral amide or ester to the corresponding carboxylic acid. Chiral additives can also be used,[1932] and the influence of chelating ligands and hydrocarbon cosolvents has been studied for $LiN(TMS)_2$-mediated enolization reactions.[1933] The addition of triethylamine influences the (*E*/*Z*) selectivity of the enolate anion.[1934] Dynamic kinetic

[1917] For a list of alkylations of silyl enol ethers, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1494–1505.
[1918] Kang, S.-K.; Ryu, H.-C.; Hong, Y.-T. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 3350. For a review, see Reetz, M.T. *Angew. Chem. Int. Ed.* ***1982***, *21*, 96.
[1919] Hirano, K.; Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* ***2004***, *45*, 2555.
[1920] Yu, W.; Jin, Z. *Tetrahedron Lett.* ***2001***, *42*, 369.
[1921] Nishimoto, Y.; Saito, T.; Yasuda, M.; Baba, A. *Tetrahedron* ***2009***, *65*, 5462.
[1922] Graening, T.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2005***, *127*, 17192.
[1923] Umeda, R.; Takahashi, Y.; Nishiyama, Y. *Tetrahedron Lett.* ***2014***, *55*, 6113.
[1924] Lin, M.-H.; Hung, S.-F.; Lin, L.-Z.; Tsai, W.-S.; Chuang, T.-H. *Org. Lett.* ***2011***, *13*, 332.
[1925] Onishi, Y.; Nishimoto, Y.; Yasuda, M.; Baba, A. *Chem. Lett.* ***2011***, *40*, 1223.
[1926] Jarugumilli, G.K.; Cook, S.P. *Org. Lett.* ***2011***, *13*, 1904.
[1927] See Zhou, J. *Synlett* ***2012***, *23*, 1.
[1928] See Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 236–245; Evans, D.A. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1984***, pp. 1–110.
[1929] See Murakata, M.; Nakajima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* ***1990***, 1657. For a review, see Cox. P.J.; Simpkins, N.S. *Tetrahedron: Asymmetry* ***1991***, *2*, 1 (pp. 6–13).
[1930] See Lafontaine, J.A.; Provencal, D.P.; Gardelli, C.; Leahy, J.W. *J. Org. Chem.* ***2003***, *68*, 4215. See Evans, D.A.; Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.* ***1984***, *106*, 4261.
[1931] Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* ***1985***, *68*, 212.
[1932] Denmark, S.E.; Stavenger, R.A. *Acc. Chem. Res.* ***2000***, *33*, 432; Machajewski, T.D.; Wong, C.-H. *Angew. Chem. Int. Ed.* ***2000***, *39*, 1352.
[1933] Godenschwager, P.F.; Collum, D.B. *J. Am. Chem. Soc.* ***2007***, *129*, 12023.
[1934] Godenschwager, P.F.; Collum, D.B. *J. Am. Chem. Soc.* ***2008***, *130*, 8726.

resolution has been used for the asymmetric alkylation of malonate derivatives using allenyl acetates.[1935]

When the compound to be alkylated is an unsymmetrical ketone, the question arises as to which side will be alkylated (regioselectivity). Which product is found in higher yield depends on the nature of the substrate, the base,[1936] the cation, and the solvent. In any case, di- and tri-substitution are frequent[1937] and it is often difficult to stop with the introduction of just one alkyl group.[1938] Several methods have been developed for ensuring that alkylation takes place regioselectively on the *desired* side of a ketone.[1939] Among these are the following.

1. Block one side of the ketone by introducing a removable group. Alkylation takes place on the other side and the blocking group is then removed. A common reaction for this purpose is formylation with ethyl formate (**16-82**), which generally blocks the less hindered side. The formyl group is easily removed by alkaline hydrolysis (**12-42**).
2. Introduce an activating group on one side; alkylation then takes place on that side (**10-67**); the activating group is then removed.
3. Reaction with the desired one of the two possible enolate anions.[1940] Of the two ions, for example, there will be a less-substituted enolate anion (the *kinetic enolate*) and a more-substituted enolate anion (the *thermodynamic enolate*). Here these are shown for heptan-2-one:



The two ions are in equilibrium as they are formed by an acid–base reaction. In the presence of the parent ketone or any stronger acid, each enolate anion is reprotonated and then deprotonated again, and the subsequent equilibrium favors the more stable product, the thermodynamic enolate anion.[1941] In the absence of such acids, with an aprotic solvent and a strong base, the dynamic equilibrium is suppressed since the enolate anion does not react with an acid and the kinetic enolate anion predominates.[1942] Therefore, by controlling the base and the solvent it is possible to react with the kinetic enolate or the thermodynamic enolate. One can thus achieve selective alkylation on either side of the ketone.[1941,1943] An alternative approach traps the predominate enolate anion by reaction with acetic anhydride or

[1935] Trost, B.M.; Fandrick, D.R.; Dinh, D.C. *J. Am. Chem. Soc.* ***2005***, *127*, 14186.
[1936] See Gaudemar, M.; Bellassoued, M. *Tetrahedron Lett.* ***1989***, *30*, 2779.
[1937] See Lissel, M.; Neumann, B.; Schmidt, S. *Liebigs Ann. Chem.* ***1987***, 263.
[1938] See Morita, J.; Suzuki, M.; Noyori, R. *J. Org. Chem.* ***1989***, *54*, 1785.
[1939] See House, H.O. *Rec. Chem. Prog.* ***1968***, *28*, 99; Podraza, K.F. *Org. Prep. Proced. Int.* ***1991***, *23*, 217.
[1940] See d'Angelo, J. *Tetrahedron* ***1976***, *32*, 2979; Stork, G. *Pure Appl. Chem.* ***1975***, *43*, 553.
[1941] Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, Amsterdam/Boston, ***2017***, pp. 669–674.
[1942] House, H.O.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* ***1971***, *36*, 2361. See also, Corey, E.J.; Gross, A.W. *Tetrahedron Lett.* ***1984***, *25*, 495.
[1943] House, H.O.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* ***1971***, *36*, 2361. For an improved procedure, see Liotta, C.L.; Caruso, T.C. *Tetrahedron Lett.* ***1985***, *26*, 1599.

trimethylsilyl chloride,[1944] to give the enol acetate or the silyl enol ether.[1945] Such treatment generally gives a mixture of the two enol acetates in which one or the other predominates, depending on the reagent. The mixtures are easily separable[1946] and subsequent treatment of the corresponding enol acetate or the silyl enol ether with 2 equivalents of methyllithium in 1,2-dimethoxyethane regenerates the desired enolate anion. Alkylation of an unsymmetrical ketone at the more substituted position was reported using an alkyl bromide, NaOH, and a calix[*n*]arene catalyst (Sec. 4.H, category 2, for calixarenes).[1947]

Metal-catalyzed alkylations that are related to this reaction are known. Monoalkylation is possible using Pd catalysts,[1948] and Pd-catalyzed asymmetric allylic alkylation is known.[1949] α-Alkylation of ketones with alcohols uses a Ru catalyst[1950] or Ni nanoparticles.[1951] A recyclable Pd catalyst is available.[1952] Zinc enolate anions have been used in enantioselective Pd-catalyzed alkylation reactions.[1953] An interesting allylic substitution at a tertiary center involves the reaction of tertiary 2-bromonitriles with *i*-PrMgBr and allyl bromide to give the 2-allyl nitrile.[1954] α-Alkylation of ketones with primary alcohols is possible using polymer-associated nanoparticulate Pd.[1955]

Enolate anions react with allylic acetates with a Pd catalyst.[1956] Both lactones[1957] and lactams are alkylated via the enolate anion.[1958] β,γ-Unsaturated carbonyl compounds are generated by reaction of an enolate anion and an alkenyl halide with a Pd catalyst.[1959] Ruthenium catalysts have been used.[1960] The Mo-catalyzed allylic alkylation of cyanoesters was reported to proceed with good enantioselectivity.[1961] The In-catalyzed propargylation of aldehydes has been reported via a S_N1-type reaction in water.[1962] Aldehydes have been converted to the α-allyl product via a dual Ir–amine catalyst,[1963] or other α-alkyl

[1944] See Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* ***1985***, *18*, 181; Rasmussen, J.K. *Synthesis* ***1977***, 91. See Bélanger, É.; Cantin, K.; Messe, O.; Tremblay, M.; Paquin, J.-F. *J. Am. Chem. Soc.* ***2007***, *129*, 1034.

[1945] Smith, M.B. *Organic Syntheisis*, 4th ed., Elsevier, Amsterdam/Boston, ***2017***, pp. 674–677.

[1946] House, H.O.; Trost, B.M. *J. Org. Chem.* ***1965***, *30*, 1341.

[1947] Shimizu, S.; Suzuki, T.; Sasaki, Y.; Hirai, C. *Synlett* ***2000***, 1664.

[1948] Ranu, B.C.; Chattopadhyay, K.; Adak, L. *Org. Lett.* ***2007***, *9*, 4595. See Zheng, W.-H.; Zheng, B.-H.; Zhang, Y.; Hou, X.-L. *J. Am. Chem. Soc.* ***2007***, *129*, 7718.

[1949] Trost, B.M.; Schroeder, G.M. *Chem. Eur. J.* ***2005***, *11*, 174.

[1950] Martínez, R.; Ramón, D.J.; Yus, M. *Tetrahedron* ***2006***, *62*, 8988.

[1951] Alonso, F.; Riente, P.; Yus, M. *Synlett* ***2007***, 1872.

[1952] Kwon, M.S.; Kim, N.; Seo, S.H.; Park, I.S.; Cheedrala, R.K.; Park, J. *Angew. Chem. Int. Ed.* ***2005***, *44*, 6913.

[1953] Kinoshita, N.; Kawabata, T.; Tsubaki, K.; Bando, M.; Fuji, K. *Tetrahedron* ***2006***, *62*, 1756. The nucleophilicity of zinc enolates in alkylation reactions has been reevaluated, see Jarugumilli, G.K.; Zhu, C.; Cook, S.P. *Eur. J. Org. Chem.* ***2012***, 1712.

[1954] Fleming, F.F.; Zhang, Z.; Liu, W.; Knochel, P. *J. Org. Chem.* ***2005***, *70*, 2200.

[1955] Yamada, Y.M.A.; Uozumi, Y. *Org. Lett.* ***2006***, *8*, 1375.

[1956] Trost, B.M.; Schroeder, G.M.; Kristensen, J. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3492.

[1957] See Ibrahim-Ouali, M.; Parrain, J.-L.; Santelli, M. *Org. Prep. Proceed. Int.* ***1999***, *31*, 467. Enolate anions of β-lactones are subject to ring opening: Mori, S.; Shindo, M. *Org. Lett.* ***2004***, *6*, 3945.

[1958] Matsuo, J.-i.; Kobayashi, S.; Koga, K. *Tetrahedron Lett.* ***1998***, *39*, 9723.

[1959] Ankner, T.; Cosner, C.C.; Helquist, P. *Chem. Eur. J.* ***2013***, *19*, 1858.

[1960] Ruiz, S.; Villuendas, P.; Urriolabeitia, E.P. *Tetrahedron Lett.* ***2016***, *57*, 3413.

[1961] Trost, B.M.; Miller, J.R.; Hoffman Jr., C.M. *J. Am. Chem. Soc.* ***2011***, *133*, 8165.

[1962] Sinisi, R.; Vita, M.V.; Gualandi, A.; Emer, E.; Cozzi, P.G. *Chem. Eur. J.* ***2011***, *17*, 7404.

[1963] Krautwald, S.; Schafroth, M.A.; Sarlah, D.; Carreira, E.M. *J. Am. Chem. Soc.* ***2014***, *136*, 3020. For the use of a Pd catalyst, see Yoshida, M.; Terumine, T.; Masaki, E.; Hara, S. *J. Org. Chem.* ***2013***, *78*, 10853.

products.[1964] Organocatalysts have been used for this reaction, with both enantioselective and diastereoselective examples.[1965] Organocatalysis has been used in asymmetric C—H functionalization.[1966] A sterically demanding proline-derived catalyst has been used for the α-benzylation reaction.[1967]

Ketones react with benzylic alcohols to give the α-alkyl product by the use of triflic acid.[1968] Primary alcohols have been used for the α-alkylation of ketones using an Ir catalyst.[1969] Organocatalysts have been used for the α-alkylation of ketones.[1970] The α-methylation of ketones has been reported, using DMF as the carbon source and a Rh catalyst.[1971] 2-Alkyl carboxylic acids are prepared with good enantioselectivity from carboxylic acids in the presence of chiral amines.[1972] The enediolate–dilithium amide mixed aggregates have been studied in the enantioselective alkylation of arylacetic acid.[1973] Amides and esters are converted to the 2-allylated product with a Co catalyst.[1974]

The α-alkylation of unactivated esters has been reported; this occurs by the reaction of alcohols with a NCP (as with pyridine and phosphinite arms) pincer/Ir catalyst and unactivated α-substituted acyclic esters, lactones, and methyl and ethyl acetates.[1975] Amides react with primary alcohols to give the α-alkyl products by use of an Ir catalyst.[1976] Amides have been converted to the α-aryl derivative with a Pd catalyst.[1977] The α-allylic alkylation of thioamides has been reported with a Pd catalyst.[1978]

For the use of an Ir catalyst, see Liu, P.; Liang, R.; Lu, L.; Yu, Z.; Li, F. *J. Org. Chem.* ***2017***, *82*, 1943. For the use of a triple catalyst, Pd catalyst, three chiral Brønsted acid TRIP, and benzhydryl amine, see Jiang, G.; List, B. *Angew. Chem. Int. Ed.* ***2011***, *50*, 9471. For a review, see Oliver, S.; Evans, P.A. *Synthesis* ***2013***, *45*, 3179.

[1964] Hodgson, D.M.; Charlton, A. *Tetrahedron.* ***2014***, *70*, 2207.

[1965] Caruana, L.; Kniep, F.; Johansen, T.K.; Poulsen, P.H.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2014***, *136*, 15929; Jiménez, J.; Landa, A.; Lizarraga, A.; Maestro, M.; Mielgo, A.; Velilla, M.O.; Palomo, C. *J. Org. Chem.* ***2012***, *77*, 747. Zhang, B.; Xiang, S.-K.; Zhang, L.-H.; Cui, Y.; Jiao, N. *Org. Lett.* ***2011***, *13*, 5212. Xiao, J. *Org. Lett.* ***2012***, *14*, 1716. Mo, J.; Yang, R.; Chen, X.; Tiwari, B.; Chi, Y.R. *Org. Lett.* ***2013***, *15*, 50. Tak-Tak, L.; Dhimane, H.; Dalko, P.I. *Angew. Chem. Int. Ed.* ***2011***, *50*, 12146. Naicker, T.; Arvidsson, P.I.; Kruger, H.G.; Maguire, G.E.M.; Govender, T. *Eur. J. Org. Chem.* ***2011***, 6923. See Varun, B.V.; Dhineshkumar, J.; Bettadapur, K.R.; Siddaraju, Y.; Alagiri, K.; Prabhu, K.R. *Tetrahedron Lett.* ***2017***, *58*, 803.

[1966] Zhao, Y.-L.; Wang, Y.; Luo, C.; Fu, X.-Z.; Xu, P.-F. *Tetrahedron Lett.* ***2015***, *56*, 3703.

[1967] List, B.; Čorić, I.; Grygorenko, O.O.; Kaib, P.S.; Komarov, I.; Lee, A.; Leutzsch, M.; Pan, S.C.; Tymtsunik, A.V.; van Gemmeren, M. *Angew. Chem. Int. Ed.* ***2014***, *53*, 282.

[1968] Koppolu, S.R.; Naveen, N.; Balamurugan, R. *J. Org. Chem.* ***2014***, *79*, 6069.

[1969] Li, F.; Ma, J.; Wang, N. *J. Org. Chem.* ***2014***, *79*, 10447; Wang, D.; Zhao, K.; Ma, P.; Xu, C.; Ding, Y. *Tetrahedron Lett.* ***2014***, *55*, 7233. For a Co-catalyzed reaction, see Zhang, Q.; Wu, J.; Zeng, H.; Zhang, S.; Yin, Z.; Zheng, S. *Org. Lett.* ***2017***, *19*, 1080. For an Fe-catalyzed reaction, see Elangovan, S.; Sortais, J.-B.; Beller, M.; Darcel, C. *Angew. Chem. Int. Ed.* ***2015***, *54*, 14483. For a Mn-catalyzed reaction, see Peña-López, M.; Piehl, P.; Elangovan, S.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* ***2016***, *55*, 14967.

[1970] Xiao, Z.-K.; Shao, L.-X. *Synthesis* ***2012***, *44*, 711. See Henrion, M.; Chetcuti, M.J.; Ritleng, V. *Chem. Commun.* ***2014***, *50*, 4624. Zhu, Y.; Cai, C.; Lu, G. *Helv. Chim. Acta* ***2014***, *97*, 1666.

[1971] Li, Y.; Xue, D.; Lu, W.; Wang, C.; Liu, Z.-T.; Xiao, J. *Org. Lett.* ***2014***, *16*, 66.

[1972] Craig, E.; Stivala, C.E.; Zakarian, A. *J. Am. Chem. Soc.* ***2011***, *133*, 11936.

[1973] Ma, Y.; Stivala, C.E.; Wright, A.M.; Hayton, T.; Liang, J.; Keresztes, I.; Lobkovsky, E.; Collum, D.B.; Zakarian, A. *J. Am. Chem. Soc.* ***2013***, *135*, 16853.

[1974] Deibl, N.; Kempe, R. *J. Am. Chem. Soc.* ***2016***, *138*, 10786.

[1975] Guo, L.; Ma, X.; Fang, H.; Jia, X.; Huang, Z. *Angew. Chem. Int. Ed.* ***2015***, *54*, 4023.

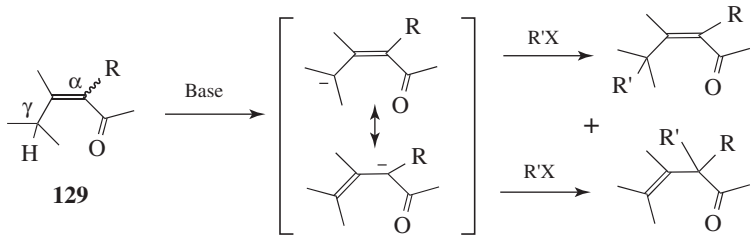
[1976] Guo, L.; Liu, Y.; Yao, W.; Leng, X.; Huang, Z. *Org. Lett.* ***2013***, *15*, 1144; Yao, W.; Ma, X.; Guo, L.; Jia, X.; Hu, A.; Huang, Z. *Tetrahedron Lett.* ***2016***, *57*, 2919.

[1977] Zheng, B.; Jia, T.; Walsh, P.J. *Org. Lett.* ***2013***, *15*, 4190.

[1978] Rong, B.; Yang, Q.; Liu, Y.; Xu, H.; Hu, Y.; Cheng, X.; Zhao, B. *Tetrahedron Lett.* ***2015***, *56*, 595.

A decarboxylative alkylation of an α-allylic unit to a cyclopentanone was reported, proceeding from an α-allylic ester with a Pd catalyst and a *t*-BuPHOX ligand.[1979] Acetophenone derivatives and aryl iodides react in the presence of excess KO*t*-Bu in DMF to give the α-aryl derivative.[1980]

Hydrazones and other compounds with C=N bonds can be similarly alkylated.[1929] Both sides of acetone have been alkylated with different alkyl groups, in one operation, by treatment of the *N*,*N*-dimethylhydrazone of acetone with *n*-BuLi, followed by a primary alkyl, benzylic, or allylic bromide or iodide; then another mole of *n*-BuLi, a second halide, and finally hydrolysis of the hydrazone.[1981] The use of chiral amines or hydrazines,[1982] followed by hydrolysis (**16-2**) of the alkylated imine, can lead to chiral alkylated ketones in high optical yields[1983] (for an example, see Sec. 4.J). Lithiated imines are generated by the treatment of an imine with a suitable base, and reaction with an alkyl halide gives the alkylated imine.[1984] α-Magnesio imines also react with alkyl halides.[1985] Imine alkylation can also be applied to the preparation of substituted amine derivatives. This reaction has also been done in the ionic liquid Bmim tetrafluoroborate (Sec. 9.D.iii).[1986]



129

In α,β-unsaturated ketones, nitriles, and esters (e.g., **129**), the γ hydrogen assumes the acidity normally held by the position α to the carbonyl group, especially when R is not hydrogen and so cannot compete. This principle, called *vinylogy* (Sec. 6.B), operates because the resonance effect is transmitted through the double bond. However, because of the resonance, alkylation at the α position (with allylic rearrangement) competes with alkylation at the γ position and usually predominates.

α-Hydroxynitriles (cyanohydrins), protected by conversion to acetals[1987] with ethyl vinyl ether (**15-5**), can be easily alkylated with primary or secondary alkyl or allylic

[1979] Craig II, R.A.; Loskot, S.A.; Mohr, J.T.; Behenna, D.C.; Harned, A.M.; Stoltz, B.M. *Org. Lett.* ***2015***, *17*, 5160. Also see Cui, L.; Chen, H.; Liu, C.; Li, C. *Org. Lett.* ***2016***, *18*, 2188.

[1980] Drapeau, M.P.; Fabre, I.; Grimaud, L.; Ciofini, I.; Ollevier, T.; Taillefer, M. *Angew. Chem. Int. Ed.* ***2015***, *54*, 10587.

[1981] Yamashita, M.; Matsuyama, K.; Tanabe, M.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 407. For α-arylation using continuous flow techinuques (Sec. 7.D), see Vega, J.A.; Alonso, J.M.; Méndez, G.; Ciordia, M.; Delgado, F.; Trabanco, A.A. *Org. Lett.* ***2017***, *19*, 938. See Huynh, U.; Uddin, Md.N.; Wengryniuk, S.E.; McDonald, S.L.; Coltart, D.M. *Tetrahedron* ***2017***, *73*, 432.

[1982] See Enders, D. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1984***, pp. 275–339.

[1983] Meyers, A.I.; Williams, D.R.; White, S.; Erickson, G.W. *J. Am. Chem. Soc.* ***1981***, *103*, 3088; Enders, D.; Bockstiegel, B. *Synthesis* ***1989***, 493; Enders, D.; Kipphardt, H.; Fey, P. *Org. Synth.* ***1987***, *65*, 183.

[1984] Zuend, S.J.; Ramirez, A.; Lobkovsky, E.; Collum, D.B. *J. Am. Chem. Soc.* ***2006***, *128*, 5939.

[1985] Hatakeyama, T.; Ito, S.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* ***2005***, *127*, 14192.

[1986] Pellissier, H.; Santelli, M. *Tetrahedron* ***2003***, *59*, 701.

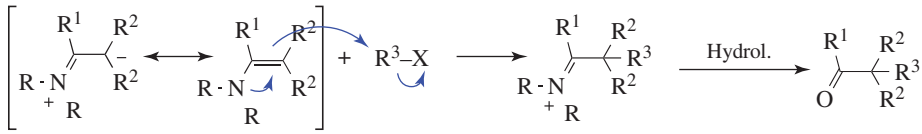
[1987] See Albright, J.D. *Tetrahedron* ***1983***, *39*, 3207.

halides.[1988] The R group can be aryl or a saturated or unsaturated alkyl and the product is easily hydrolyzed to a ketone,[1989] so this is a method for converting an aldehyde RCHO to a ketone RCOR′.[1990] In this procedure the normal mode of reaction of a carbonyl carbon is reversed. The C atom of an aldehyde molecule is normally electrophilic and is attacked by nucleophiles (Chapter 16), but by conversion to the protected cyanohydrin this carbon atom has been induced to perform as a nucleophile.[1991] The German word *Umpolung*[1992] is used to describe this kind of reversal (another example is found in **10-71**). This method fails for formaldehyde (R = H), but other masked formaldehydes have proved successful.[1993]

Carboxylic acids were first converted to silyl ketene acetals. Subsequent reaction with aryl triflates in the presence of a Pd catalyst, followed by treatment with trifluoroacetic acid, gave the corresponding α-aryl carboxylic acid.[1994]

OS **III**, 44, 219, 221, 223, 397; **IV**, 278, 597, 641, 962; **V**, 187, 514, 559, 848; **VI**, 51, 115, 121, 401, 818, 897, 958, 991; **VII**, 153, 208, 241, 424; **VIII**, 141, 173, 241, 403, 460, 479, 486; **X**, 59, 460; ***80***, 31.

10-69 The Stork Enamine Reaction[1995]



When enamines are treated with alkyl halides, an alkylation occurs to give an iminium salt via electron transfer from the electron pair on nitrogen, through the C=C to the electrophilic carbon of the alkyl halide.[1996] In effect, an enamine behaves as a "nitrogen enolate anion" and generally reacts as a carbon nucleophile.[1997] Hydrolysis of the iminium salt gives a ketone. Since the enamine is normally formed from a ketone (**16-12**), the net result is alkylation of the ketone at the α position. Known as the *Stork enamine reaction*,[1998] this method is an alternative to the ketone alkylation described in **10-68**, and generally gives monoalkylation of the ketone. Alkylation usually takes place on the less-substituted side of the original

[1988] Stork, G.; Depezay, J.C.; D'Angelo, J. *Tetrahedron Lett.* ***1975***, 389. See also, Hünig, S.; Marschner, C.; Peters, K.; von Schnering, H.G. *Chem. Ber.* ***1989***, *122*, 2131, and papers in this series.

[1989] See Martin, S.F. *Synthesis* ***1979***, 633.

[1990] Also see Hünig, S. *Chimia* ***1982***, *36*, 1.

[1991] See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 56–67; Gröbel, B.; Seebach, D. *Synthesis* **1977**, 357. Also see Hase, T.A.; Koskimies, J.K. *Aldrichimica Acta* ***1981***, *14*, 73; Hase, T.A. *Umpoled Synthons*, Wiley, NY, ***1987***, pp. xiii–xiv, 7–18, 219–317. For lists of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1435–1438.

[1992] See Hase, T.A. *Umpoled Synthons*, Wiley, NY, **1987**; Seebach, D. *Angew. Chem. Int. Ed.* ***1979***, *18*, 239.

[1993] Stork, G.; Ozorio, A.A.; Leong, A.Y.W. *Tetrahedron Lett.* ***1978***, 5175.

[1994] Huang, Z.; Liu, Z.; Zhou, J. *J. Am. Chem. Soc.* ***2011***, *133*, 15882.

[1995] This is the IUPAC name with respect to the halide as substrate.

[1996] See Adams, J.P. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 125.

[1997] See Kempf, B.; Hampel, N.; Ofial, A.R.; Mayr, H. *Chem. Eur. J.* ***2003***, *9*, 2209.

[1998] See Hickmott, P.W. *Tetrahedron* ***1984***, *40*, 2989; Granik, V.G. *Russ. Chem. Rev.* ***1984***, *53*, 383. Also see in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, the articles by Alt, G.H.; Cook, A.G. pp. 181–246 and by Gadamasetti, G.; Kuehne, M.E. pp. 531–689; Whitesell, J.K.; Whitesell, M.A. *Synthesis* ***1983***, 517; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 570–582, 766–772. See Yan, X.; Chen, C.; Zhou, Y.; Xi, C. *Org. Lett.* ***2012***, *14*, 4750.

ketone. The most commonly used amines are the cyclic amines piperidine, morpholine, and pyrrolidine. There are metal-catalyzed enamine alkylation reactions, including the use of Ir catalysts.[1999] The Pd-catalyzed reaction of β-enaminines, with microwave irradiation, led to the allyl product.[2000] Enamides have been coupled to alkenes in the presence of $Cu(OAc)_2$ and $Pd(OAc)_2$ catalysts, in the presence of oxygen, to give the corresponding dienamide product.[2001]

The method is not used as much nowadays, but it has proven to be useful for particularly active alkyl halides, such as allylic, benzylic, and propargylic halides, and for α-halo ethers and esters. Other primary and secondary halides can show sluggish reactivity. Tertiary halides do not give the reaction at all and elimination predominates. The reaction can also be applied to activated aryl halides (e.g., 2,4-dinitrochlorobenzene; see Chapter 13), to epoxides,[2002] and to activated alkenes, such as acrylonitrile. The latter is a *Michael-type reaction* (**15-20**) with respect to the alkene. Enamines react with carboxylic acids in a PhIO-mediated reaction to give the β-acyloxyl enamine, which undergoes a cyclodehydration reaction to give an oxazole.[2003] Acylation[2004] can be accomplished by reaction with acyl halides or with anhydrides. Hydrolysis of the resulting iminium salt leads to a 1,3-diketone. The acylation of the enamine can take place by the same mechanism as alkylation.

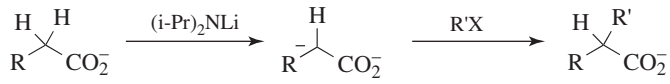
N-Alkylation can be a problem, particularly with enamines derived from aldehydes. An alternative method, which gives good yields of alkylation with primary and secondary halides, is alkylation of enamine *salts*, which are prepared by treating an imine with ethylmagnesium bromide in THF.[2005] The enamine salt method has also been used to give good yields of mono α alkylation of α,β-unsaturated ketones.[2006] Enamines prepared from aldehydes and butylisobutylamine can be alkylated by simple primary alkyl halides in good yields.[2007] *N*-Alkylation in this case is presumably prevented by steric hindrance.

When the nitrogen of the substrate contains a chiral R group, both the Stork enamine synthesis and the enamine salt method can be used to perform enantioselective syntheses.[2008] The use of *S*-proline can generate a chiral enamine *in situ*, thus allowing alkylation to occur, giving the alkylated product with good enantioselectivity. It is noted that reactions are catalyzed by enamines, including asymmetric reactions.[2009] The reaction has been done intramolecularly.[2010] Conjugate addition (*Michael addition*) occurs when enamines react with conjugated ketones. This reaction is discussed in **15-20**.

OS **V**, 533, 869; **VI**, 242, 496, 526; **VII**, 473.

[1999] Weix, D.J.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2007***, *129*, 7720.
[2000] Erray, I.; Rezgui, F.; Oble, J.; Poli, G. *Synlett* ***2014***, *25*, 2196.
[2001] Gigant, N.; Gillaizeau, I. *Org. Lett.* ***2012***, *14*, 3304.
[2002] Britten, A.Z.; Owen, W.S.; Went, C.W. *Tetrahedron* ***1969***, *25*, 3157.
[2003] Liu, X.; Cheng, R.; Zhao, F.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.* ***2012***, *14*, 5480.
[2004] See Hickmott, P.W. *Chem. Ind. (London)* ***1974***, 731; Hünig, S.; Hoch, H. *Fortschr. Chem. Forsch.* ***1970***, *14*, 235.
[2005] Stork, G.; Dowd, S.R. *J. Am. Chem. Soc*., ***1963***, *85*, 2178.
[2006] Stork, G.; Benaim, J. *J. Am. Chem. Soc*., ***1971***, *93*, 5938.
[2007] Curphey, T.J.; Hung, J.C.; Chu, C.C.C. *J. Org. Chem*., ***1975***, *40*, 607. See also, Ho, T.; Wong, C.M. *Synth. Commun.* ***1974***, *4*, 147.
[2008] See Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 248–255; Whitesell, J.K. *Acc. Chem. Res.* ***1985***, *18*, 280; Bergbreiter, D.E.; Newcomb, M. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***, pp. 243–273.
[2009] Mukherjee, S.; Yang, J.W.; Hoffmann, S.; List, B. *Chem. Rev.* ***2007***, *107*, 5471.
[2010] Vignola, N.; List, B. *J. Am. Chem. Soc.* ***2004***, *126*, 450.

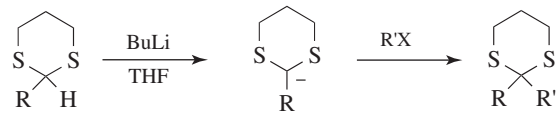
10-70 Alkylation of Carboxylic Acid Salts



Carboxylic acids can be alkylated in the α position by conversion of their salts to dianions (which have resonance contributors[2011]) by treatment with a strong base such as LDA.[2012] The use of Li^+ as the counterion increases the solubility of the dianionic salt. The reaction has been applied[2013] to primary alkyl, allylic, and benzylic halides, and to carboxylic acids of the form RCH_2CO_2H and RR^2CHCO_2H.[1896] This procedure is an alternative to the malonic ester synthesis (**10-67**) as a means of preparing carboxylic acids and has the advantage that acids of the form $RR'R^2CCO_2H$ can also be prepared. In a related reaction, methylated aromatic acids can be alkylated at the methyl group by a similar procedure,[2014] thus 2-methylbenzoic acid was treated with LDA and then an alkyl halide to give the 2-alkylbenzoate anion.

OS **V**, 526; **VI**, 517; **VII**, 249. See also OS **VII**, 164.

10-71 Alkylation at a Position α to a Heteroatom



The presence of a sulfur atom on a carbon enhances the acidity of a proton on that carbon, and in dithioacetals and dithioketals that proton ($RSCH_2SR$) is even more acidic. 1,3-Dithianes can be alkylated[2015] if a proton is removed by treatment with butyllithium in THF in a reaction that is quite slow at − 78 °C.[2016] Since 1,3-dithianes can be prepared by treatment of an aldehyde or its acetal (see OS **VI**, 556) with 1,3-propanedithiol (**16-10**) and can be hydrolyzed (**10-7**), this is a method for the conversion of an aldehyde to a ketone[2017] (see also **10-68** and **18-9**).

[2011] Mladenova, M.; Blagoev, B.; Gaudemar, M.; Dardoize, F.; Lallemand, J.Y. *Tetrahedron* ***1981***, *37*, 2153.
[2012] Pfeffer, P.E.; Silbert, L.S.; Chirinko Jr., J.M. *J. Org. Chem.* ***1972***, *37*, 451.
[2013] For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1717–1720 *ff*.
[2014] Cregar, P.L. *J. Am. Chem. Soc.* ***1970***, *92*, 1396.
[2015] Seebach, D.; Corey, E.J. *J. Org. Chem.* ***1975***, *40*, 231. See Page, P.C.B.; van Niel, M.B.; Prodger, J.C. *Tetrahedron* ***1989***, *45*, 7643; Ager, D.J. in Hase, T.A. *Umpoled Synthons*, Wiley, NY, ***1987***, pp. 19–37; Seebach, D. *Synthesis* ***1969***, 17 (especially pp. 24–27); Olsen, R.K.; Curriev Jr., Y.O. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 536–547.
[2016] See Lipshutz, B.H.; Garcia, E. *Tetrahedron Lett.* ***1990***, *31*, 7261.
[2017] Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1451–1454.

The formation and reactivity of the dithiane anion makes the anion an "acyl anion equivalent," and constitutes an Umpolung.

If a stabilizing group other than sulfur is attached to the S—CH_2 unit of a thioether ($RSCH_2X$, where X is a stabilizing group), formation of the anion and alkylation is more efficient. For example, benzylic and allylic thioethers ($RSCH_2Ar$ and $RSCH_2CH{=}CH_2$)[2018] and thioethers of the form $RSCH_3$ (R = tetrahydrofuranyl or 2-tetrahydropyranyl)[2019] have been successfully alkylated at the carbon adjacent to the sulfur atom.[2020] Stabilization by one thioether group has also been used in a method for the homologation of primary halides.[2021]

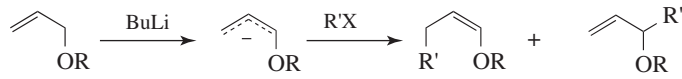
Vinylic sulfides containing an α hydrogen can also be alkylated[2022] by alkyl halides or epoxides. This is a method for converting an alkyl halide RX to an α,β-unsaturated aldehyde, which is the synthetic equivalent of the unknown $^-HC{=}CH{-}CHO$ ion; another Umpolung.[2023] Even simple alkyl aryl sulfides RCH_2SAr and RR'CHSAr have been alkylated α to the sulfur.[2024] Sulfones[2025] and sulfonic esters can also be alkylated in the α position if strong enough bases are used.[2026] Sulfones and sulfonamides have been α-arylated using a Pd catalyst.[2027] Alkylation at the α position of selenoxides allows the formation of alkenes, since selenoxides easily undergo elimination (**17-10**).[2028]

Alkylation can also be carried out, in certain compounds, at positions α to other heteroatoms,[2029] for example, at a position α to the nitrogen of tertiary amines.[2030] Alkylation α to the nitrogen of primary or secondary amines is not generally feasible because an NH hydrogen is usually more acidic than a CH hydrogen. α-Lithiation of *N*-Boc amines has been accomplished and these react with halides in the presence of a Pd catalyst.[2031] Alkylation α to the nitrogen atom of a carbamate occurs when the carbamate is treated with a Grignard reagent under electrolysis conditions.[2032] α-Methoxy amides also react with allyl halides and zinc metal to give alkylation via replacement of the OMe unit.[2033] It has been accomplished, however, by replacing the NH hydrogens with other (removable) groups.[2034] In one example, a secondary amine is converted to its *N*-nitroso derivative

[2018] Uemoto, K.; Kawahito, A.; Matsushita, N.; Skamoto, I.; Kaku, H.; Tsunoda, T. *Tetrahedron Lett.* ***2001***, *42*, 905.
[2019] Block, E.; Aslam, M. *J. Am. Chem. Soc.* ***1985***, *107*, 6729.
[2020] Biellmann, J.F.; Ducep, J.B. *Tetrahedron* ***1971***, *27*, 5861. See also, Narasaka, K.; Hayashi, M.; Mukaiyama, T. *Chem. Lett.* ***1972***, 259.
[2021] Corey, E.J.; Jautelat, M. *Tetrahedron Lett.* ***1968***, 5787.
[2022] Oshima, K.; Shimoji, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* ***1973***, *95*, 2694.
[2023] See Funk, R.L.; Bolton, G.L. *J. Am. Chem. Soc.* ***1988***, *110*, 1290.
[2024] Dolak, T.M.; Bryson, T.A. *Tetrahedron Lett.* ***1977***, 1961.
[2025] See Magnus, P.D. *Tetrahedron* ***1977***, *33*, 2019 (p. 2022); Hendrickson, J.B.; Sternbach, D.D.; Bair, K.W. *Acc. Chem. Res.* ***1977***, *10*, 306.
[2026] See Truce, W.E.; Hollister, K.R.; Lindy, L.B.; Parr, J.E. *J. Org. Chem.* ***1968***, *33*, 43; Julia, M.; Arnould, D. *Bull. Soc. Chim. Fr.* ***1973***, 743, 746.
[2027] Knauber, T.; Tucker, J. *J. Org. Chem.* ***2016***, *81*, 5636.
[2028] Reich, H.J.; Shah, S.K. *J. Am. Chem. Soc.* ***1975***, *97*, 3250.
[2029] See Krief, A. *Top. Curr. Chem.* ***1987***, *135*, 1. Also see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 336–341.
[2030] See Ahlbrecht, H.; Dollinger, H. *Tetrahedron Lett.* ***1984***, *25*, 1353.
[2031] Dieter, R.K.; Li, S. *Tetrahedron Lett.* ***1995***, *36*, 3613.
[2032] Suga, S.; Okajima, M.; Yoshida, J.-i. *Tetrahedron Lett.* ***2001***, *42*, 2173.
[2033] Kise, N.; Yamazaki, H.; Mabuchi, T.; Shono, T. *Tetrahedron Lett.* ***1994***, *35*, 1561.
[2034] For a review, see Beak, P.; Zajdel, W.J.; Reitz, D.B. *Chem. Rev.* ***1984***, *84*, 471.

(**12-49**).[2035] The *N*-nitroso product is easily hydrolyzed to the product amine (**19-55**).[2036] Alkylation of secondary and primary amines has also been accomplished with > 10 other protecting groups, involving conversion of amines to amides, carbamates,[2037] formamidines,[2038] and phosphoramides.[2033] In the case of formamidines (R—N—C=N—R), use of a chiral R′ leads to a chiral amine, in high enantiomeric excess, even when R is not chiral.[2039]

A proton can be removed from an allylic ether by treatment with an alkyllithium at about – 70 °C (at higher temperatures the Wittig rearrangement, **18-22**, takes place) to give the alkoxy allylic ion, which reacts with alkyl halides The α-arylation of cyclic ethers has been reported using 2 equivalents of a persulfate salt, an Ir complex photocatalyst, and TFA,[2040] to give the two products shown in the equation:[2041]



Similar reactions[2042] have been reported for allylic[2043] and vinylic tertiary amines.[2044]

N-Aryltetrahydroisoquinolines react with a variety of nucleophiles, including allyltin reagents, nitromethane, cyanide, etc., with excess acetic acid, and exposure to oxygen gave the α-substituted amine.[2045] Amines have been converted to α-alkyl amines using a copper(I) carboxylate catalyst.[2046]

Benzylic phosphonates react with aryl bromides with excess NaO*t*-Bu with a $Pd(OAc)_2$/CataCXium A-based catalyst (a water-soluble organophosphorus compound derived from fluorene) to give the α-aryl phosphonate.[2047] Phosphonates and phosphine oxides have been converted to the α-amine derivative using a Cu catalyst.[2048] The Umpolung chemistry of boron and phosphorus has been reviewed.[2049]

OS **VI**, 316, 364, 542, 704, 869; **VIII**, 573.

[2035] Seebach, D.; Enders, D.; Renger, B. *Chem. Ber.* ***1977***, *110*, 1852; Renger, B.; Kalinowski, H.; Seebach, D. *Chem. Ber.* ***1977***, *110*, 1866. For a review, see Seebach, D.; Enders, D. *Angew. Chem. Int. Ed.* ***1975***, *14*, 15.

[2036] Fridman, A.L.; Mukhametshin, F.M.; Novikov, S.S. *Russ. Chem. Rev.* ***1971***, *40*, 34 (pp. 41–42).

[2037] For the use of *tert*-butyl carbamates, see Beak, P.; Lee, W. *Tetrahedron Lett.* ***1989***, *30*, 1197.

[2038] For a review, see Meyers, A.I. *Aldrichimica Acta* ***1985***, *18*, 59.

[2039] Meyers, A.I.; Miller, D.B.; White, F. *J. Am. Chem. Soc.* ***1988***, *110*, 4778; Gonzalez, M.A.; Meyers, A.I. *Tetrahedron Lett.* ***1989***, *30*, 43, 47 and references cited therein.

[2040] Jin, J.; MacMillan, D.W.C. *Angew. Chem. Int. Ed.* ***2015***, *54*, 1565.

[2041] Funk, R.L.; Bolton, G.L. *J. Am. Chem. Soc.* ***1988***, *110*, 1290. See Hommes, H.; Verkruijsse, H.D.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* ***1980***, *99*, 113, and references cited therein.

[2042] See Biellmann, J.F.; Ducep, J. *Org. React.* ***1982***, *27*, 1.

[2043] Martin, S.F.; DuPriest, M.T. *Tetrahedron Lett.* ***1977***, 3925 and references cited therein.

[2044] For a review, see Ahlbrecht, H. *Chimia* ***1977***, *31*, 391.

[2045] Ueda, H.; Yoshida, K.; Tokuyama, H. *Org. Lett.* ***2014***, *16*, 4194. For a biomimetic approach to α-aminophosphonates, see Kowalczyk, D.; Albrecht, Ł. *Chem. Commun.* ***2015***, *51*, 3981.

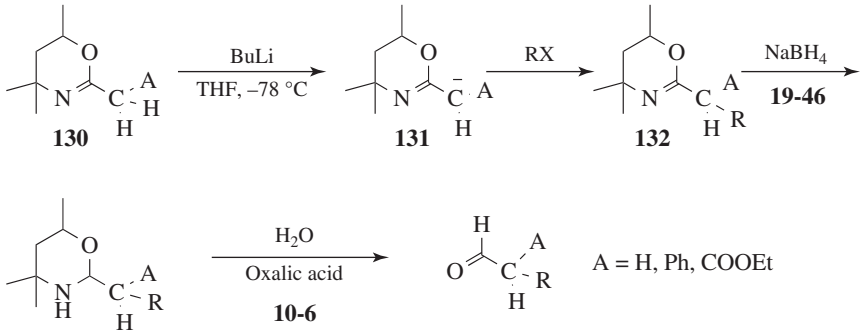
[2046] Das, D.; Sun, A.X.; Seidel, D. *Angew. Chem. Int. Ed.* ***2013***, *52*, 3765.

[2047] Montel, S.; Raffier, L.; He, Y.; Walsh, P.J. *Org. Lett.* ***2014***, *16*, 1446. Also see Ordóñez, M.; Viveros-Ceballos, J.L.; Cativiela, C.; Sayago, F.J. *Tetrahedron* ***2015***, *71*, 1745.

[2048] McDonald, S.L.; Wang, Q. *Angew. Chem. Int. Ed.* ***2014***, *53*, 1867.

[2049] Stephan, D.W. *Angew. Chem. Int. Ed.* ***2017***, *56*, 5984. Also see Unsworth, P.J.; Löffler, L.E.; Noble, A.; Aggarwal, V.K. *Synlett* ***2015***, *26*, 1567.

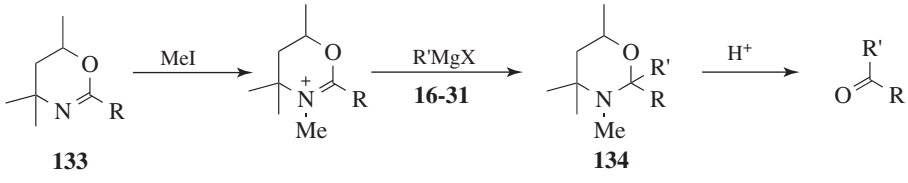
10-72 Alkylation of Dihydro-1,3-Oxazine: The Meyers Synthesis



A synthesis of aldehydes[2050] developed by Meyers and co-workers[2051] begins with the commercially available dihydro-1,3-oxazine derivatives **130** (A = H, Ph, or COOEt).[2052] Removal of a proton from the pendant carbon in **130** leads to the resonance-stabilized and bidentate anion **131**. Alkylation occurs regioselectively at carbon using many alkyl bromides and iodides. The R group of RX can be primary or secondary alkyl, allylic, or benzylic and can carry another halogen or a CN group.[2053] The alkylated oxazine **132** is then reduced and hydrolyzed to give an aldehyde containing two more carbons than the starting RX. This method thus complements **10-71**, which converts RX to an aldehyde containing one more carbon. Since A can be H, mono- or disubstituted acetaldehydes can be produced by this method.

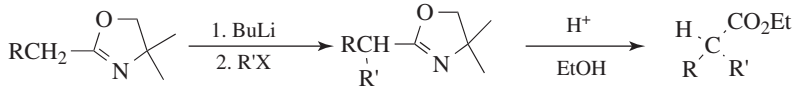
The ion **131** also reacts with epoxides, to form γ-hydroxy aldehydes after reduction and hydrolysis,[2054] and reacts with aldehydes and ketones (**16-38**). Similar aldehyde synthesis has also been carried out with thiazoles[2055] and thiazolines[2056] (five-membered rings containing N and S in the 1 and 3 positions).

The reaction has been extended to the preparation of ketones:[2057] Treatment of a dihydro-1,3-oxazine (**133**) with iodomethane forms the iminium salt which, when treated with a Grignard reagent or organolithium compound, produces **134**. Hydrolysis gives a ketone.



[2050] Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1461–1465.
[2051] Meyers, A.I.; Nabeya, A.; Adickes, H.W.; Politzer, I.R.; Malone, G.R.; Kovelesky, A.C.; Nolen, R.L.; Portnoy, R.C. *J. Org. Chem.* ***1973***, *38*, 36.
[2052] See Schmidt, R.R. *Synthesis* ***1972***, 333; Collington, E.W. *Chem. Ind. (London)* ***1973***, 987.
[2053] Meyers, A.I.; Malone, G.R.; Adickes, H.W. *Tetrahedron Lett.* ***1970***, 3715.
[2054] Adickes, H.W.; Politzer, I.R.; Meyers, A.I. *J. Am. Chem. Soc.* ***1969***, *91*, 2155.
[2055] Altman, L.J.; Richheimer, S.L. *Tetrahedron Lett.* ***1971***, 4709.
[2056] Meyers, A.I.; Durandetta, J.L. *J. Org. Chem.* ***1975***, *40*, 2021.
[2057] Meyers, A.I.; Smith, E.M. *J. Org. Chem.* ***1972***, *37*, 4289.

Note that the heterocycles **130**, **133**, and **135** do not react directly with Grignard reagents. In another procedure, 2-oxazolines[2058] (e.g., **135**) can be alkylated to give **136**,[2059] which are easily converted directly to the esters by heating in 5–7% ethanolic sulfuric acid.

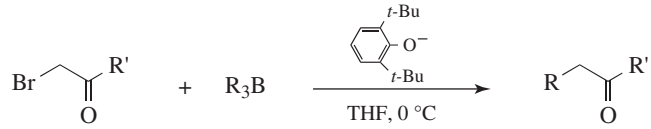


135 **136**

By this reaction, 2-oxazolines **135** and **136** are synthons for carboxylic acids; this is another indirect method for the α-alkylation of a carboxylic acid.[2060] The method can be adapted to the preparation of optically active carboxylic acids by the use of a chiral reagent.[2061] Note that **135** can be alkylated even if R is alkyl. However, the C=N bond of **135** and **136** cannot be effectively reduced, so that aldehyde synthesis is not feasible here.[2062]

OS **VI**, 905.

10-73 Alkylation With Boranes, Boronic Acids, and Boronates



The alkylation of activated halogen compounds is one of several reactions of trialkylboranes developed by H.C. Brown[2063] (see also **15-11**, **15-23**, **18-23**, **18-24**, and **18-25**). Trialkylboranes react rapidly and in high yields with α-halo ketones,[2064] α-halo esters sulfonyl derivatives (sulfones, sulfonic esters, sulfonamides)[2065] react with boranes in the presence of a base to give, respectively, alkylated ketones, esters, and sulfonyl derivatives.[2066] Potassium *tert*-butoxide is often a suitable base, but potassium 2,6-di-*tert*-butylphenoxide at 0 °C in THF gives better results in most cases, possibly because the large bulk of the two *tert*-butyl groups prevents the base from coordinating with the R_3B.[2067] With appropriate boranes, the

[2058] For a review, see Meyers, A.I.; Mihelich, E.D. *Angew. Chem. Int. Ed.* ***1976***, *15*, 270.

[2059] Meyers, A.I.; Temple Jr., D.L.; Nolen, R.L.; Mihelich, E.D. *J. Org. Chem.* ***1974***, *39*, 2778; Meyers, A.I.; Mihelich, E.D.; Nolen, R.L. *J. Org. Chem.* ***1974***, *39*, 2783.

[2060] See Meyers, A.I. *Pure Appl. Chem.* ***1979***, *51*, 1255; *Acc. Chem. Res.* ***1978***, *11*, 375. See also, Meyers, A.I.; Snyder, E.S.; Ackerman, J.J.H. *J. Am. Chem. Soc.* ***1978***, *100*, 8186.

[2061] See Lutomski, K.A.; Meyers, A.I. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1984***, pp. 213–274.

[2062] Meyers, A.I.; Temple Jr., D.L. *J. Am. Chem. Soc.* ***1970***, *92*, 6644, 6646.

[2063] Brown, H.C. *Organic Syntheses via Boranes*, Wiley, NY, ***1975***; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***.

[2064] Brown, H.C.; Rogic, M.M.; Rathke, M.W. *J. Am. Chem. Soc.* ***1968***, *90*, 6218.

[2065] Truce, W.E.; Mura, L.A.; Smith, P.J.; Young, F. *J. Org. Chem.* ***1974***, *39*, 1449.

[2066] See Negishi, E.; Idacavage, M.J. *Org. React.* ***1985***, *33*, 1 (pp. 42–43, 143–150); Weill-Raynal, J. *Synthesis* ***1976***, 633; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 372–391, 404–409; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 275–278, 283–287.

[2067] Brown, H.C.; Nambu, H.; Rogic, M.M. *J. Am. Chem. Soc.* ***1969***, *91*, 6852, 6854, 6855.

R group transferred to α-halo ketones, nitriles, and esters can be vinylic,[2068] or (for α-halo ketones and esters) aryl.[2069] Allylic boranes reacted with allylic chlorides, with a Pd catalyst, to give the corresponding 1,5-diene.[2070] Trialkylboranes reacted with allylic chlorides with a Cu catalyst and in the presence of KOMe to give the cross-coupling product with displacement of the pinanylborane unit.[2071]

The reaction can be extended to α,α-dihalo esters[2072] and α,α-dihalo nitriles.[2073] It is possible to replace just one halogen or both. In the latter case, the two alkyl groups can be the same or different. When dialkylation is applied to dihalo nitriles, the two alkyl groups can be primary or secondary, but with dihalo esters, dialkylation is limited to primary R.

Another extension is the reaction of boranes (BR_3) with γ-halo-α,β-unsaturated esters.[2074] Alkylation takes place in the γ position, but the double bond migrates out of conjugation with the CO_2Et unit.[2075] The mechanism is not known with certainty,[2076] but the first step is probably removal of the acidic proton by the base to give an enolate anion that combines with the borane (Lewis acid–base reaction). An R group then migrates, displacing the halogen leaving group.[2077] Another migration follows, this time of BR_2 from carbon to oxygen to give the enol borinate,[2078] which is hydrolyzed. Configuration at the alkyl group R is retained.[2079]

Alkylboranes are coupled to alkyl halides in the presence of a Ni catalyst.[2080] Note that alkylboronic acids are coupled in the presence of Ag_2O and a catalytic amount of $CrCl_2$ to give the symmetrical alkyl derivative.[2081] The Pd-catalyzed coupling of allylB(pin) with allylic electrophiles as been reported.[2082] Allylic chlorides reacted with 1,1-diborylalkanes, with a Cu catalyst, to give alkylboronates.[2083] Organoboranes also react with diazo compounds to give the corresponding ketone.[2084] The reaction of vinylmagnesium chloride with R-B(pin) in the presence of a catalytic amount of Pd and NaOTf gave chiral nonracemic chiral organoboronic esters.[2085]

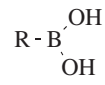
Alkenylboranes ($R'_2C{-}CHBZ_2$; Z = various groups) couple in high yields with vinylic,[2086] alkynyl, aryl, benzylic, and allylic halides or triflates in the presence of a Pd catalyst and a base to give $R'_2C{-}CHR$.[2087] 9-Alkyl-9-BBN compounds (**15-11**) also

[2068] Brown, H.C.; Bhat, N.G.; Campbell Jr., J.B. *J. Org. Chem.* ***1986***, *51*, 3398.
[2069] Brown, H.C.; Rogic, M.M. *J. Am. Chem. Soc.* ***1969***, *91*, 4304.
[2070] Brozek, L.A.; Ardolino, M.J.; Morken, J.P. *J. Am. Chem. Soc.* ***2011***, *133*, 16778.
[2071] Shido, Y.; Yoshida, M.; Tanabe, M.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* ***2012***, *134*, 18573.
[2072] Brown, H.C.; Rogic, M.M.; Rathke, M.W.; Kabalka, G.W. *J. Am. Chem. Soc.* ***1968***, *90*, 1911.
[2073] Nambu, H.; Brown, H.C. *J. Am. Chem. Soc.* ***1970***, *92*, 5790.
[2074] Brown, H.C.; Nambu, H. *J. Am. Chem. Soc.* ***1970***, *92*, 1761.
[2075] Brown, H.C.; Rogic, M.M.; Rathke, M.W.; Kabalka, G.W. *J. Am. Chem. Soc.* ***1968***, *90*, 818.
[2076] See Prager, R.H.; Reece, P.A. *Aust. J. Chem.* ***1975***, *28*, 1775.
[2077] See Midland, M.M.; Zolopa, A.R.; Halterman, R.I. *J. Am. Chem. Soc.* ***1979***, *101*, 248. See also, Midland, M.M.; Preston, S.B. *J. Org. Chem.* ***1980***, *45*, 747.
[2078] Pasto, D.J.; Wojtkowski, P.W. *J. Org. Chem.* ***1971***, *36*, 1790.
[2079] Brown, H.C.; Rogic, M.M.; Rathke, M.W.; Kabalka, G.W. *J. Am. Chem. Soc.* ***1969***, *91*, 2150.
[2080] Saito, B.; Fu, G.C. *J. Am. Chem. Soc.* ***2008***, *130*, 6694.
[2081] Falck, J.R.; Mohaptra, S.; Bondlela, M.; Venkataraman, S.K. *Tetrahedron Lett.* ***2002***, *43*, 8149.
[2082] Le, H.; Batten, A.; Morken, J.P. *Org. Lett.* ***2014***, *16*, 2096.
[2083] Kim, J.; Park, S.; Park, J.; Cho, S.H. *Angew. Chem. Int. Ed.* ***2016***, *55*, 1498.
[2084] Li, H.; Zhang, Y.; Wang, J. *Synthesis* ***2013***, *45*, 3090.
[2085] Lovinger, G.J.; Aparece, M.D.; Morken, J.P. *J. Am. Chem. Soc.* ***2017***, *139*, 3153.
[2086] Occhiato, E.G.; Trabocchi, A.; Guarna, A. *Org. Lett.* ***2000***, *2*, 1241.
[2087] Rivera, I.; Soderquist, J.A. *Tetrahedron Lett.* ***1991***, *32*, 2311; and references cited therein. For a review, see Matteson, D.S. *Tetrahedron* ***1989***, *45*, 1859.

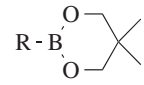
couple with vinylic and aryl halides[2088] as well as with α-halo ketones, nitriles, and esters.[2089]

The reaction has also been applied to compounds with other leaving groups. Diazo ketones, diazo esters, diazo nitriles, and diazo aldehydes[2090] react with trialkylboranes in a similar manner. The mechanism is probably similar. In this case a base is not needed since the carbon already has an available pair of electrons. The reaction with diazo aldehydes[2091] is especially notable, since successful reactions cannot be obtained with α-halo aldehydes.[2092]

Boranes



Boronic acids



Boronates

Boronic acids also react with benzylic ammonium triflates to give the coupling product.[2093] Alkyl[2094] and aryl[2095] boronic acids [$RB(OH)_2$] react with allylic acetates to give the alkylated product in the presence of a Pd catalyst.[2096] A cyclopropylboronic acid was coupled to an allylic bromide with silver oxide/KOH and a Pd catalyst.[2097] Alkylboronic acids can also be coupled to aromatic compounds in the presence of $Cu(OAc)_2$ and a Pd catalyst.[2098] The Pd-catalyzed coupling of vinyl halides and alkylboronic acids[2099] gives substituted alkenes and is related to the *Suzuki-Miyara coupling* (**13-11**).

The Ni-catalyzed cross-coupling between boronic acids and redox-active esters has been reported.[2100] The reaction of styryl epoxides with arylboronic acids using a Ni catalyst complexed with a biaryldialkyl monophosphine ligand opens the epoxide to give the 1,2-diarylethanol derivative.[2101] Cyclopropylboronic esters react with aromatic and aliphatic secondary acyclic amides, in the presence of $Cu(OAc)_2$, Cs_2CO_3, with excess pyridine, and when heated in the presence of dry air.[2102] Secondary alcohols react with alkyl boronic esters in the presence of *in situ* generated *N*-heterocyclic carbene–Ni catalysts to generate

[2088] Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* ***1989***, *111*, 314. See also, Soderquist, J.A.; Santiago, B. *Tetrahedron Lett.* ***1990***, *31*, 5541.

[2089] Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* ***1992***, 691. See Matteson, D.S.; Tripathy, P.B.; Sarkar, A.; Sadhu, K.M. *J. Am. Chem. Soc.* ***1989***, *111*, 4399.

[2090] Mikhailov, B.M.; Gurskii, M.E. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1973***, *22*, 2588.

[2091] Hooz, J.; Morrison, G.F. *Can. J. Chem.* ***1970***, *48*, 868.

[2092] See Hooz, J.; Bridson, J.N.; Calzada, J.G.; Brown, H.C.; Midland, M.M.; Levy, A.B. *J. Org. Chem.* ***1973***, *38*, 2574.

[2093] Shacklady-McAtee, D.M.; Roberts, K.M.; Basch, C.H.; Song, Y.-G.; Watson, M.P. *Tetrahedron* ***2014***, *70*, 4257.

[2094] Kondolff, I.; Doucet, H.; Santelli, M. *Tetrahedron* ***2004***, *60*, 3813.

[2095] Nobre, S.M.; Monteiro, A.L. *Tetrahedron Lett.* ***2004***, *45*, 8225.

[2096] Ohmiya, H.; Makida, Y.; Tanaka, T.; Sawamura, M. *J. Am. Chem. Soc.* ***2008***, *130*, 17276.

[2097] Chen, H.; Deng, M.-Z. *J. Org. Chem.* ***2000***, *65*, 4444.

[2098] Chen, X.; Goodhue, C.E.; Yu, J.-Q. *J. Am. Chem. Soc.* ***2006***, *128*, 12634.

[2099] Bellina, F.; Anselmi, C.; Rossi, R. *Tetrahedron Lett.* ***2001***, *42*, 3851. See also, Yoshida, H.; Yamaryo, Y.; Oshita, J.; Kunai, A. *Tetrahedron Lett.* ***2003***, *44*, 1541.

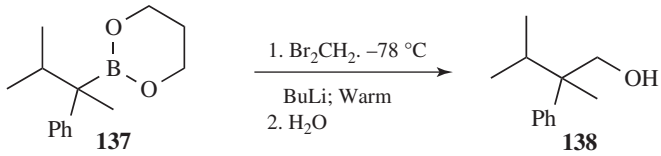
[2100] Wang, J.; Qin, T.; Chen, T.-G.; Wimmer, L.; Edwards, J.T.; Cornella, J.; Vokits, B.; Shaw S.A.; Baran, P.S. *Angew. Chem. Int. Ed.* ***2016***, *55*, 9676.

[2101] Nielsen, D.K.; Doyle, A.G. *Angew. Chem. Int. Ed.* ***2011***, *50*, 6056.

[2102] Racine, E.; Monnier, F.; Vors J.-P.; Taillefer, M. *Chem. Commun.* ***2013***, *49*, 7412.

a variety of tertiary alcohols.[2103] The CuBr-catalyzed coupling of amides and alkylboronic acids using the mild base $NaOSiMe_3$ and di-*tert*-butyl peroxide gives *N*-alkyl amides.[2104] The Cu-catalyzed *N*-arylation of lactams with arylboronic acids occurs under base and ligand-free conditions.[2105] bis-Aryl maleimides have been prepared using maleimide and arylboronic acids using a Pd catalyst.[2106] Arylboronic acids undergo a coupling reaction with epoxides in the presence of a Pd catalyst.[2107] Allylic alcohols can be coupled with arylboronic acids in an ionic liquid solvent and a Rh catalyst.[2108]

It has been reported that $BrCH_2Li$ reacts in poor yield with *tert*-alkylboronic esters due to the *O*-migratory propensity of the alkyl unit on boron, but reacted with alkyl boronic esters to give a good yield of the corresponding alcohol, The conversion of **137** to **138** in 73% yield is one example.[2109]



137 **138**

Boronic esters reacted with acyltrimethylsilanes, photochemically, to give the B—C bond insertion product, which was hydrolyzed with 1 M HCl in air to give the corresponding ketone.[2110] Phenols react with vinyl boronates and a Cu catalyst to give aryl vinyl ethers.[2111] Epoxides and also *N*-tosyl azirdines (**10-66**) react with alkylboronates and with a Cu catalyst to give the ring-opened alcohol (or amine).[2112] Arylation of sp^3 C—H positions can be done using arylboronates and a Rh catalyst.[2113]

Potassium alkyl, aryl, and 1-alkenyltrifluoroborates (RBF_3K, $ArBF_3K$, and RBF_3K) are easily prepared from organoboronic acids or esters. In general, the trifluoroborates have greater air stability and greater nucleophilicity[2114] when compared to the corresponding organoboranes and organoboronic acid derivatives. Potassium alkyltrifluoroborates undergo the Pd-catalyzed coupling reaction with arenediazonium tetrafluoroborates,[2115] diaryliodonium salts,[2116] aryl halides,[2117] as well as with aryl triflates. An example of the latter reaction converted potassium benzyltrifluoroboronate, **139**, to diphenylmethane via coupling with phenyl triflate.[2118] Alkenyltrifluoroborates can be

[2103] Berini, C.; Navarro, O. *Chem. Commun.* ***2012***, *48*, 1538.
[2104] Rossi, S.A.; Shimkin, K.W.; Xu, Q.; Mori-Quiroz, L.M.; Watson, D.A. *Org. Lett.* ***2013***, *15*, 2314.
[2105] Bathini, T.; Rawat, V.S.; Sreedhar, B. *Synlett* ***2015***, *26*, 1348.
[2106] Jafarpour, F.; Shamsianpour, M.; Issazadeh, S.; Dorrani, M.; Hazrati, H. *Tetrahedron* ***2017***, *73*, 1668.
[2107] Yoshida, M.; Ueda, H.; Ihara, M. *Tetrahedron Lett.* ***2005***, *46*, 6705.
[2108] Kabalka, G.W.; Dong, G.; Venkataiah, B. *Org. Lett.* ***2003***, *5*, 893.
[2109] Elliott, M.C.; Smith, K.; Jones, D.H.; Hussain, A.; Saleh, B.A. *J. Org. Chem.* ***2013***, *78*, 3057.
[2110] Ito, K.; Tamashima, H.; Iwasawa, N.; Kusama, H. *J. Am. Chem. Soc.* ***2011***, *133*, 3716.
[2111] McKinley, N.F.; O'Shea, D.F. *J. Org. Chem.* ***2004***, *69*, 5087.
[2112] Lu, X.-Y.; Yang, C.-T.; Liu, J.-H.; Zhang, Z.-Q.; Lu, X.; Lou, X.; Xiao, B.; Fu, Y. *Chem. Commun.* ***2015***, *51*, 2388.
[2113] Pastine, S.J.; Gribkov, D.V.; Sames, D. *J. Am. Chem. Soc.* ***2006***, *128*, 14220.
[2114] Batey, R.A.; Thadani, A.N.; Smil, D.V.; Lough, A.J. *Synthesis* ***2000***, 990.
[2115] Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* ***1999***, 1875.
[2116] Xia, M.; Chen, Z.-C. *Synth. Commun.* ***1999***, *29*, 2457.
[2117] Molander, G.A.; Gormisky, P.E. *J. Org. Chem.* ***2008***, *73*, 7481.
[2118] Molander, G.A.; Ito, T. *Org. Lett.* ***2001***, *3*, 393.

coupled to aryl halides.[2119] Potassium alkynyltrifluoroborates have been coupled to 2-chloroacetates or 2-chloroacetamides using a Pd catalyst.[2120] Trifluoroborates are methylated in reactions catalyzed by a Ru catalyst.[2121] Potassium alkyltrifluoroborates such as **139** undergo C—H alkylation in the presence of MnF_3 and a $Pd(OAc)_3$ catalyst.[2122] Note that dppf = diphenylphosphinoferrocene.

$$\underset{\mathbf{139}}{PhCH_2\mathbf{BF}_3K} + PhOTf \xrightarrow[9\%\ PdCl_2(dppf)\bullet CH_2Cl_2]{3\ eq\ Cs_2CO_3,aq\ THF} PhCH_2Ph$$

OS **VI**, 919; **IX**, 107.

10-74 Alkylation at an Alkynyl Carbon

$$RX + R'C{\equiv}C^- \longrightarrow RC{\equiv}CR'$$

The reaction between alkyl halides and acetylide ions is useful but of limited scope.[2123] Only primary halides unbranched in the β position give good yields, although allylic halides can be used if CuI is present.[2124] If acetylene is the reagent, two different groups can be successively attached. Sulfates, sulfonates, and epoxides[2125] are sometimes used as substrates. The acetylide ion is often prepared by treatment of an alkyne with a strong base such as $NaNH_2$. Magnesium acetylides (prepared as in **12-22**) are also frequently used, although they react only with active substrates, such as allylic, benzylic, and propargylic halides, and not with primary alkyl halides. Alternatively, the alkyl halide can be treated with a lithium acetylide–ethylenediamine complex.[2126] If 2 equivalents of a very strong base are used, alkylation can be effected at a carbon α to a terminal triple bond:[2127]

$$RCH_2C{\equiv}CH + 2BuLi \rightarrow R^-CHC{\equiv}C^{:-} + R'Br \rightarrow RR'CHC{\equiv}C{:}^-$$

For another method of alkylating at an alkynyl carbon, see **18-26**. As an alternative method for generating an alkyne anion, a trialkylsilyl alkyne was treated with potassium carbonate in methanol, and then MeLi/LiBr.[2128] In the presence of an alkyl iodide, alkylation at the alkynyl carbon occurred.

Catalytic asymmetric propargylation has been reviewed.[2129] The chemistry of alkynyl copper compounds has been reviewed.[2130] Terminal alkynes react with alkylzinc reagents

[2119] Molander, G.A.; Rivero, M.R. *Org. Lett.* ***2002***, *4*, 107.
[2120] Molander, G.A.; Traister, K.M. *Org. Lett.* ***2013***, *15*, 5052.
[2121] Tonin, M.D.L.; Zell, D.; Müller, V.; Ackermann, L. *Synthesis* ***2017***, *49*, 127.
[2122] Neufeldt, S.R.; Seigerman, C.K.; Sanford, M.S. *Org. Lett.* ***2013***, *15*, 2302.
[2123] See Ben-Efraim, D.A. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, Wiley, NY, ***1978***, pp. 790–800; Ziegenbein, W. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 185–206, 241–244. Also see Bernadou, F.; Mesnard, D.; Miginiac, L. *J. Chem. Res. (S)* ***1978***, 106; ***1979***, 190.
[2124] Jeffery, T. *Tetrahedron Lett.* ***1989***, *30*, 2225.
[2125] See Krause, N.; Seebach, D. *Chem. Ber.* ***1988***, *121*, 1315.
[2126] Smith, W.N.; Beumel Jr., O.F. *Synthesis* ***1974***, 441.
[2127] Bhanu, S.; Scheinmann, F. *J. Chem. Soc., Perkin Trans.1*, ***1979***, 1218; Quillinan, A.J.; Scheinmann, F. *Org. Synth.* ***VI***, 595.
[2128] Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. *Tetrahedron Lett.* ***2003***, *44*, 9087.
[2129] Ding, C.-H.; Hou, X.-L. *Chem. Rev.* ***2011***, *111*, 1914.
[2130] Adeleke, A.F.; Brown, A.P.N.; Cheng, L.-J.; Mosleh, K.A.M.; Cordier, C.J. *Synthesis* ***2017***, *49*, 790.

in the presence of a Pd catalyst.[2131] Alkynes couple with alkyl halides in the presence of SmI_2/Sm[2132] or a Cu catalyst.[2133] The reaction of benzylic amines with terminal alkynes in the presence of copper triflate and *t*-BuOOH leads to incorporation of the alkyne group α to the nitrogen.[2134] In the presence of $GaCl_3$, $ClC{\equiv}CSiMe_3$ reacts with silyl enol ethers to give, after treatment with methanolic acid, an α-ethynyl ketone.[2135] In a related reaction, terminal alkynes react with silanes (R_3SiH) in the presence of an Ir catalyst[2136] or zinc triflate[2137] to give the 1-trialkylsilyl alkyne. Similar products are obtained when terminal alkynes react with *N*-trialkylsilylamines and $ZnCl_2$.[2138]

In the presence of a Pd catalyst, an alkynyltin reagent reacts with an alkylzinc compound to give the corresponding alkyne.[2139] Alkynylzinc compounds undergo Pd-catalyzed cross-coupling reactions.[2140] Terminal alkynes react with allylic bromides in the presence of a Ni catalyst.[2141] The reaction of a terminal alkyne with Zn(II) compounds allows reaction with silanes to give the 1-silylalkyne.[2142]

The cross-coupling of alkyl halides and terminal alkynes gave an internal alkyne using a Cu catalyst with 2 equivalents of C_2CO_3.[2143] Terminal alkynes were coupled with alkyl triflates in the presence of a *N*-heterocyclic carbene–Cu catalyst.[2144] Terminal alkynes reacted with allylic acetates using a Pd catalyst in the presence of AlOTf to give the internal alkyne.[2145] The methylation of terminal alkynes was carried out using a Pd catalyst in a reaction with dimethyl sulfonium ylids.[2146] Terminal alkynes have been coupled with an excess of trimethyltrifluoromethylsilane to give the trifluoromethyl terminal alkyne, in the presence of CuCl/phen and KF.[2147]

Alkynes react with hypervalent iodine compounds[2148] and with reactive alkanes such as adamantane in the presence of AIBN.[2149] The alkynylation of nucleophilic fluorocarbons has been reported using hypervalent iodine compounds under Cinchona-based phase-transfer catalysis.[2150] Secondary allylic phosphates gave skipped enynes with excellent γ-regioselectivity and (*E*)-stereoselectivity using a CuCl/phen catalyst in the presence of LiO*t*-Bu.[2151]

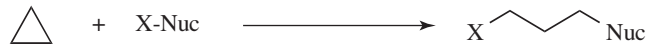
[2131] Chen, M.; Zheng, X.; Li, W.; He, J.; Lei, A. *J. Am. Chem. Soc.* ***2010***, *132*, 4101.
[2132] Murakami, M.; Hayashi, M.; Ito, Y. *Synlett* ***1994***, 179.
[2133] Bieber, L.W.; da Silva, M.F. *Tetrahedron Lett.* ***2007***, *48*, 7088.
[2134] Li, Z.; Li, C.-J. *Org. Lett.* ***2004***, *6*, 4997.
[2135] Arisawa, M.; Amemiya, R.; Yamaguchi, M. *Org. Lett.* ***2002***, *4*, 2209.
[2136] Shimizu, R; Fuchikami, T. *Tetrahedron Lett.* ***2000***, *41*, 907.
[2137] Jiang, H.; Zhu, S. *Tetrahedron Lett.* ***2005***, *46*, 517.
[2138] Andreev, A.A.; Konshin, V.V.; Komarov, N.V.; Rubin, M.; Brouwer, C.; Gevorgyan, V. *Org. Lett.* ***2004***, *6*, 421.
[2139] Zhao, Y.; Wang, H.; Hou, X.; Hu, Y.; Lei, A.; Zhang, H.; Zhu, L. *J. Am. Chem. Soc.* ***2006***, *128*, 15048.
[2140] Qian, M.; Negishi, E. *Tetrahedron Lett.* ***2005***, *46*, 2927.
[2141] Nadal, M.L.; Bosch, J.; Vila, J.M.; Klein, G.; Ricart, S.; Moretó, J.M. *J. Am. Chem. Soc.* ***2005***, *127*, 10476.
[2142] Rahaim, Jr., R.J.; Shaw, J.T. *J. Org. Chem.* ***2008***, *73*, 2912.
[2143] Luo, F.-X.; Xu, X.; Wang, D.; Cao, Z.-C.; Zhang, Y.-F.; Shi, Z.-J. *Org. Lett.* ***2016***, *18*, 2040.
[2144] Jin, L.; Hao,W.; Xu, J.; Sun, N.; Hu, B.; Shen Z.; Mo, W.; Hu, X. *Chem. Commun.* ***2017***, *53*, 4124.
[2145] Yang, Q.; Zhou, Y.; Chen, J.; He, X.; Xu, J.; Kwong, F.Y.; Fan, B. *Eur. J. Org. Chem.* ***2015***, 5330.
[2146] Liu, Y.-Y.; Yang, X.-H.; Huang, X.-C.; Wei, W.-T.; Song, R.-J.; Li, J.-H. *J. Org. Chem.* ***2013***, *78*, 10421.
[2147] Zhang, K.; Qiu, X.-L.; Huang, Y.; Qing, F.-L. *Eur. J. Org. Chem.* ***2012***, 58.
[2148] Kang, S.-K.; Lim, K.-H.; Ho, P.-S.; Kim, W.-Y. *Synthesis* ***1997***, 874.
[2149] Xiang, J.; Jiang, W.; Fuchs, P.L. *Tetrahedron Lett.* ***1997***, *38*, 6635.
[2150] Kamlar, M.; Putaj, P.; Veselý, J. *Tetrahedron Lett.* ***2013***, *54*, 2097.
[2151] Makida, Y.; Takayama, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem. Int. Ed.* ***2013***, *52*, 5350.

1-Haloalkynes react with various substrates in the presence of a metal catalyst. 1-Haloalkynes such as R—C≡C—X react with $ArSnBu_3$ and CuI to give R—C≡C—Ar.[2152] Organozirconium compounds react in a similar manner.[2153] Acetylene reacts with 2 equivalents of iodobenzene, in the presence of a Pd catalyst and CuI, to give 1,2-diphenylethyne.[2154] 1-Trialkylsilyl alkynes react with 1-haloalkynes, in the presence of a CuCl catalyst, to give diynes[2155] and react with aryl triflates to give 1-aryl alkynes.[2156] The enolate anion derived from a β-keto ester couples with 1-bromoalkynes to give the corresponding substitution product.[2157] 1-Bromoalkynes react with nitrogen compounds such as imidazole in the presence of a Cu catalyst to give the corresponding alkyne.[2158] 1-Bromoalkynes react with Grignard-derived reagents in the presence of an Fe catalyst.[2159]

Acyl chlorides have been coupled to terminal alkynes using a Pd complex and CuI catalysts to give the alkynyl ketone derivative.[2160]

OS **IV**, 117; **VI**, 273, 564, 595; **VIII**, 415; **IX**, 117, 477, 688; **76**, 263. Also see OS **IV**, 801; **VI**, 925.

10-75 Ring Opening of Cyclopropane Derivatives



Cyclopropanes with ketone, diester, or dinitrile substituents are ring opened and converted to 1,3-dichorides upon treatment with $PhICl_2$ (iodobenzenedichloride).[2161] Dicarboalkoxycyclopropanes react with thiols in the presence of $Ca(acac)_2$ or proline to give the γ-thioalkyl derivative.[2162] Similar cyclopropanes are ring opened and isomerized to (2-arylalkylidene)malonates in the presence of $GaCl_3$.[2163]

Functionalized cyclic β-enamino esters have been formed by the reaction of 1,1-carbomethoxycyclopropanes with malonitrile derivatives, in the presence of NaH and a $Yb(OTf)_3$ catalyst.[2164] Similarly substituted cyclopropane derivatives react with RSX or RSeX to give the α-thioalkyl or α-selenoalkyl γ-halo diester.[2165] 2,2-difluorocyclopropyl ketones were opened by reaction with Lewis acids such as BX_3 to give β-CF_2X ketones.[2166] Bicyclic nitrocyclopropanes reacted with zinc powder under acidic conditions to give

[2152] Kang, S.-K.; Kim, W.-Y.; Jiao, X. *Synthesis* ***1998***, 1252.
[2153] Liu, Y.; Xi, C.; Hara, R.; Nakajima, K.; Yamazaki, A.; Kotora, M.; Takahashi, T. *J. Org. Chem.* ***2000***, *65*, 6951.
[2154] Pal, M.; Kundu, N.G. *J. Chem. Soc., Perkin Trans 1*, ***1996***, 449. Also see, Nguefack, J.-F.; Bolitt, V.; Sinou, D. *Tetrahedron Lett.* ***1996***, *37*, 5527.
[2155] Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* ***1998***, *39*, 4075.
[2156] See Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Chem. Lett.* ***1997***, 1233.
[2157] Poulsen, T.B.; Bernardi, L.; Alemán, J.; Overgaard, J.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2007***, *129*, 441.
[2158] Laroche, C.; Li, J.; Freyer, M.W.; Kerwin, S.M. *J. Org. Chem.* ***2008***, *73*, 6462.
[2159] Castagnolo, D.; Botta, M. *Eur. J. Org. Chem.* ***2010***, 3224.
[2160] Huang, B.; Yin, L.; Cai, M. *New J. Chem.* ***2013***, 3137.
[2161] Garve, L.K.B.; Barkawitz, P.; Jones, P.G.; Werz, D.B. *Org. Lett.* ***2014***, *16*, 5804.
[2162] Xia, Y.; Lin, L.; Chang, F.; Fu, X.; Liu, X.; Feng, X. *Angew. Chem. Int. Ed.* ***2015***, *54*, 13748.
[2163] Novikov, R.A.; Tarasova, A.V.; Tomilov, Y.V. *Synlett* ***2016***, *27*, 1267.
[2164] Ghorai, M.K.; Talukdar, R.; Tiwari, D.P. *Org. Lett.* ***2014***, *16*, 2204. See Green, J.R.; Snieckus, V. *Synlett* ***2014***, *25*, 2258.
[2165] Wallbaum, J.; Garve, L.K.B.; Jones, P.G.; Werz, D.B. *Org. Lett.* ***2017***, *19*, 98.
[2166] Yang, T.-P.; Li, Q.; Lin, J.-H.; Xiao, J.-C. *Chem. Commun.* ***2014***, *50*, 1077.

double cleavage of C—C bonds in the cyclopropane to give a vinyl nitrile.[2167] The ring opening and isomerization reaction of cyclopropane derivatives catalyzed by $B(C_6F_5)_5$ has been reported to give the corresponding alkene.[2168]

The synthetic applications of vinylcyclopropane ring opening have been reviewed.[2169] The 1,5 additon of alcohols to dimethyl 2-vinylcyclopropane-1,1-dicarboxylate, catalyzed by Lewis acids [$Sn(OTf)_2$, $GaCl_3$, $Sc(OTf)_3$, and $Al(OTf)_3$] gave methyl 4-alkoxy-2-methoxycarbonyl-5-hexenoates.[2170] Cyclopropene derivatives react with a Ag^+ catalyst in the presence of amines to give the allylic amine.[2171] Vinylidene cyclopropanes reacted with secondary amines to give the corresponding α,β-unsaturated amide.[2172]

Cyclopropanol reacted with 1-bromoalkynes to give alk-4-yn-1-ones upon treatment with Et_2Zn and CuCN•2LiCl.[2173] Cyclpropanol derivatives reacted with alkynyl iodonium compounds in the presence of $AgNO_3$ and $K_2S_2O_8$ to give β-alkynyl ketones.[2174] Cyclopropyl derivatives also reacted with trifluoromethyl iodonium compounds with LiCl and a CuCl catalyst to give β-trifluoromethyl ketones.[2175]

10-76 Preparation of Nitriles

$$RX + {}^{-}CN \longrightarrow RCN$$

The reaction between cyanide ion and alkyl halides is a convenient method for the preparation of nitriles.[2176] The reaction proceeds by an S_N2 mechanism,[2177] so primary, benzylic, and allylic halides give good yields of nitriles; secondary halides give moderate yields. The reaction fails for tertiary halides, which give elimination under these conditions. Many other groups on the molecule do not interfere. A number of solvents have been used, but the high yields and short reaction times observed with DMSO make it a very good solvent for this reaction.[2178] In general, polar aprotic solvents are the best choice. Other ways to obtain high yields under mild conditions are to use a phase-transfer catalyst[2179] in alternative solvents, such as PEG 400 (a polyethylene glycol),[2180] or with ultrasound.[2181] This is

[2167] Kamimura, A.; Ikeda, K.; Moriyama, T.; Uno, H. *Tetrahedron Lett.* ***2013***, *54*, 1842.
[2168] Zhang, Z.-Y.; Liu, Z.-Y.; Guo, R.-T.; Zhao, Y.-Q.; Li, X.; Wang, X.-C. *Angew. Chem. Int. Ed.* ***2017***, *56*, 4028.
[2169] Meazza, M.; Guu, H.; Rios, R. *Org. Biomol. Chem.* ***2017***, *15*, 2479.
[2170] Matsuoka, S.-i.; Numata, K.; Suzuki, M. *Chem. Lett.* ***2015***, *44*, 1532.
[2171] Phan, D.T.H.; Dong, Vy.M. *Tetrahedron* ***2013***, *69*, 5726.
[2172] Lu, B.-L.; Shi, M. *Chem. Eur. J.* ***2011***, *17*, 9070.
[2173] Murali, R.V.N.S.; Rao, N.N.; Cha, J.K. *Org. Lett.* ***2015***, *17*, 3854.
[2174] Wang, C.-Y.; Song, R.-J.; Xie, Y.-X.; Li, J.-H. *Synthesis* ***2016***, *48*, 223.
[2175] Kananovich, D.G.; Konik, Y.A.; Zubrytski, D.M.; Järving, I.; Lopp, M. *Chem. Commun.* ***2015***, *51*, 8349.
[2176] See in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, Wiley, NY, ***1983***, the articles by Fatiadi, A.J. pt. 2, pp. 1057–1303, and Friedrich, K. pt. 2, pp. 1343–1390; Friedrich, K.; Wallenfels, K. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 77–86.
[2177] For a discusion about the influence of solvent on this transition state, see Fang, Y.-r.; MacMillar, S.; Eriksson, J.; Kołodziejska-Huben, M.; Dybała-Defratyka, A.; Paneth, P.; Matsson, O.; Westaway, K.C. *J. Org. Chem.* ***2006***, *71*, 4742.
[2178] Smiley, R.A.; Arnold, C. *J. Org. Chem.* ***1960***, *25*, 257; Friedman, L.; Shechter, H. *J. Org. Chem.* ***1960***, *25*, 877.
[2179] Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***, pp. 94–112; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 96–108. See also, Bram, G.; Loupy, A.; Pedoussaut, M. *Tetrahedron Lett.* ***1986***, *27*, 4171; *Bull. Soc. Chim. Fr.* ***1986***, 124.
[2180] Cao, Y.-Q.; Che, B.-H.; Pei, B.-G. *Synth. Commun.* ***2001***, *31*, 2203.
[2181] Ando, T.; Kawate, T.; Ichihara, J.; Hanafusa, T. *Chem. Lett.* ***1984***, 725.

an important way of increasing the length of a carbon chain by one carbon, since nitriles are easily hydrolyzed to carboxylic acids (**16-4**). Substrates that react with cyanide may contain leaving groups other than halides, such as esters of sulfuric and sulfonic acids (sulfates and sulfonates, respectively). Vinylic triflates give vinylic cyanides when treated with LiCN, a crown ether, and a palladium catalyst.[2182]. Vinylic bromides can be converted to vinylic cyanides with CuCN,[2183] with KCN, a crown ether, and a Pd complex,[2184] or with KCN and a Ni(0) catalyst.[2185]

The cyanide ion is an ambident nucleophile (it can react via N or via C) and isonitriles (also called isocyanides, R—N≡C) may be side products.[2186] If the preparation of isocyanides is desired (see **10-39**), they can be made the main products by the use of reagents with more covalent metal–carbon bonds, such as AgCN or CuCN[2187] (Sec. 10.G.vii, category 3). However, the use on an excess of LiCN in acetone/THF gave the nitrile as the major product.[2188] Tosyl cyanide ($TolSO_2CN$) has been used in some cases.[2189] A radical cyanation of alkyl iodides has been reported using diethylphosphoryl cyanide[2190] (see Chapter 14). Halides can be converted to the corresponding nitriles by treatment with trimethylsilyl cyanide in the presence of catalytic amounts of $SnCl_4$:[2191]

$$R_3CCl + Me_3SiCN \rightarrow R_3CCN$$

Alkyl nitriles were generated by the reaction of alkyl chlorides with tetrabutylammonium cyanide under photolytic conditions, using a CuI catalyst.[2192] Benzylic chlorides reacted with $K_4[Fe(CN)_6]$ with a Pd catalyst to give benzyl nitriles.[2193] Allylic compounds were converted to the corresponding nitrile by reaction with Me_3SiCN and a Cu catalyst.[2194] Primary halides have been converted to nitriles via a Pd-catalyzed reaction with NaN_3.[2195] Benzonitriles have been formed from aryl iodides using DMF and ammonium carbonate, with a Cu catalyst.[2196] Styrene was converted to benzonitrile by reaction with NBS and Cu-promoted reaction via C=C double bond cleavage.[2197]

[2182] Piers, E.; Fleming, F.F. *J. Chem. Soc., Chem. Commun.* ***1989***, 756.
[2183] See Lapouyade, R.; Daney, M.; Lapenue, M.; Bouas-Laurent, H. *Bull. Soc. Chim. Fr.* ***1973***, 720.
[2184] Yamamura, K.; Murahashi, S. *Tetrahedron Lett.* ***1977***, 4429.
[2185] Procházka, M.; Siroky, M. *Collect. Czech. Chem. Commun.* ***1983***, *48*, 1765.
[2186] Luanay, D.; Booth, S.; Clemens, I.; Merritt, A.; Bradley, M. *Tetrahedron Lett.* ***2002***, *43*, 7201.
[2187] See Jackson, H.L.; McKusick, B.C. *Org. Synth.* ***IV***, 438.
[2188] Ciaccio, J.A.; Smrtka, M.; Maio, W.A.; Rucando, D. *Tetrahedron Lett.* ***2004***, *45*, 7201.
[2189] Kim, S.; Song, H.-J. *Synlett* ***2002***, 2110.
[2190] Cho, C.H.; Lee, J.Y.; Kim, S. *Synlett* ***2009***, 81.
[2191] Zieger, H.E.; Wo, S. *J. Org. Chem.* ***1994***, *59*, 3838; Iranpoor, N.; Shekarriz, M. *Synth. Commun.* ***1999***, *29*, 2249.
[2192] Ratani, T.S.; Bachman, S.; Fu, G.C.; Peters, J.C. *J. Am. Chem. Soc.* ***2015***, *137*, 13902.
[2193] Ren, Y.; Yan, M.; Zhao, S.; Sun, Y.; Wang, J.; Yin, W.; Liu, Z. *Tetrahedron Lett.* ***2011***, *52*, 5107. For an example of this reaction using a Cu catalyst, see Ren, Y.; Dong, C.; Zhao, S.; Sun, Y.; Wang, J.; Ma, J.; Hou, C. *Tetrahedron Lett.* ***2012***, *53*, 2825.
[2194] Munemori, D.; Tsuji, H.; Uchida, K.; Suzuki, T.; Isa, K.; Minakawa, M.; Kawatsura, M. *Synthesis* ***2014***, *46*, 2747. For a reaction using N-doped nanoparticles, see Shang, S.; Dai, W.; Wang, L.; Lv, Y.; Gao, S. *Chem. Commun.* ***2017***, *53*, 1048.
[2195] Zou, T.; Yu, X.; Feng, X.; Bao, M. *Chem. Commun.* ***2015***, *51*, 10714.
[2196] Pawar, A.B.; Chang, S. *Chem. Commun.* ***2014***, *50*, 448.
[2197] Zong, X.; Zheng, Q.-Z.; Jiao, N. *Org. Biomol. Chem.* ***2014***, *12*, 1198.

Tetrabutylammonium cyanide converted a primary alcohol to the corresponding nitrile in the presence of PPh_3/DDQ.[2198] Alcohols are converted to cyanides by reaction with triphenylphosphine and cyanogen bromide.[2199] Primary alcohols have been converted to the corresponding nitrile by reaction with 5 equivalents of iodine in aqueous ammonia.[2200] Benzylic alcohols reacted with Me_3SiCN at 100 °C, with a $Zn(Tf)_2$ catalyst, to give the benzylic substituted nitrile.[2201] 3-Phenylpropanol reacted with 2.2 equivalents of $PhI(OAc)_2$, 4 equivalents of NH_4OAc, and with a catalytic amount of TEMPO to give 3-phenylpropionitrile.[2202] Alkyl nitriles were formed by the reaction of primary alcohols and ammonia in the presence of a catalytic amount of CuI, bpy, TEMPO, and oxygen.[2203]

Silyl enol ethers or arylsiloxanes reacted with Cu(II), ammonium iodide and DMF, in the presence of oxygen, and gave the corresponding nitrile.[2204] The $FeCl_3$-catalyzed reaction of aryl and vinyl ethers and trimethylsilyl cyanide gave the corresponding aryl or vinyl nitrile.[2205] The α position of ethers or amines were converted to the α-cyano derivatives using TsCN under photochemical conditions in acetone.[2206]

Aromatic and aliphatic carboxylic acids gave the corresponding nitriles by a multistep procedure.[2207] Carboxylic acids or their derivatives (esters, lactones, amides) were converted to nitriles by reaction with an aminoalane, prepared from Dibal-H and ammonium chloride.[2208] The transformation of benzoic acid to benzonitrile under continuous-flow conditions (Sec. 7.D) used supercritical MeCN (350 °C and 65 bar).[2209]

Esters were converted to the corresponding nitriles by reaction with sodium diisobutyl-*tert*-butoxyaluminium hydride followed by treatment with molecular iodine in aqueous ammonia.[2210] Alkenyl nitriles were prepared from allyl esters via Pd-catalyzed substitution and subsequent oxidative rearrangement.[2211]

Benzaldehyde derivatives were converted to benzonitrile derivatives with $NH_2OH{\bullet}HCl$ with choline chloride–urea with microwave irradiation.[2212] Aldehydes were converted to nitriles using chloramine-T/KI in aqueous ammonia.[2213] C-2 selectivity was observed when NaCN and $B(OMe)_3$ were reacted with a disubstituted epoxide.[2214] Cyanides opened epoxides to give the corresponding hydroxynitrile using a binuclear Ti complex.[2215]

[2198] Iranpoor, N.; Firouzabadi, H.; Akhlaghinia, B.; Nowrouzi, N. *J. Org. Chem.* ***2004***, *69*, 2562.
[2199] Tarrade-Matha, A.; Pillon, F.; Doris, E. *Synth. Commun.* ***2010***, *40*, 1646.
[2200] Shimojo, H.; Moriyama, K.; Togo, H. *Synthesis* ***2013***, *45*, 2155.
[2201] Theerthagiri, P.; Lalitha, A. *Tetrahedron Lett.* ***2012***, *53*, 5535.
[2202] Vatèle, J.-M. *Synlett* ***2014***, *25*, 1275.
[2203] Yin, W.; Wang, C.; Huang, Y. *Org. Lett.* ***2013***, *15*, 1850.
[2204] Wang, Z.; Chang, S. *Org. Lett.* ***2013***, *15*, 1990.
[2205] Fan, X.; Guo, K.; Guan, Y.-H.; Fu, L.-A.; Cui, X.-M.; Lv, H.; Zhu, H.-B. *Tetrahedron Lett.* ***2014***, *55*, 1968.
[2206] Alkenyl carboxylic: Hoshikawa, T.; Yoshioka, S.; Kamijo, S.; Inoue, M. *Synthesis* ***2013***, *45*, 874. For a Au-catalyzed reaction, see Zhang, Y.; Peng, H.; Zhang, M.; Cheng, Y.; Zhu, C. *Chem. Commun.* ***2011***, *47*, 2354.
[2207] Miyagi, K.; Moriyama, K.; Togo, H. *Eur. J. Org. Chem.* ***2013***, 5886.
[2208] Wojtkielewicz, A.; Łotowski, Z.; Morzycki, J.W. *Synlett* ***2015***, *26*, 2288.
[2209] Cantillo, D.; Kappe, C.O. *J. Org. Chem.* ***2013***, *78*, 10567.
[2210] Suzuki, Y.; Moriyama, K.; Togo, H. *Tetrahedron* ***2011***, *67*, 7956.
[2211] Zhou, W.; Xu, J.; Zhang, L.; Jiao, N. *Synlett* ***2011***, *22*, 887.
[2212] Patil, U.B.; Shendage, S.S.; Nagarkar, J.M. *Synthesis* ***2013***, *45*, 3295.
[2213] Zhu, Y.-Z.; Zhang, X.-Q.; Liu, F.; Gu, H.-M.; Xhu, H.-L. *Synth. Commun.* ***2013***, *43*, 2943.
[2214] Sasaki, M.; Tanino, K.; Hirai, A.; Miyashita, M. *Org. Lett.* ***2003***, *5*, 1789.
[2215] Maleev, V.I.; Chusov, D.A.; Yashkina, L.V.; Ikonnikov, N.S.; Il'in, M.M. *Tetrahedron: Asymmetry* ***2014***, *25*, 838.

N,*N*-Dimethylaniline reacted with trimethylsilyl cyanide, in the presence of *t*-BuOOH and a Co catalyst, and gave *N*-aryl *N*-methyl α-acetonitrile.[2216]

The Cu-mediated oxidative coupling reaction between alkynes and CuCN gave the 1-cyano alkyne.[2217] The *N*-cyanation of secondary amines has been reported, using trichloroacetonitrile followed by treatment with an alkoxide base.[2218]

OS **I**, 46, 107, 156, 181, 254, 256, 536; **II**, 292, 376; **III**, 174, 372, 557; **IV**, 438, 496, 576; **V**, 578, 614.

10-77 Direct Conversion of Alkyl Halides to Aldehydes and Ketones

$$RX + Na_2Fe(CO)_4 \xrightarrow{PPh_3} RCOFe(CO)_3PPh_3^- \xrightarrow{HOAc} RCHO$$

The direct conversion of alkyl bromides to aldehydes, with an increase in the chain length by one carbon, can be accomplished[2219] by treatment with sodium tetracarbonylferrate(−2)[2220] (*Collman's reagent*) in the presence of triphenylphosphine and subsequent quenching of $RCOFe(CO)_3PPh_3$ with acetic acid. The reagent $Na_2Fe(CO)_4$ can be prepared by treatment of iron pentacarbonyl, $Fe(CO)_5$, with sodium amalgam in THF. Good yields are obtained from primary alkyl bromides; secondary bromides give lower yields. The reaction is generally not satisfactory for benzylic bromides, but a good yield of the ketone was obtained using benzyl chloride and aryl iodides.[2221] The initial species produced from RX and $Na_2Fe(CO)_4$ is the ion $RFe(CO)_4^-$ (which can be isolated[2222]); it then reacts with Ph_3P to give $RCOFe(CO)_3PPh_3$.[2223]

The synthesis can be extended to the preparation of ketones in six distinct ways.[2224] These include: (i) quenching $RCOFe(CO)_3PPh_3$ with a second alkyl halide (R′X) rather than acetic acid; (ii) omitting PPh_3 with first RX and then adding the second R′X; (iii) treatment with RX in the presence of CO,[2220] followed by treatment with R′X′; (iv) treatment with an acyl halide followed by treatment with an alkyl halide or an epoxide, which gives an α,β-unsaturated ketone.[2225] The final variations involve reaction of alkyl halides or tosylates with $Na_2Fe(CO)_4$ in the presence of ethylene to give alkyl ethyl ketones;[2226] when 1,4-dihalides are used, five-membered cyclic ketones are prepared.[2227] Electrolysis conditions with the alkyl chloride, $Fe(CO)_5$, and a Ni catalyst gives the ketone directly, in one step.[2228]

[2216] Sakai, N.; Mutsuro, A.; Ikeda, R.; Konakahara, T. *Synlett* ***2013***, *24*, 1283.
[2217] Li, Y.; Shi, D.; Zhu, P.; Jin, H.; Li, S.; Mao, F.; Shi, W. *Tetrahedron Lett.* ***2015***, *56*, 390.
[2218] Ayres, J.N.; Ling, K.B.; Morrill, L.C. *Org. Lett.* ***2016***, *18*, 5528. See Shen H.; Zhang, X.; Liu, Q.; Pan, J.; Xiong, Y.; Zhu, X. *Tetrahedron Lett.* ***2015***, *56*, 5628.
[2219] Cooke Jr., M.P. *J. Am. Chem. Soc.* ***1970***, *92*, 6080.
[2220] See Collman, J.P. *Acc. Chem. Res.* ***1975***, *8*, 342. Also see Brunet, J. *Chem. Rev.* ***1990***, *90*, 1041.
[2221] Dolhem, E.; Barhdadi, R.; Folest, J.C.; Nédélec, J.Y.; Troupel, M. *Tetrahedron* ***2001***, *57*, 525.
[2222] Siegl, W.O.; Collman, J.P. *J. Am. Chem. Soc.* ***1972***, *94*, 2516.
[2223] See Collman, J.P.; Finke, R.G.; Cawse, J.N.; Brauman, J.I. *J. Am. Chem. Soc.* ***1978***, *100*, 4766.
[2224] See Collman, J.P.; Hoffman, N.W. *J. Am. Chem. Soc.* ***1973***, *95*, 2689.
[2225] Yamashita, M.; Yamamura, S.; Kurimoto, M.; Suemitsu, R. *Chem. Lett.* ***1979***, 1067.
[2226] Cooke Jr., M.P.; Parlman, R.M. *J. Am. Chem. Soc.* ***1975***, *97*, 6863. However, see McMurry, J.E.; Andrus, A. *Tetrahedron Lett.* ***1980***, *21*, 4687, and references cited therein.
[2227] Yamashita, M.; Uchida, M.; Tashika, H.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 2728.
[2228] Dolhem, E.; Ocafrain, M.; Nédélec, J.Y.; Troupel, M. *Tetrahedron* ***1997***, *53*, 17089.

Symmetrical ketones R_2CO can be prepared by treatment of a primary alkyl or benzylic halide with $Fe(CO)_5$ and a phase-transfer catalyst,[2229] or can be prepared from a halide RX (R = primary alkyl, aryl, allylic, or benzylic) and CO by an electrochemical method involving a Ni complex.[2230] Aryl, benzylic, vinylic, and allylic halides have been converted to aldehydes by treatment with CO and Bu_3SnH, with a Pd catalyst.[2231] Various other groups do not interfere. Vinylic halides reacted with vinylic tin reagents in the presence of CO to give unsymmetrical divinyl ketones.[2232] In addition, SmI_2 can be used to convert alkyl chlorides to ketones, in the presence of 50 atm of CO.[2233]

Other acyl organometallic reagents are known. An acyl zirconium reagent, such as $RCOZr(Cl)Cp_2$, reacted with allylic bromide in the presence of CuI to give the corresponding ketone, but with allylic rearrangement.[2234] The reaction of benzoyl chloride and alkyl iodides with a Ni catalyst, 3 equivalents of Zn, and 1.5 equivalents of $MgCl_2$ gave the corresponding phenyl alkyl ketone.[2235]

A method for the conversion of halides to acid derivatives has been reported that also makes use of $Na_2Fe(CO)_4$. Treatment of $RFe(CO)_4^-$ or $RCOFe(CO)_4^-$ with oxygen or sodium hypochlorite gives, after hydrolysis, a carboxylic acid.[2236] Alternatively, $RFe(CO)_4^-$ or $RCOFe(CO)_4^-$ reacts with a halogen (e.g., I_2) in the presence of an alcohol to give a carboxylic ester,[2236] or in the presence of a secondary amine or water to give, respectively, the corresponding amide or free acid. Carboxylic esters RCO_2R' have also been prepared by treating primary alkyl halides RX with alkoxides $R'O^-$ in the presence of $Fe(CO)_5$.[2237] $RCOFe(CO)_4^-$ is presumably an intermediate.

OS **VI**, 807.

10-78 Carbonylation of Alkyl Halides, Alcohols, Amines, or Alkanes

$$RX + CO + R'OH \xrightarrow[-70\circ C]{SbCl_5-SO_2} RCOOR'$$

A direct method for preparing a carboxylic acid treats an alkyl halide with $NaNO_2$ in acetic acid and DMSO.[2238] Reaction of an alkyl halide with $ClCOCO_2Me$ and $(Bu_3Sn)_2$ under photochemical conditions leads to the corresponding methyl ester.[2239]

Several methods, all based on carbon monoxide or metal carbonyls, have been developed for converting an alkyl halide to a carboxylic acid or an acid derivative with the chain

[2229] des Abbayes, H.; Clément, J.; Laurent, P.; Tanguy, G.; Thilmont, N. *Organometallics* ***1988***, *7*, 2293.
[2230] Garnier, L.; Rollin, Y.; Périchon, J. *J. Organomet. Chem.* ***1989***, *367*, 347.
[2231] Baillargeon, V.P.; Stille, J.K. *J. Am. Chem. Soc.* ***1986***, *108*, 452. See also, Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Chem. Soc., Chem. Commun.* ***1989***, 1816.
[2232] Goure, W.F.; Wright, M.E.; Davis, P.D.; Labadie, S.S.; Stille, J.K. *J. Am. Chem. Soc.* ***1984***, *106*, 6417. See Merrifield, J.H.; Godschalx, J.P.; Stille, J.K. *Organometallics* ***1984***, *3*, 1108.
[2233] Ogawa, A.; Sumino, Y.; Nanke, T.; Ohya, S.; Sonoda, N.; Hirao, T. *J. Am. Chem. Soc.* ***1997***, *119*, 2745.
[2234] Hanzawa, Y.; Narita, K.; Taguchi, T. *Tetrahedron Lett.* ***2000***, *41*, 109.
[2235] Lu, W.; Liang, Z.; Zhang, Y.; Wu, F.; Qian, Q.; Gong, H. *Synthesis* ***2013***, *45*, 2234.
[2236] Collman, J.P.; Winter, S.R.; Komoto, R.G. *J. Am. Chem. Soc.* ***1973***, *95*, 249.
[2237] Yamashita, M.; Mizushima, K.; Watanabe, Y.; Mitsudo, T.; Takegami, Y. *Chem. Lett.* ***1977***, 1355. See also, Tanguy, G.; Weinberger, B.; des Abbayes, H. *Tetrahedron Lett.* ***1983***, *24*, 4005.
[2238] Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* ***1997***, *62*, 234.
[2239] Kim, S.; Jon, S.Y. *Tetrahedron Lett.* ***1998***, *39*, 7317.

extended by one carbon.[2240] When an alkyl halide is treated with $SbCl_5$–SO_2 at – 70 °C, it dissociates into the corresponding carbocation (Sec. 5.A.ii), and if CO and an alcohol are present, a carboxylic ester is formed.[2241] This conversion has also been accomplished with concentrated H_2SO_4 saturated with CO.[2242] Not surprisingly, only tertiary halides perform satisfactorily; secondary halides give mostly rearrangement products. An analogous reaction takes place with alkanes possessing a tertiary hydrogen atom, using HF–SbF_5–CO.[2243]

Carboxylic acids or esters are the products, depending on whether the reaction mixture is solvolyzed with water or an alcohol. Alcohols with more than seven carbons are cleaved into smaller fragments by this procedure.[2244] Similarly, tertiary alcohols[2245] react with H_2SO_4 and CO (which is often generated from HCOOH and the H_2SO_4 in the solution) to give trisubstituted acetic acids in a process called the *Koch-Haaf reaction* (see also **15-31**).[2246] If a primary or secondary alcohol is the substrate, the carbocation initially formed rearranges to a tertiary ion before reacting with the CO. Better results are obtained if trifluoromethanesulfonic acid (F_3CSO_2OH) is used instead of H_2SO_4.[2247] Iodo alcohols were transformed into lactones under radical conditions (AIBN, allyl$SnBu_3$) and 45 atmospheres of CO.[2248]

Another method[2249] for the conversion of alkyl halides to carboxylic esters is treatment of a halide with nickel carbonyl, $Ni(CO)_4$, in the presence of an alcohol and its conjugate base.[2250] When R′ is primary, RX may only be a vinylic or an aryl halide; retention of configuration is observed at a vinylic R. Consequently, a carbocation intermediate is not involved here. When R′ is tertiary, R may be primary alkyl as well as vinylic or aryl. This is thus one of the few methods for preparing esters of tertiary alcohols. Alkyl iodides give the best results, then bromides. In the presence of an amine, an amide can be isolated directly, at least in some instances.

Palladium complexes also catalyze the carbonylation of halides.[2251] Aryl (see **13-15**),[2252] vinylic,[2253] benzylic, and allylic halides (especially iodides) can be converted to carboxylic

[2240] See Colquhoun, H.M.; Holton, J.; Thompson, D.J.; Twigg, M.V. *New Pathways for Organic Synthesis*, Plenum, NY, ***1984***, pp. 199–204, 212–220, 234–235. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1684–1685, 1694–1698, 1702–1704.

[2241] Puzitskii, K.V.; Pirozhkov, S.D.; Ryabova, K.G.; Myshenkova, T.N.; Éidus, Ya.T. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1974***, *23*, 192.

[2242] Takahashi, Y.; Yoneda, N. *Synth. Commun.* ***1989***, *19*, 1945.

[2243] Akhrem, I.; Afanas'eva, L.; Petrovskii, P.; Vitt, S.; Orlinkov, A. *Tetrahedron Lett.* ***2000***, *41*, 9903.

[2244] Yoneda, N.; Takahashi, Y.; Fukuhara, T.; Suzuki, A. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 2819.

[2245] See Bahrmann, H.; Cornils, B. in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, pp. 226–241; Piacenti, F.; Bianchi, M. in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 1–42.

[2246] See Bahrmann, H. in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, pp. 372–413.

[2247] Booth, B.L.; El-Fekky, T.A. *J. Chem. Soc., Perkin Trans. 1* ***1979***, 2441.

[2248] Kreimerman, S.; Ryu, I.; Minakata, S.; Komatsu, M. *Org. Lett.* ***2000***, *2*, 389.

[2249] See Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA, ***1987***, pp. 749–768; Anderson, G.K.; Davies, J.A. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 3, Wiley, NY, pp. 335–359 (pp. 348–356).

[2250] Corey, E.J.; Hegedus, L.S. *J. Am. Chem. Soc.* ***1969***, *91*, 1233. See also, Crandall, J.K.; Michaely, W.J. *J. Organomet. Chem.* ***1973***, *51*, 375.

[2251] See Gulevich, Yu.V.; Bumagin, N.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1988***, *57*, 299 (pp. 303–309); Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 348–356, 366–370. See Kormos, C.M.; Leadbeater, N.E. *Synlett* ***2007***, 2006.

[2252] See Bessard, Y; Crettaz, R. *Heterocycles* ***1999***, *51*, 2589.

[2253] See Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* ***1985***, *26*, 1109.

esters with CO, an alcohol or alkoxide, and a Pd complex.[2254] Vinylic halides were similarly converted with CO and nickel cyanide, under phase-transfer conditions.[2255] Allylic *O*-phosphates were converted to allylic amides with CO and ClTi=NTMS, in the presence of a Pd catalyst.[2256] Terminal alkynes were converted to the alkynyl ester using CO, $PdBr_2$, $CuBr_2$ in methanol, and sodium bicarbonate.[2257] The Pd-catalyzed carbonylation of organoindium compounds in the presence of methanol gives methyl esters.[2258] Similar reactivity was reported with vinyl triflates.[2259] The use of an amine instead of the alcohol or alkoxide leads to an amide.[2260] Reaction with an amine, AIBN, CO, and a tetraalkyltin catalyst also leads to an amide.[2261]

Benzylic halides were converted to carboxylic esters with CO in the presence of a Rh complex.[2262] The reaction of an alkene, a primary alcohol, and CO, in the presence of a Rh catalyst, led to carbonylation of the alkene and formation of the corresponding ester.[2263] Vinyl triflates were converted to the conjugated carboxylic acid with CO_2 and a Ni catalyst.[2264] Reaction with an α,ω-diiodide, Bu_4NF, and $Mo(CO)_6$ gave the corresponding lactone.[2265]

The carbonylation of unactivated aliphatic C—H bonds of amides with CO using a Ru catalyst with 2 equivalents of water gave the imide.[2266] The reaction of alkyl or aryl halides with phenyl formate in the presence of a Pd catalyst gave the corresponding phenyl ester.[2267] Aryl halides reacted with amines and $Mo(CO)_6$, in the presence of DABCO, to give the aryl amide.[2268] Arylboronic acids react with CO in the presence of $AgNO_3$ with a Pd catalyst to give the diaryl ketone.[2269] A dealkylative carbonylation of tertiary amines to give amides has been reported using a Pd catalyst.[2270] Arylzinc compounds react with CO in the presence of a Rh catalyst to give diaryl ketones.[2271]

A number of double carbonylations have been reported. In these reactions, two molecules of CO are incorporated in the product, leading to α-keto acids or their derivatives.[2272] When the catalyst is a Pd complex, best results are obtained in the formation of

[2254] Kiji, J.; Okano, T.; Higashimae, Y.; Kukui, Y. *Bull. Chem. Soc. Jpn.* ***1996***, *69*, 1029.
[2255] Alper, H.; Amer, I.; Vasapollo, G. *Tetrahedron Lett.* ***1989***, *30*, 2615. See also, Amer, I.; Alper, H. *J. Am. Chem. Soc.* ***1989***, *111*, 927.
[2256] Ueda, K.; Mori, M. *Tetrahedron Lett.* ***2004***, *45*, 2907. For an intramolecular carbonylation to generate a cyclic amide, see Trost, B.M.; Ameriks, M.K. *Org. Lett.* ***2004***, *6*, 1745.
[2257] Li, J.; Jiang, H.; Chen, M. *Synth. Commun.* ***2001***, *31*, 199.
[2258] Zhao, Y.; Jin, L.; Li, P.; Lei, A. *J. Am. Chem. Soc.* ***2008***, *130*, 9429.
[2259] Jutand, A.; Négri, S. *Synlett* ***1997***, 719.
[2260] See Satoh, T.; Ikeda, M.; Kushino, Y.; Miura, M.; Nomura, M. *J. Org. Chem.* ***1997***, *62*, 2662.
[2261] Ryu, I.; Nagahara, K.; Kambe, N.; Sonoda, N.; Kreimerman, S.; Komatsu, M. *Chem. Commun.* ***1998***, 1953.
[2262] For an example, see Giroux, A.; Nadeau, C.; Han, Y. *Tetrahedron Lett.* ***2000***, *41*, 7601.
[2263] Yokoa, K.; Tatamidani, H.; Fukumoto, Y.; Chatani, N. *Org. Lett.* ***2003***, *5*, 4329.
[2264] Senboku, H.; Kanaya, H.; Tokuda, M. *Synlett* ***2002***, 140.
[2265] Imbeaux, M.; Mestdagh, H.; Moughamir, K.; Rolando, C. *J. Chem. Soc., Chem. Commun.* ***1992***, 1678.
[2266] Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* ***2011***, *133*, 8070.
[2267] Ueda, T.; Konishi, H.; Manabe, K. *Org. Lett.* ***2012***, *14*, 3100. Also see Ueda, T.; Konishi, H.; Manabe, K. *Tetrahedron Lett.* ***2012***, *53*, 5171.
[2268] Iranpoor, N.; Firouzabadi, H.; Motevalli, S.; Talebi, M. *Tetrahedron* ***2013***, *69*, 418.
[2269] Li, Y.; Lu, W.; Xue, D.; Wang, C.; Liu, Z.-T.; Xiao, J. *Synlett* ***2014***, *25*, 1097.
[2270] Fang, T.; Gao, X.-H.; Tang, R.-Y.; Zhang, X.-G.; Deng, C.-L. *Chem. Commun.* ***2014***, *50*, 14775.
[2271] Kobayashi, K.; Nishimura, Y.; Gao, F.; Gotoh, K.; Nishihara, Y.; Takagi, K. *J. Org. Chem.* ***2011***, *76*, 1949.
[2272] For a review, see Collin, J. *Bull. Soc. Chim. Fr.* ***1988***, 976.

α-keto amides,[2273] and the R is usually aryl or vinylic.[2274] The formation of α-keto acids[2275] or α-keto esters[2276] requires more severe conditions. α-Hydroxy acids were obtained from aryl iodides when the reaction was carried out in the presence of an alcohol, which functioned as a reducing agent.[2277] Cobalt catalysts have also been used and require lower CO pressures.[2272]

OS **V**, 20, 739.

10-79 Carboxylation of Alkyl, Alkenyl, and Alkynyl Substrates with CO_2 or CO

The carboxylation and carbonylation of organic substrates leads to carboxylic acid derivatives or ketone derivatives.[2278] Other C—C bond-forming reactions have been discussed.[2279] The reaction of alkynes with CO_2 and allylic, propargylic, or benzylic chlorides in the presence of Cs_2CO_3 and a AgI catalyst gave functionalized 2-alkynoates.[2280] The reaction of bromostyrenes with CO_2 using electrolysis with a Ag electrode, followed by reaction with iodomethane, gave the corresponding vinyl benzoic acid methyl ester. Aryl terminal alkynes reacted with benzylic halides in the presence of CO_2, Cs_2CO_3, and a AgI catalyst to give the corresponding benzylic ester.[2281]

Allylic tin or allylborates[2282] react with CO_2 in the presence of a Pd catalyst to give the corresponding ester.[2283] α-Substituted propargylic bromides are carboxylated with CO_2 in the presence of zinc to give the corresponding carboxylic acid.[2284] The carboxylation of (hetero)arenes with CO_2 has been reported using Au and Cu complexes of *N*-heterocyclic carbenes.[2285] Propargyl acetates reacted with CO_2 and Mn, with a Co catalyst, to give the corresponding carboxylic acid.[2286] Cycloalkanes were coupled with amides in the presence of CO and a Cu catalyst to give the corresponding imide.[2287]

Allylic alcohols reacted with alcohols in the presence of CO, with a Pd catalyst and 10% of TFA, to give β,γ-unsaturated esters.[2288] Alcohols react with alcohols and CO, with a Pd catalyst and a catalytic amount of sulfuric acid, to give the corresponding ester.[2289] Alcohols reacted with allyl chloride, with CO, triethylamine, and a Pd catalyst, to give the corresponding ester.[2290]

[2273] See Ozawa, F.; Sugimoto, T.; Yuasa, Y.; Santra, M.; Yamamoto, T.; Yamamoto, A. *Organometallics* ***1984***, *3*, 683.
[2274] Son, T.; Yanagihara, H.; Ozawa, F.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 1251.
[2275] Tanaka, M.; Kobayashi, T.; Sakakura, T. *J. Chem. Soc., Chem. Commun.* ***1985***, 837.
[2276] See Ozawa, F.; Kawasaki, N.; Okamoto, H.; Yamamoto, T.; Yamamoto, A. *Organometallics* ***1987***, *6*, 1640.
[2277] Kobayashi, T.; Sakakura, T.; Tanaka, M. *Tetrahedron Lett.* ***1987***, *28*, 2721.
[2278] For a review, see Cai, X.; Xie, B. *Synthesis* ***2013***, *45*, 3305.
[2279] Tsuji, Y.; Fujihara, T. *Chem. Commun.* ***2012***, *48*, 9956.
[2280] Zhang, X.; Zhang, W.-Z.; Shi, L.-L.; Zhu, C.; Jiang, J.-L.; Lu, X.-B. *Tetrahedron* ***2012***, *68*, 9085.
[2281] Guo, F.-J.; Zhang, Z.-Z.; Wang, J.-Y.; Sun, J.; Fang, X.-C.; Zhou, M.D. *Tetrahedron* ***2017***, *73*, 900.
[2282] See Makida, Y.; Marelli, E.; Slawin, A.M.Z.; Nolan, S.P. *Chem. Commun.* ***2014***, *50*, 8010.
[2283] Wu, J.; Hazari, N. *Chem. Commun.* ***2011***, *47*, 1069.
[2284] Miao, B.; Li, G.; Ma, S. *Chem. Eur. J.* ***2015***, *21*, 17224.
[2285] Ackermann, L. *Angew. Chem. Int. Ed.* ***2011***, *50*, 3842.
[2286] Nogi, K.; Fujihara, T.; Terao, J.; Tsuji Y. *Chem. Commun.* ***2014***, *50*, 13052.
[2287] Li, Y.; Dong, K.; Zhu, F.; Wang, Z.; Wu, X.-F. *Angew. Chem. Int. Ed.* ***2016***, *55*, 7227.
[2288] Liu, Q.; Wu, L.; Jiao, H.; Fang, X.; Jackstell, R.; Beller, B. *Angew. Chem. Int. Ed.* ***2013***, *52*, 8064.
[2289] Dong, K.; Sang, R.; Liu, J.; Razzaq, R.; Franke, R.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed.* ***2017***, *56*, 6203.
[2290] Tommasi, S.; Perrone, S.; Rosato, F.; Salomone, A.; Troisi, L. *Synthesis* ***2012***, *44*, 4123.

CHAPTER 11

Aromatic Substitution, Electrophilic

Most substitutions at an aliphatic carbon are by nucleophiles. In aromatic systems the situation is reversed, because the high electron density at the aromatic ring leads to its reactivity as a Lewis base or a Brønsted-Lowry base, depending on the positive species. In electrophilic substitutions, a positive ion or the positive end of a dipole or induced dipole is attacked by the aromatic ring. The leaving group (the electrofuge) must necessarily depart without its electron pair. In nucleophilic substitution reactions, the chief leaving groups are those best able to carry the unshared pair: Br^-, H_2O, OTs^-, and so on, that is, the weakest bases. In electrophilic substitution reactions the most important leaving groups are those that can best exist *without* the pair of electrons necessary to fill the outer shell, that is, the weakest Lewis acids. The influence of solvents will vary with the reaction in many cases, and such details are discussed where appropriate in the reactions section (Sec.11.F).[1]

11.A. MECHANISMS

Electrophilic aromatic substitutions[2] largely proceed by the *arenium ion mechanism*,[3] where the electrophile (which can be viewed as a Lewis acid) is attacked by the π electrons of the aromatic ring (which can be viewed as a Lewis base) in the first step. This reaction leads to formation of a new C—X bond and a new sp^3 carbon in a positively charged intermediate called an arenium ion, where X is the electrophile. The positively charged intermediate (the arenium ion) is resonance stabilized, but not aromatic. The second mechanistic step is the loss of a proton from the sp^3 carbon that is "adjacent" to the positive carbon in the arenium ion, in what is effectively an E1 process (Sec. 17.A.ii), driven by rearomatization of the ring from the arenium ion to give the aromatic substitution product. A proton therefore becomes the leaving group in this overall transformation, where X replaces H. The IUPAC designation for this mechanism is $A_E + D_E$. Hyperaromatic stabilization of arenium

[1] For a review of electrophilic aromatic reactions in ionic liquids, see Borodkin, G.I.; Cubin, V.G. *Russ. J. Org. Chem.* ***2006***, *42*, 1745.

[2] See Galabov, B.; Nalbantova, D.; Schleyer, P.v.R.; Schaefer III, H.F. *Acc. Chem. Res.* ***2016***, *49*, 1191.

[3] See Taylor, R. *Electrophilic Aromatic Substitution*, Wiley, NY, ***1990***; Katritzky, A.R.; Taylor, R. *Electrophilic Substitution of Heterocycles: Quantitative Aspects* (Vol. 47 of *Adv. Heterocycl. Chem.*), Academic Press, NY, ***1990***; Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 1–406.

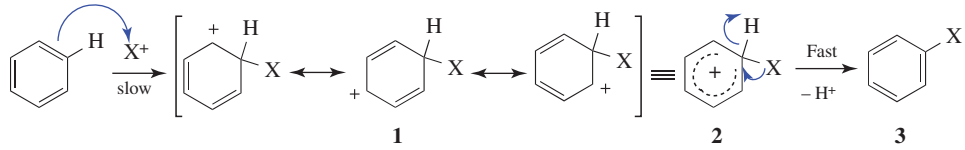
March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

ions has been discussed.[4] Another mechanism, much less common, consists of the opposite behavior: a leaving group departs *before* the electrophile arrives. In this case, a substituent (*not* H) is attached to the aromatic ring, and the substituent is lost prior to incorporation of the electrophile. This mechanism, the S_EAr mechanism, corresponds to the S_NAr mechanism of nucleophilic substitution. Simultaneous attack and departure mechanisms (corresponding to S_N2) are not found at all. An addition–elimination mechanism has been postulated in one case (see **11-4**).

11.A.i. The Arenium Ion Mechanism[5]

In the arenium ion mechanism the electrophilic species may be produced in various ways, but when H is replaced by X, conversion of the aromatic ring to an arenium ion is basically the same in all cases. For this reason most attention in the study of this mechanism centers on the identity of the electrophilic entity and how it is produced. This mechanism is *electrophilic aromatic substitution*, known as the S_EAr mechanism.

The electrophile may be a positive ion (X^+) or a molecule that has a positive dipole. If it is a positive ion, it is attacked by the ring (a pair of electrons from the aromatic sextet is donated to the electrophile) and the product is a resonance-stabilized carbocation, **1**, which is sometimes represented as in **2**. In other words, the electron-rich aromatic ring donates electrons to the electron-deficient carbocation. Ions of this type[6] have been called *Wheland intermediates*[7] and σ *complexes*, but nowadays *arenium ions*[8] is the appropriate designation. The arenium ion is a highly reactive intermediate, although there are cases in which it has been isolated (see below). For this type of ion the most likely pathway[9] is loss of either X^+ or H^+ but this reaction proceeds with loss of the proton and rearomatization of the final product **3**. The second step is nearly always faster than the first, making the first step rate determining, and the reaction is second order. The electrostatic modulation of aromatic rings via the solvation of substituents has been discussed.[10]



If the electrophilic species is not an ion but a molecule with a polarized covalent bond, the product must have a negative charge unless part of the dipole, with its pair of electrons, is broken off somewhere in the process, as in the conversion of **4** to **2**. Note that when the aromatic ring attacks X, Z may be lost directly to give **2**. However, benzene is a rather

[4] Lawlor, D.A.; Kudavalli, J.S.; MacCormac, A.C.; Coyne, D.A.; Boyd, D.R.; More O'Ferrall, R.A. *J. Am. Chem. Soc.* ***2011***, *133*, 19718.

[5] This mechanism is sometimes called the S_E2 mechanism because it is bimolecular, but in this book that name is used for aliphatic substrates (see Chapter 12).

[6] See Olah, G.A. *J. Am. Chem. Soc.* ***1972***, *94*, 808.

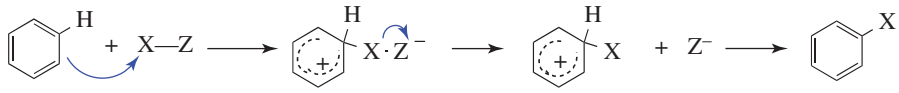
[7] Hadzic, M.; Braïda, B.; Volatron, F. *Org. Lett.* ***2011***, *13*, 1960.

[8] See Brouwer, D.M.; Mackor, E.L.; MacLean, C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 837–897; Perkampus, H. *Adv. Phys. Org. Chem.* ***1966***, *4*, 195.

[9] Also see de la Mare, P.B.D. *Acc. Chem. Res.* ***1974***, *7*, 361.

[10] Muchowska, K.B.; Adam, C.; Matiand, I.K.; Cockroft, S.L. *J. Am. Chem. Soc.* ***2013***, *135*, 9976.

weak electron-donating species unless electron-releasing substituents are attached, and in most cases a cation such as X^+ must be generated in the presence of the benzene ring for a reaction to occur.



4 **2** **3**

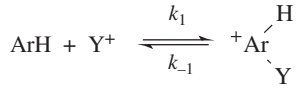
The electrophilic entities, X^+, and how they are formed, are discussed for each reaction in the reactions section of this chapter.

The evidence for the arenium ion mechanism is mainly of two kinds:

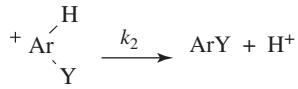
1. *Isotope effects*. If the hydrogen ion departs before the arrival of the electrophile (S_E1 mechanism) or if the arrival and departure are simultaneous, there should be a substantial isotope effect (i.e., deuterated substrates should undergo substitution more slowly than nondeuterated compounds) because, in each case, the C—H bond is broken in the rate-determining step. However, in the arenium ion mechanism, the C—H bond is not broken in the rate-determining step, so no isotope effect should be found. Many such studies have been carried out and, in most cases, especially in the case of nitrations, there is no isotope effect.[11] This result is incompatible with either the S_E1 or the simultaneous mechanism.

   However, in many instances, isotope effects have been found. Since the values are generally much lower than expected for either the S_E1 or the simultaneous mechanisms (e.g., 1–3 for k_H/k_D instead of 6–7), there must be another explanation. For the case where hydrogen is the leaving group, the arenium ion mechanism can be summarized as:

Step 1



Step 2

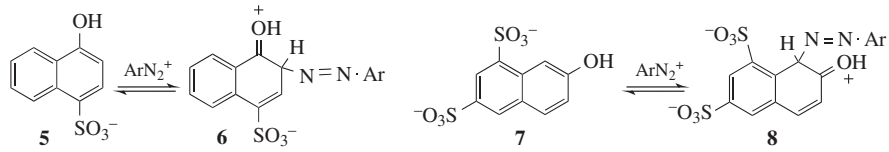


   The small isotope effects found most likely arise from the reversibility of step 1 by a *partitioning effect*.[12] The rate at which $ArHY^+$ reverts to ArH should be essentially the same as that at which $ArDY^+$ (or $ArTY^+$) reverts to ArD (or ArT), since the Ar—H bond is not being cleaved. However, $ArHY^+$ should go to ArY faster than either $ArDY^+$ or $ArTY^+$, since the Ar—H bond is broken in this step. If $k_2 \gg k_{-1}$, this does not matter; since a large majority of the intermediates go to product, the rate is determined only by the slow step ($k_2$1[ArH][Y^+]), and no isotope effect is predicted. However, if $k_2 \leq k_{-1}$, reversion to starting materials is important. If k_2 for $ArDY^+$ (or $ArTY^+$) is $< k_2$ for $ArHY^+$, but k_{-1} is the same, then a larger proportion

[11] Berglund-Larsson, U.; Melander, L. *Ark. Kemi* ***1953***, *6*, 219. See also, Zollinger, H. *Adv. Phys. Org. Chem.* ***1964***, *2*, 163.

[12] See Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, ***1970***, pp. 172–182.

of $ArDY^+$ reverts to starting compounds. That is, k_2/k_{-1} (the *partition factor)* for $ArDY^+$ is less than that for $ArHY^+$. Consequently, the reaction is slower for ArD than for ArH and an isotope effect is observed.



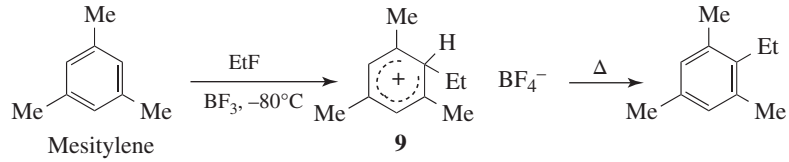
One circumstance that could affect the k_2/k_{-1} ratio is steric hindrance. Thus, diazonium coupling of **5** gave no isotope effect, while coupling of **7** gave a k_H/k_D ratio of 6.55.[13] For steric reasons, it is much more difficult for **8** to lose a proton (it is harder for a base to approach) than it is for **6**, so k_2 is greater for the latter. Since no base is necessary to remove ArN_2^+, k_{-1} does not depend on steric factors[14] and is about the same for each. Thus the partition factor k_2/k_{-1} is sufficiently different for **7** and **8** that **7** exhibits a large isotope effect and **5** exhibits none.[15] Base catalysis can also affect the partition factor, since an increase in base concentration increases the rate at which the intermediate goes to product without affecting the rate at which it reverts to starting materials. In some cases, isotope effects can be diminished or eliminated by a sufficiently high concentration of base.

Evidence for the arenium ion mechanism has also been obtained from other kinds of isotope-effect experiments, involving substitutions of the type

$$ArMR_3 + H_3O^+ \longrightarrow ArH + R_3MOH_2^+$$

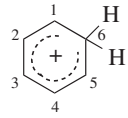
where M is Si, Ge, Sn, or Pb, and R is methyl or ethyl. In these reactions the proton is the electrophile. If the arenium ion mechanism is operating, then the use of D_3O^+ should give rise to an isotope effect, since the D—O bond would be broken in the rate-determining step. Isotope effects of 1.55–3.05 were obtained,[16] in accord with the arenium ion mechanism.

2. *Isolation of arenium ion intermediates*. Very strong evidence for the arenium ion mechanism comes from the isolation of arenium ions in a number of instances.[17] Compound **9** was isolated as a solid with a melting point of −15 °C by treatment of mesitylene with fluooroethane using a BF_3 catalyst at −80 °C.

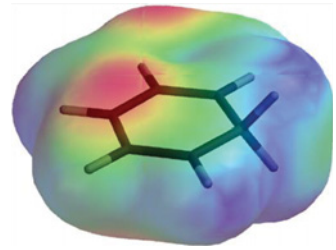


[13] Zollinger, H. *Helv. Chim. Acta* ***1955***, *38*, 1597, 1617, 1623.
[14] Snyckers, F.; Zollinger, H. *Helv. Chim. Acta* ***1970***, *53*, 1294.
[15] See Myhre, P.C.; Beug, M.; James, L.L. *J. Am. Chem. Soc.* ***1968***, *90*, 2105; Márton, J. *Acta Chem. Scand.* ***1969***, *23*, 3321, 3329.
[16] Bott, R.W.; Eaborn, C.; Greasley. P.M. *J. Chem. Soc.* ***1964***, 4803.
[17] See Koptyug, V.A. *Top. Curr. Chem.* ***1984***, *122*, 1; Shteingarts, V.D. *Russ. Chem. Rev.* ***1981***, *50*, 735; Farcasiu, D. *Acc. Chem. Res.* ***1982***, *15*, 46.

When **9** was heated, the normal substitution product, 2-ethyl-1,3,5-trimethylbenzene, was obtained.[18] Even the simplest such ion, the benzenonium ion (**10**) has been prepared in HF-SbF_5-SO_2ClF-SO_2F_2 at −134 °C, where it could be studied spectrally.[19] The ^{13}C NMR spectra of the benzenonium ion[20] and the pentamethylbenzenonium ion[21] give graphic evidence for the charge distribution shown in **1** (as represented in the electron-density map for the arenium ion, **11**). According to this, the 1, 3, and 5 carbons, each of which bears a positive charge of ∼+1/3 [note that C-1, C-3, and C-5 (numbering from **10**) are lighter, indicating less electron density in **11** whereas C-2 and C-4 are darker for higher electron density], should have a greater chemical shift in the NMR than the 2 and 4 carbons, which are uncharged. Support for this electron distribution is seen in the ^{13}C NMR chemical shifts for **10** are C-3: 178.1; C-1 and C-5: 186.6; C-2 and C-4: 136.9, and C-6: 52.2.[20]

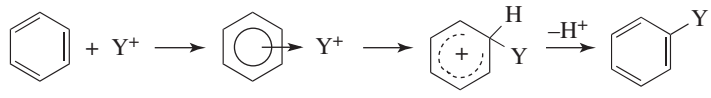


10



11

In Chapter 3, it was mentioned that positive ions can form addition complexes with π systems. Since the initial step of electrophilic substitution involves attack of a positive ion by an aromatic ring, it has been suggested[22] that such a complex, called a π *complex* (represented as **12**), is formed first, and then is converted to the arenium ion **13**.[23]



12 **13**

Stable solutions of arenium ions or π complexes (e.g., with Br_2, I_2, picric acid, Ag^+, or HCl) can be formed.[24] For example, π complexes are formed when aromatic hydrocarbons are treated with HCl alone, but the use of HCl plus a Lewis acid (e.g., $AlCl_3$) gives arenium ions. The two types of solution have very different properties. For example, a solution of an arenium ion is colored and conducts electricity, which shows that positive and negative

[18] Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* ***1958***, *80*, 6541. See Effenberger, F. *Acc. Chem. Res.* ***1989***, *22*, 27.
[19] Olah, G.A.; Schlosberg, R.H.; Porter, R.D.; Mo, Y.K.; Kelly, D.P.; Mateescu, G.D. *J. Am. Chem. Soc.* ***1972***, *94*, 2034.
[20] Olah, G.A.; Staral, J.S.; Asencio, G.; Liang, G.; Forsyth, D.A.; Mateescu, G.D. *J. Am. Chem. Soc.* ***1978***, *100*, 6299.
[21] Lyerla, J.R.; Yannoni, C.S.; Bruck, D.; Fyfe, C.A. *J. Am. Chem. Soc.* ***1979***, *101*, 4770.
[22] Dewar, M.J.S. *Electronic Theory of Organic Chemistry*, Clarendon Press, Oxford, ***1949***.
[23] See Hubig, S.M.; Kochi, J.K. *J. Org. Chem.* ***2000***, *65*, 6807.
[24] See Rosokha, S.V.; Kochi, J.K. *J. Org. Chem.* ***2002***, *67*, 1727.

TABLE 11.1 Relative stabilities of arenium ions and π complexes and relative rates of chlorination and nitration.[25,26,31] In each case, *p*-xylene = 1.00

Substituents	Relative arenium ion stability[25]	Relative π complex stability[25]	Rate of chlorination[26]	Rate of nitration[31]
None (benzene)	0.09	0.61	0.0005	0.51
Me	0.63	0.92	0.157	0.85
p-di-Me_3	1.00	1.00	1.00	1.00
o-di-Me_3	1.1	1.13	2.1	0.89
m-di-Me_3	26	1.26	200	0.84
1,2,4-tri-Me_3	63	1.36	340	
1,2,3-tri-Me_3	69	1.46	400	
1,2,3,4-tetra-Me_3	400	1.63	2 000	
1,2,3,5-tetra-Me_3	16,000	1.67	240 000	
penta-Me_3	29,900		360 000	

ions are present, while a π complex formed from HCl and benzene is colorless and does not conduct a current. Furthermore, when DCl is used to form a π complex, no deuterium exchange takes place (because there is no covalent bond between the electrophile and the ring), while formation of an arenium ion with DCl and $AlCl_3$ gives deuterium exchange.

The relative stabilities of some methylated arenium ions and π complexes are shown in Table 11.1. The arenium ion stabilities listed were determined by the relative basicity of the substrate toward HF.[25] The π-complex stabilities are relative equilibrium constants for the reaction[26] between the aromatic hydrocarbon and HCl. As shown in Table 11.1, the relative stabilities of the two types of species are very different: the π complex stability changes very little with methyl substitution, but the arenium ion stability changes a great deal. It is noted that stable arenium ions have been obtained from large methylene-bridged polycyclic aromatic hydrocarbons.[27]

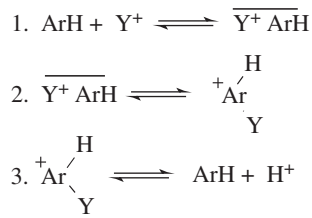
How can we tell if **12** is present on the reaction path? If it is present, there are two possibilities: (i) the formation of **12** is rate determining (the conversion of **12** to **13** is much faster), or (ii) the formation of **12** is rapid, and the conversion **12** to **13** is rate determining. One way to ascertain which species is formed in the rate-determining step in a given reaction is to use the stability information given in Table 11.1. The relative rates of reaction of a given electrophile are measured with the series of compounds listed in Table 11.1. If the relative rates resemble the arenium ion stabilities, we conclude that the arenium ion is formed in the slow step; but if they resemble the stabilities of the π complexes, the latter are formed in the slow step.[28] When such experiments are carried out, it is found in most cases that the relative rates are similar to the arenium ion and not similar to the π complex stabilities.

[25] Kilpatrick, M.; Luborsky, F.E. *J. Am. Chem. Soc.* ***1953***, *75*, 577.
[26] Brown, H.C.; Brady, J.D. *J. Am. Chem. Soc.* ***1952***, *74*, 3570.
[27] Laali, K.K.; Okazaki, T.; Harvey, R.G. *J. Org. Chem.* ***2001***, *66*, 3977.
[28] Condon, F.E. *J. Am. Chem. Soc.* ***1952***, *74*, 2528.

For example, Table 11.1 lists chlorination rates.[26] Similar results were obtained in room-temperature bromination with Br_2 in acetic acid[29] and in acetylation with CH_3CO^+ SbF_6^-.[30] It is clear that in these cases the π complex either does not form at all, or, if it does, its formation is not rate determining (unfortunately, it is very difficult to distinguish between these two possibilities).

On the other hand, in nitration with the powerful electrophile NO_2^+ (in the form of NO_2^+ BF_4^-), the relative rates resembled π complex stabilities much more than arenium ion stabilities.[31] Similar results were obtained for bromination with Br_2 and $FeCl_3$ in nitromethane.

These results were taken to mean[32] that in these cases π-complex formation is rate determining. However, graphical analysis of the NO_2^+ data showed that a straight line could not be drawn when the nitration rate was plotted against π-complex stability,[33] which casts doubt on the rate-determining formation of a π complex in this case.[34] There is other evidence, from positional selectivities (discussed in Sec. 11.D), that *some* intermediate is present before the arenium ion is formed, whose formation can be rate determining with powerful electrophiles. Not much is known about this intermediate, which is given the non-descriptive name *encounter complex* and generally depicted as Y^+ArH. The arenium complex mechanism is therefore written as[35]



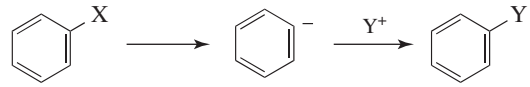
For the reason given above and for other reasons, it is unlikely that the encounter complex is a π complex, but just what kind of attraction exists between Y^+ and ArH is not known, other than the presumption that they are together within a solvent cage (see also, Sec. 11.D). There is evidence (from isomerizations occurring in the alkyl group, as well as other observations) that π complexes are present on the pathway from substrate to arenium ion in the gas phase protonation of alkylbenzenes.[36]

11.A.ii. The S_E1 Mechanism

The S_E1 mechanism (*substitution electrophilic unimolecular*) is rare, being found only in certain cases in which carbon is the leaving atom (see **11-33**, **11-35**) or when a very strong

[29] Brown, H.C.; Stock, L.M. *J. Am. Chem. Soc.* ***1957***, *79*, 1421.
[30] Olah, G.A.; Kuhn, S.J.; Flood, S.H.; Hardie, B.A. *J. Am. Chem. Soc.* ***1964***, *86*, 2203.
[31] Olah, G.A.; Kuhn, S.J.; Flood, S.H. *J. Am. Chem. Soc.* ***1961***, *83*, 4571, 4581.
[32] Olah, G.A.; Kuhn, S.J.; Flood, S.H.; Hardie, B.A. *J. Am. Chem. Soc.* ***1964***, *86*, 1039, 1044.
[33] DeHaan, F.P.; Covey, W.D.; Delker, G.L.; Baker, N.J.; Feigon, J.F.; Miller, K.D.; Stelter, E.D. *J. Am. Chem. Soc.* ***1979***, *101*, 1336; Santiago, C.; Houk, K.N.; Perrin, C.L. *J. Am. Chem. Soc.* ***1979***, *101*, 1337.
[34] See Ridd, J.H. *Acc. Chem. Res.* ***1971***, *4*, 248; also see Olah, G.A. *Acc. Chem. Res.* ***1971***, *4*, 240; Sedaghat-Herati, M.R.; Sharifi, T. *J. Organomet. Chem.* ***1989***, *363*, 39; Banthorpe, D.V. *Chem. Rev.* ***1970***, *70*, 295, especially sections VI and IX.
[35] See Ridd, J.H. *Adv. Phys. Org. Chem.* ***1978***, *16*, 1.
[36] Holman, R.W.; Gross, M.L. *J. Am. Chem. Soc.* ***1989***, *111*, 3560.

base is present (see **11-1**, **11-10**, and **19-58**).[37] It consists of two steps with an intermediate carbanion. The IUPAC designation is $D_E + A_E$.



Reactions **12-40**, **12-44**, and **12-45** also take place by this mechanism when applied to aryl substrates.

11.B. ORIENTATION AND REACTIVITY

11.B.i. Orientation and Reactivity in Monosubstituted Benzene Rings[38]

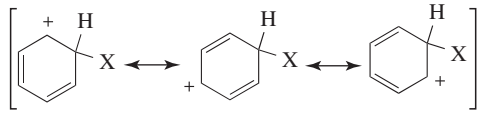
When an electrophilic substitution reaction is performed on a monosubstituted benzene, the new group may be directed primarily to the *ortho*, *meta*, or *para* position and the substitution may be slower or faster than with benzene itself.[39] The group already on the ring determines which position the new group will take and whether the reaction will be slower or faster than with benzene. Groups that are electron donating increase the reaction rate and are called *activating*; groups that are electron withdrawing slow the reaction rate and are called *deactivating*. Electron-withdrawing groups are predominantly *meta* directing whereas electron-donating groups are *ortho*/*para* directing. Halogen substituents are weakly deactivating but are *ortho*/*para* directing. Groups direct *predominantly*, but usually not *exclusively*, so the electrophilic substitution reaction is regioselective and not regiospecific. For example, nitration of nitrobenzene gave 93% *m*-dinitrobenzene, 6% of the *ortho* isomer, and 1% of the *para* isomer.

The orientation and reactivity effects are explained on the basis of resonance and field effects of each group on the stability of the intermediate arenium ion formed from each compound. To understand why this approach can be used, it is necessary to know that in these reactions the product is usually kinetically controlled and not thermodynamically controlled (Sec. 6.F). There are three possible intermediates, resulting from reaction of the aromatic ring with the "X" group at C2, C3, or C4 relative to the carbon bearing the "X" group, the so-called *ipso* carbon[40]. Which of the three possible intermediates is formed is dependent not on the thermodynamic stability of the products, but on the activation energy necessary to form each of the three intermediates. It is necessary to make the assumption that the free-energy profile resembles either Figure 6.2(a) or (b). In either case, the transition state is closer in energy to the arenium ion intermediate than to the starting compounds. Invoking the *Hammond postulate* (Sec. 6.G), assume that the geometry of the transition state also resembles that of the intermediate and that anything that increases the stability of the intermediate will also lower the activation energy necessary to attain it. Formation of the

[37] Also see Eaborn, C.; Hornfeld, H.L.; Walton, D.R.M. *J. Chem. Soc. B* ***1967***, 1036.
[38] See Hoggett, J.G.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, ***1971***, pp. 122–145, 163–220.
[39] For a computational approach to evaluate substituent constants, see Galabov, B.; Ilieva, S.; Schaefer III, H.F. *J. Org. Chem.* ***2006***, *71*, 6382.
[40] Perrin, C.L.; Skinner, G.A. *J. Am. Chem. Soc.* ***1971***, *93*, 3389; Traynham, J.G. *J. Chem. Educ.* ***1983***, *60*, 937.

intermediate is the slow step (the rate-determining step) and, once formed, the intermediate is rapidly converted to products. The relative stabilities of the three intermediates can be used as guides to predict which products will predominantly form. Of course, if reversible reactions are allowed to proceed to equilibrium, product ratios that are quite different may be obtained. For example, the sulfonation of naphthalene at 80 °C, where the reaction does not reach equilibrium, gives mostly α-naphthalenesulfonic acid,[41] while at 160 °C, where equilibrium is attained, the β isomer predominates[42] (the α isomer is thermodynamically less stable because of steric interaction between the SO_3H group and the hydrogen at the 8 position).

The nine possible ions from incorporation of Y at each of the *ortho*, *meta*, and *para* positions are shown below, and each arenium ion obviously has a positive charge in the ring. Any group, Z, that has an electron-donating field effect (+*I*, Z will have a − charge or a δ− dipole in most cases) should stabilize all ions (relative to **1**), since electron donation to a positive center is stabilizing.

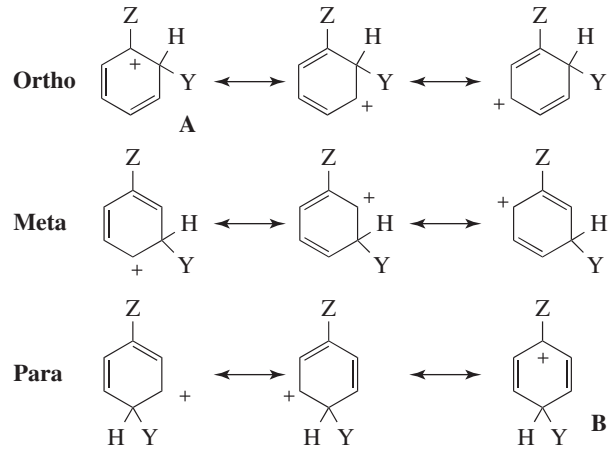


1

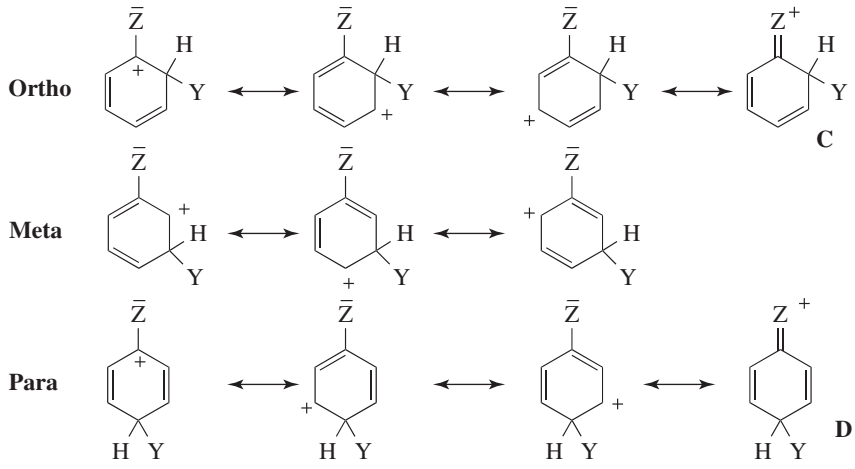
However, examination of the three resonance contributors show that the (+) charge is adjacent to the electron-donating (δ−) X group only with the intermediate arising from *ortho* or *para* attack, but not *meta* attack, so the *ortho* and *para* intermediates are particularly stabilized (opposite charges attract). On the other hand, electron-withdrawing groups (−*I*, Z will have a+ charge or a δ+ dipole in most cases) will increase the positive charge on the ring (like charges repel), and destabilize the arenium ion. Examination of the three resonance contributors show that the (+) charge is adjacent to the electron-withdrawing (δ+) X group only with the intermediate arising from *ortho* or *para* attack, but not *meta* attack and so those two intermediates are particularly destabilized (like charges repel).

Formation of a stabilized ion should be faster than benzene (which generates **1**), or activating, but formation of a destabilized ion should be slower, or deactivating. Such field effects should taper off with distance and are thus strongest at the carbon connected to the group Z (known as the ipso carbon). Since none of the canonical forms of the *meta* ion has a positive charge at the ipso carbon, +*I* groups should stabilize all three ions but mostly the *ortho* and *para*, so they should be not only activating but *ortho*/*para* directing as well. On the other hand, −*I* groups, by removing electron density, should destabilize all three ions but mostly the *ortho* and *para*, and should be not only deactivating but also *meta* directing. In many cases, there is *resonance interaction* between Z and the ring; this also affects the relative stability, in some cases in the same direction as the field effect, in others differently.

[41] Fierz, H.E.; Weissenbach, P. *Helv. Chim. Acta* ***1920***, *3*, 312.
[42] Witt, O.N. *Ber.* ***1915***, *48*, 743.



Some substituents have a pair of electrons (usually unshared) that may be contributed *toward* the ring. The *ortho* and *para* arenium ions would then have a fourth resonance contributor. The same three canonical forms can be drawn for each ion as before, but now an extra form for the *ortho* and *para* ions can be drawn. The stability of these two intermediate ions is increased by the extra form not only because it is another canonical form, but also because it is more stable than the others and makes a greater contribution to the hybrid. Every atom (except of course hydrogen) in these forms (**C** and **D**) has a complete octet, while all the other forms have one carbon atom with a sextet. No corresponding form can be drawn for the *meta* isomer. The inclusion of this form in the hybrid lowers the energy not only because of rule 6 (see Sec. 2.E), but also because it spreads the positive charge over a larger area, out onto the group Z. Groups with a pair of electrons to contribute (e.g., the halogens) would be expected, then, in the absence of field effects, not only to direct *ortho* and *para*, but also to activate these positions for electrophilic attack.



On the basis of these discussions, we can distinguish three types of groups.

1. *Groups that contain an unshared pair of electrons on the atom connected to the ring are electron donating with a (−) charge or (δ−) dipole.* In this category are O^-, NR_2, NHR, NH_2,[43] OH, OR, NHCOR, OCOR, SR, and the four halogens.[44] The halogens deactivate the aromatic ring to substitution (the rate of reaction is slower than that of benzene), and this effect may arise from the unique energy level of the halogen lone pair orbital, which is higher than the adjacent π-molecular orbital of benzene (π_1).[45] The resonance explanation predicts that all these groups should be *ortho/para* directing, and they are, though all except O^- are electron withdrawing by the field effect (Sec. 1.I). Therefore, for these groups, resonance is more important than the field effect. This is especially true for NR_2, NHR, NH_2, and OH, which are *strongly* activating, as is O^-.

   Halogen substituents are deactivating since they are polarized δ+ relative to the electron rich aromatic ring. However, the halogens are polarizable and this property allows the halogens to have a $-I$ effect because once the arenium ion is form and the ring has a formal (+) charge the halogen takes a δ− dipole and thus the *ortho* arenium ions are more stabilized than the *meta* arenium ions. Thus, the halogens are *ortho/para* directing. The SH group would probably belong here too, except that in the case of thiophenols electrophiles usually attack the sulfur rather than the ring, and ring substitution is not feasible with these substrates.[46] Fluorine[47] is the least deactivating, and fluorobenzenes usually show a reactivity approximating that of benzene itself. The other three halogens deactivate about equally.
2. *Groups that lack an unshared pair on the atom connected to the ring are electron withdrawing with a (+) charge or (δ+) dipole*. In this category are, in approximate order of decreasing deactivating ability, NR_3^+, NO_2, CF_3,[48] CN, SO_3H, CHO, COR, CO_2H, CO_2R, $CONH_2$, CCl_3, and NH_3^+. Also in this category are all other groups with a positive charge on the atom directly connected to the ring[49] (SR_2^+, PR_3^+, etc.) and many groups with positive charges on atoms farther away, since these are often still powerful $-I$ groups. The field-effect explanation predicts that these should all be *meta* directing and deactivating, and (except for NH_3^+) this is the case. The NH_3^+ group is an anomaly, since this group directs *para* about as much as or a

[43] It must be remembered that in acidic solutions amines are converted to their conjugate acids, which for the most part are *meta* directing (type 2). However, unless the solution is highly acidic, there will be a small amount of free amine present, and since amino groups are activating and the conjugate acids deactivating, *ortho/para* direction is often found even under acidic conditions.

[44] See Chuchani, G. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 250–265; for ether groups see Kohnstam, G.; Williams, D.L.H. in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 132–150.

[45] Tomoda, S.; Takamatsu, K.; Iwaoka, M. *Chem. Lett.* ***1998***, 581.

[46] Tarbell, D.S.; Herz, A.H. *J. Am. Chem. Soc.* ***1953***, *75*, 4657. Ring substitution *is* possible if the SH group is protected. See Walker, D. *J. Org. Chem.* ***1966***, *31*, 835.

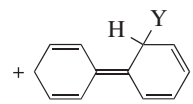
[47] Carroll, T.X.; Thomas, T.D.; Bergersen, H.; Børve, K.J.; Sæthre, L.J. *J. Org. Chem.* ***2006***, *71*, 1961.

[48] See Castagnetti, E.; Schlosser, M. *Chem. Eur. J.* ***2002***, *8*, 799.

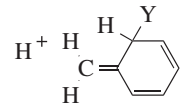
[49] See Gilow, H.M.; De Shazo, M.; Van Cleave, W.C. *J. Org. Chem.* ***1971***, *36*, 1745; Hoggett, J.G.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, ***1971***, pp. 167–176.

little more than it directs *meta*,[50] often because the ammonium ion is in equilibrium with the amine. The NH_2Me^+, $NHMe_2^+$, and NMe_3^+ groups all give more *meta* than *para* substitution, with the percentage of *para* product decreasing with the increasing number of methyl groups.[51]

3. *Groups that lack an unshared pair on the atom connected to the ring and that are ortho/para directing*. In this category are alkyl groups,[52] aryl groups, and the COO^- group,[53] all of which activate the ring. Since aryl groups are $-I$ groups, they might seem to belong to category 2. They are nevertheless *ortho*/*para* directing and activating. This can be explained in a similar manner as in category 1, with a pair of electrons from the aromatic sextet playing the part played by the unshared pair, so that forms like **E** are generated The effect of negatively charged groups like CO_2^- is easily explained by the field effect (negatively charged groups are of course electron donating), since there is no resonance interaction between the group and the ring. The effect of alkyl groups can be explained in the same way, but, in addition, canonical forms can be drawn, even though there is no unshared pair. These of course are hyperconjugation forms like **F**. This effect, like the field effect, predicts activation and *ortho*/*para* direction, so that it is not possible to say how much each effect contributes to the result. Another way of looking at the effect of alkyl groups (which sums up both field and hyperconjugation effects) is that (for Z = R) the *ortho* and *para* arenium ions are more stable because each contains a form (**A** and **B**) that is a tertiary carbocation, while all the canonical forms for the *meta* ion and for **1** are secondary carbocations. In activating ability, alkyl groups usually follow the *Baker-Nathan order* (Sec. 2.M), but not always.[54]



E



F

11.B.ii. The *Ortho*/*Para* Ratio[55]

When an *ortho*/*para*-directing group is on a ring, it is usually difficult to predict how much of the product will be the *ortho* isomer and how much the *para* isomer. Indeed, these proportions can depend greatly on the reaction conditions. For example, chlorination of toluene gives an *ortho*/*para* ratio anywhere from 62:38 to 34:66.[56] Nevertheless, certain points can be made. On a purely statistical basis there would be 67% *ortho* and 33%

[50] Hartshorn, S.R.; Ridd, J.H. *J. Chem. Soc. B* ***1968***, 1063. Also see Ridd, J.H. in *Aromaticity, Chem. Soc. Spec. Publ., no. 21*, ***1967***, pp. 149–162.

[51] Brickman, M.; Utley, J.H.P.; Ridd, J.H. *J. Chem. Soc.* ***1965***, 6851.

[52] For a discussion of the substituent effect of the methyl group, see Myrseth, V.; Sæthre, L.J.; Børve, K.J.; Thomas, T.D. *J. Org. Chem.* ***2007***, *72*, 5715.

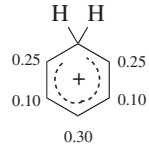
[53] Spryskov, A.A.; Golubkin, L.N. *J. Gen. Chem. USSR* ***1961***, *31*, 833. Since the CO_2^- group is present only in alkaline solution, and electrophilic substitution is not often done in alkaline solution, the group is seldom encountered.

[54] See, however, Schubert, W.M.; Gurka, D.F. *J. Am. Chem. Soc.* ***1969***, *91*, 1443; Himoe, A.; Stock, L.M. *J. Am. Chem. Soc.* ***1969***, *91*, 1452.

[55] See Effenberger, F.; Maier, A.J. *J. Am. Chem. Soc.* ***2001***, *123*, 3429.

[56] Stock, L.M.; Himoe, A. *J. Am. Chem. Soc.* ***1961***, *83*, 4605.

para, since there are two *ortho* positions and only one *para*. However, the phenonium ion **10**, which arises from protonation of benzene, has the approximate charge distribution shown[57] (see **11** as well).



10

If this model were accepted for the arenium ion in aromatic substitution, a *para* substituent would have a greater stabilizing effect on the adjacent carbon than an *ortho* substituent. If other effects are absent, this would mean that >33% *para* and <67% *ortho* substitution would be found. In hydrogen exchange (reaction **11-1**), where other effects are absent, it has been found for a number of substituents that the average ratio of the logarithms of the partial rate factors for these positions (Sec. 11.C for a definition of partial rate factor) was close to 0.865,[58] which is close to the value predicted from the ratio of charge densities in **10**. This picture is further supported by the fact that *meta*-directing groups, which destabilize a positive charge, give *ortho*/*para* ratios >67:33[59] (of course the total amount of *ortho* and *para* substitution with these groups is small, but the *ratios* are generally >67:33). Another important factor is the steric effect. If either the group on the attacking ring or the group on the electrophile is large, steric hindrance inhibits formation of the *ortho* product and increases the amount of the *para* isomer. An example may be seen in the nitration, under the same conditions, of toluene and *tert*-butylbenzene. The former gave 58% of the *ortho* compound and 37% of the *para*, while the more bulky *tert*-butyl group gave 16% of the *ortho* product and 73% of the *para*.[60] Some groups are so large that they direct almost entirely *para*.

When the *ortho*/*para*-directing group is one with an unshared pair (this of course applies to most of them), there is another effect that increases the amount of *para* product at the expense of the *ortho*. A comparison of the intermediates involved (Sec. 11.B.i) shows that **C** is a canonical form with an *ortho* quinoid structure, while **D** has a *para* quinoid structure. *para*-Quinones are more stable than the *ortho* isomers, so it seems reasonable to assume that **D** is more stable than **C**, and therefore contributes more to the hybrid and increases its stability compared to the *ortho* intermediate.

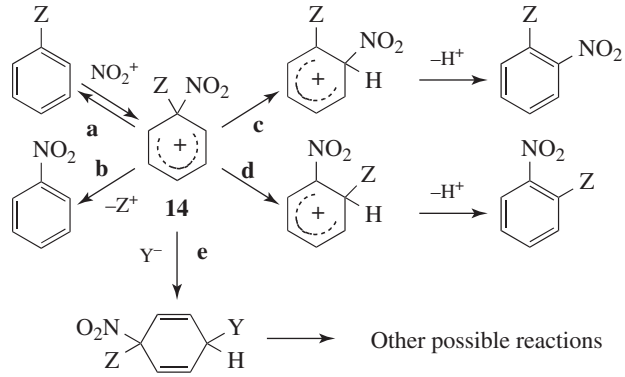
It has been shown that it is possible to compel regiospecific *para* substitution by enclosing the substrate molecules in a cavity from which only the *para* position projects. Anisole was chlorinated in solutions containing a cyclodextrin, a molecule in which the anisole is almost entirely enclosed (see Figure 3.4). With a high-enough concentration of

[57] Olah, G.A. *Acc. Chem. Res.* ***1970***, *4*, 240 (p. 248).
[58] Ansell, H.V.; Le Guen, J.; Taylor, R. *Tetrahedron Lett.* ***1973***, 13.
[59] Hoggett, J.G.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, ***1971***, pp. 176–180.
[60] Nelson, K.L.; Brown, H.C. *J. Am. Chem. Soc.* ***1951***, *73*, 5605. See Baas, J.M.A.; Wepster, B.M. *Recl. Trav. Chim. Pays-Bas* ***1972***, *91*, 285, 517, 831.

cyclodextrin, it was possible to achieve a *para*/*ortho* ratio of 21.6[61] (in the absence of the cyclodextrin the ratio was only 1.48). This behavior is a model for the regioselectivity found in the action of enzymes. The *Bell-Evans-Polanyi principle* states that the difference in activation energy between two reactions of the same family is proportional to the difference of their enthalpy.[62] This principle has been linked to the regioselectivity of electrophilic aromatic substitution.[63]

11.B.iii. Ipso Attack

Orientation has been discussed previously in the case of monosubstituted benzenes entirely in terms of attachment at the *ortho*, *meta*, and *para* positions, but attachment at the position bearing the substituent (called the *ipso position*) can also be important. Ipso attack has mostly been studied for nitration.[64] When attack of NO_2^+ leads to incorporation at the ipso position there are at least five possible fates for the resulting arenium ion (**14**).



- Path **a**. The arenium ion can lose NO_2^+ and revert to the starting compounds, resulting in no net reaction and is often undetectable.
- Path **b**. The arenium ion can lose Z^+, in which case this is simply aromatic substitution with a leaving group other than H (see **11-33** to **11-38**).
- Path **c**. The electrophilic group (in this case NO_2^+) can undergo a 1,2-migration, followed by loss of the proton. The product in this case is the same as that obtained by direct attachment of NO_2^+ at the *ortho* position of PhZ. It is not always easy to tell how much of the *ortho* product in any individual case arises from this pathway,[65] though there is evidence that it can be a considerable proportion. Because of this possibility, many of the reported conclusions about the relative reactivity of the *ortho*, *meta*, and *para* positions are cast into doubt, since some of the product may have arisen not from

[61] Breslow, R.; Campbell, P. *Bioorg. Chem.* ***1971***, *1*, 140. See also, Chênevert, R.; Ampleman, G. *Can. J. Chem.* ***1987***, *65*, 307; Komiyama, M. *Polym. J. (Tokyo)* ***1988***, *20*, 439.

[62] Bell, R.P. *Proc.R. Soc. London, Ser. A* ***1936***, *154*, 414; Evans, M.G.; Polanyi, M. *J. Chem. Soc., Faraday Trans.* ***1936***, *32*, 1340.

[63] Wubbels, G.G. *Tetrahedron Lett.* ***2015***, *56*, 1716.

[64] See Moodie, R.B.; Schofield, K. *Acc. Chem. Res.* ***1976***, *9*, 287. See also, Fischer, A.; Henderson, G.N.; RayMahasay, S. *Can. J. Chem.* ***1987***, *65*, 1233, and other papers in this series.

[65] See Gibbs, H.W.; Moodie, R.B.; Schofield, K. *J. Chem. Soc., Perkin Trans. 2* ***1978***, 1145.

direct attachment at the *ortho* position, but from attachment at the ipso position followed by rearrangement.[66]

- Path **d**. The ipso substituent (Z) can undergo 1,2-migration, which also produces the *ortho* product (although the rearrangement would become apparent if there were other substituents present). The evidence is that this pathway is very minor, at least when the electrophile is NO_2^+.[67]
- Path **e**. Attack of a nucleophile on **14**. In some cases, the products of such an attack (cyclohexadienes) have been isolated[68] (this is 1,4-addition to the aromatic ring), but further reactions are also possible.

11.B.iv. Orientation in Benzene Rings With More Than One Substituent[69]

When two or more substituents are attached to the benzene ring, it is often possible to predict the correct isomer resulting from electrophilic substitution. Activating substituents lead to faster reactions at the *ortho*/*para* position relative to the activating group, and the more powerful activating group controls the substitution compared to a group with a lesser electron-withdrawing effect. In many cases, the groups already on the ring reinforce each other. Thus, 1,3-dimethylbenzene is substituted at the 4 position (*ortho* to one group and *para* to the other), but not at the 5 position (*meta* to both). Likewise, the incoming group in *p*-chlorobenzoic acid goes to the position *ortho* to the chloro and *meta* to the carboxyl group. 1,3,5-Trifluorobenzene was used as a starting material for a regioselective approach to multisubstituted benzene derivatives.[70]

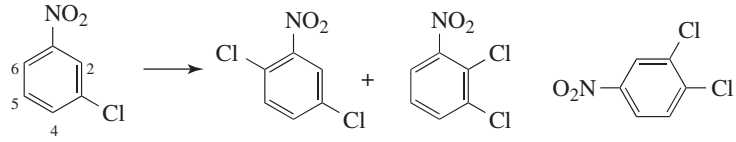
When the groups oppose each other with respect to electron donating vs. electron donating, the activating group dominates the regioselectivity when compared to an electron-withdrawing group. However, when both groups are relatively weak or have about the same directing strength, predictions may be more difficult. Consider *N*-acetyl-2-methoxyaniline. Here, the two groups of about equal directing ability are in competing positions, so all four products can be expected, and it is not easy to predict the proportions, except that steric hindrance should probably reduce the yield of substitution *ortho* to the acetamido group, especially for large electrophiles. Mixtures of about equal proportions are frequent in such cases. Nevertheless, even when groups on a ring oppose each other, there are some regularities.

1. If a strong activating group competes with a weaker one or with a deactivating group, the former controls. Thus *o*-cresol gives substitution mainly *ortho* and *para* to the *hydroxyl* group and not to the methyl. For this purpose we can arrange the groups in the following order: NH_2, OH, NR_2, $O^- >$ OR, OCOR, NHCOR > R, Ar > halogen > *meta*-directing groups.
2. All other things being equal, a third group is least likely to enter between two groups in the *meta* relationship. This is the result of steric hindrance and increases in

[66] This was first pointed out by Myhre, P.C. *J. Am. Chem. Soc.* ***1972***, *94*, 7921.
[67] See Hartshorn, M.P.; Readman, J.M.; Robinson, W.T.; Sies, C.W.; Wright, G.J. *Aust. J. Chem.* ***1988***, *41*, 373.
[68] See Banwell, T.; Morse, C.S.; Myhre, P.C.; Vollmar, A. *J. Am. Chem. Soc.* ***1977***, *99*, 3042; Fischer, A.; Greig, C.C. *Can. J. Chem.* ***1978***, *56*, 1063.
[69] For a quantitative discussion, see Sec. 11.C.
[70] Seo, H.; Ohmori, K.; Suzuki, K. *Chem. Lett.* ***2011***, *40*, 744.

importance with the size of the groups on the ring and with the size of the attacking species.[71]

3. When a *meta*-directing group is *meta* to an *ortho*/*para*-directing group, the incoming group primarily goes *ortho* to the *meta*-directing group rather than *para*. For example, chlorination of **15** gives mostly **16**. The importance of this effect is underscored by the fact that **17**, which is in violation of the preceding rule, is formed in smaller amounts, but **18** is not formed at all. This is called the *ortho effect*,[72] and many such examples are known.[73]



15 **16** **17** **18**

Another is the nitration of *p*-bromotoluene, which gives 2,3-dinitro-4-bromotoluene. In this case, once the first nitro group came in, the second was directed *ortho* to it rather than *para*, even though this means that the group has to come in between two groups in the *meta* position. There is no good explanation yet for the *ortho* effect, though possibly there is intramolecular assistance from the *meta*-directing group.

It is interesting that chlorination of **15** illustrates all three rules. Of the four positions open to the electrophile, the 5 position violates rule 1, the 2 position violates rule 2, and the 4 position violates rule 3. The principal attachment is therefore at position 6.

11.B.v. Orientation in Other Ring Systems[74]

In fused ring systems, the positions are not equivalent and there is usually a preferred orientation, even in the unsubstituted hydrocarbon. The preferred positions may often be predicted as for benzene rings. Thus it is possible to draw more canonical forms for the arenium ion when attack by naphthalene leads to attachment of the electrophile at the α position than when attack by naphthalene leads to attachment of the electrophile at the β position. Therefore, the α position is the preferred site of attachment,[75] although, as previously mentioned (Sec. 11.B.i), the isomer formed by substitution at the β position is thermodynamically more stable and is the product if the reaction is reversible and equilibrium is reached. Because of the more extensive delocalization of charges in the corresponding arenium ions, naphthalene is more reactive than benzene and substitution is faster at both positions. Similarly,

[71] See Kruse, L.I.; Cha, J.K. *J. Chem. Soc., Chem. Commun.* ***1982***, 1333.

[72] This is not the same as the *ortho* effect mentioned at the end of Sec. 9.C.

[73] See Hammond, G.S.; Hawthorne, M.F. in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, pp. 164–200, 178–182.

[74] See Hafner, H.; Moritz, K.L. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 4, Wiley, NY, ***1965***, pp. 127–183; Bublitz, D.E.; Rinehart Jr., K.L. *Org. React.* ***1969***, *17*, 1.

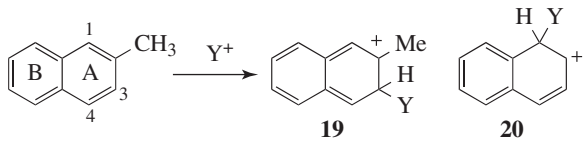
[75] See de la Mare, P.B.D.; Ridd, J.H. *Aromatic Substitution, Nitration and Halogenation*, Academic Press, NY, ***1959***, pp. 169–209.

anthracene, phenanthrene, and other fused polycyclic aromatic hydrocarbons are also substituted faster than benzene.

Furan Thiophene Pyrrole Pyridine

Heterocyclic compounds, too, have nonequivalent positions, and the principles are similar,[76] in terms of mechanism, and rate data is available.[77] Furan, thiophene, and pyrrole are chiefly substituted at the 2 position, and all are substituted faster than benzene.[78] Pyrrole is particularly reactive, with a reactivity approximating that of aniline or the phenoxide ion. For pyridine,[79] it is not the free base that must attack the electrophile but the conjugate acid (the pyridinium ion),[80] making the reactivity much less than that of benzene, being similar to that of nitrobenzene. The 3 position is most reactive in electrophilic substitution reactions of pyridine. However, groups can be introduced into the 4 position of a pyridine ring indirectly, by performing the reaction on the corresponding pyridine *N*-oxide.[81] Note that calculations show that the 2-pyridyl and 2-pyrimidyl cations are best represented as *ortho* hetarynium ions, being more stable than their positional, nonconjugated isomers by as much as 18–28 kcal mol^{-1} (75–117 kJ mol^{-1}).[82]

When fused ring systems contain substituents, successful predictions can often be made by using a combination of the above principles. Thus, ring A of 2-methylnaphthalene is activated by the methyl group; ring B is not (although the presence of a substituent in a fused ring system affects all the rings,[83] the effect is generally greatest on the ring to which it is attached). Substitution is therefore expected in ring A. The methyl group activates positions 1 and 3, which are *ortho* to itself, but not position 4, which is *meta* to it. However, substitution at the 3 position gives rise to an arenium ion for which it is impossible to write a low-energy canonical form in which ring B has a complete sextet. Only forms like **19** are possible, in which the sextet is no longer intact. In contrast, substitution at the 1 position gives rise to a more stable arenium ion, for which two canonical forms (one of them is **20**) can be written in which ring B is benzenoid.

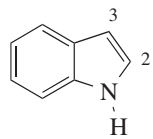


19 **20**

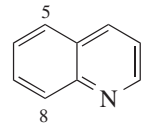
[76] See Katritzky, A.R.; Taylor, R. *Electrophilic Substitution of Heterocycles: Quantitative Aspects* (Vol. 47 of *Adv. Heterocycl. Chem.*), Academic Press, NY, ***1990***.
[77] Katritzky, A.R.; Fan, W.-Q. *Heterocycles* ***1992***, *34*, 2179.
[78] See Marino, G. *Adv. Heterocycl. Chem.* ***1971***, *13*, 235.
[79] See Comins, D.L.; O'Connor, S. *Adv. Heterocycl. Chem.* ***1988***, *44*, 199; Katritzky, A.R.; Johnson, C.D. *Angew. Chem. Int. Ed.* ***1967***, *6*, 608; Abramovitch, R.A.; Saha, J.G. *Adv. Heterocycl. Chem.* ***1966***, *6*, 229. Also see Anderson, H.J.; Loader, C.E. *Synthesis* ***1985***, 353.
[80] Katritzky, A.R.; Kingsland, M. *J. Chem. Soc. B* ***1968***, 862.
[81] Jaffé, H.H. *J. Am. Chem. Soc.* ***1954***, *76*, 3527.
[82] Gozzo, F.C.; Eberlin, M.N. *J. Org. Chem.* ***1999***, *64*, 2188.
[83] See Ansell, H.V.; Sheppard, P.J.; Simpson, C.F.; Stroud, M.A.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* ***1979***, 381.

We thus predict predominant substitution at C-1, and that is what is generally found.[84] However, in some cases predictions are much harder to make. For example, chlorination or nitration of 1-(*N*-acetyl)-2-ethoxynaphthalene gave mainly the 4 derivative, but bromination yielded chiefly the 6 compound.[85]

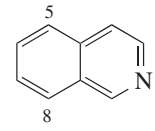
For fused heterocyclic systems too, predictions can be made based on the above principles, although many exceptions are known. Thus, indole is chiefly substituted in the pyrrole ring (at position 3) and reacts faster than benzene, while quinoline and isoquinoline generally react in the benzene ring, at the 5 and 8 positions, and react slower than benzene but faster than pyridine.



Indole

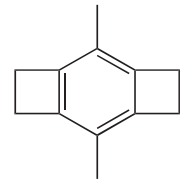


Quinoline



Isoquinoline

When strain due to a ring fused on an aromatic ring deforms that ring out of planarity, the molecule is more reactive to electrophilic aromatic substitution.[86] This effect has been explained by the presence of a shortened bond for the sp^2-hybridized carbon, increasing the strain at that position, and this is known as the *Mills-Nixon effect*.[87] There is EPR evidence (Sec. 5.C.i) for 3,6-dimethyl-1,2,4,5-tetrahydrobenzo-*bis*-cyclobutene (**21**) that supports the Mills-Nixon effect,[88] and a theoretical study supports this.[89] However, *ab initio* studies of triannelated benzene rings shows *no evidence* for the Mills-Nixon effect, and a new motif for bond-alternating benzenes was proposed.[90] Indeed, it is argued that the Mills-Nixon effect is not real.[91]



21

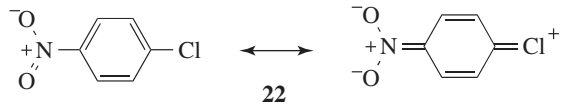
11.C. QUANTITATIVE TREATMENTS OF REACTIVITY IN THE SUBSTRATE

Quantitative rate studies of aromatic substitutions are complicated by the fact that there are usually several hydrogen atoms that can leave, so that measurements of overall rate ratios

[84] Kim, J.B.; Chen, C.; Krieger, J.K.; Judd, K.R.; Simpson, C.C.; Berliner, E. *J. Am. Chem. Soc.* ***1970***, *92*, 910. See Gore, P.H.; Siddiquei, A.S.; Thorburn, S. *J. Chem. Soc., Perkin Trans. 1* ***1972***, 1781.
[85] Bell, F. *J. Chem. Soc.* ***1959***, 519.
[86] Taylor, R. *Electrophilic Aromatic Substitution*, Wiley, Chichester, ***1990***, pp. 53.
[87] Mills, W.H.; Nixon, I.G. *J. Chem. Soc.* ***1930***, 2510.
[88] Davies, A.G.; Ng, K.M. *J. Chem. Soc., Perkin Trans. 2* ***1992***, 1857.
[89] Eckert-Maksić, M.; Maksić, Z.B.; Klessinger, M. *J. Chem. Soc., Perkin Trans. 2* ***1994***, 285.
[90] Baldridge, K.K.; Siegel, J.J. *J. Am. Chem. Soc.* ***1992***, *114*, 9583.
[91] Siegel, J.S. *Angew. Chem. Int. Ed.* ***1994***, *33*, 1721.

do not give a complete picture as they do in nucleophilic substitutions, where it is easy to compare substrates that have only one possible leaving group in a molecule. What is needed is not, say, the overall rate ratio for acetylation of toluene versus that for benzene, but the *rate ratio at each position*. These can be calculated from the overall rates and a careful determination of the proportion of isomers formed, provided that the products are kinetically controlled, as is usually the case. The *partial rate factor* may be defined for a given group and a given reaction as the rate of substitution at a single position relative to a single position in benzene. For example, for acetylation of toluene the partial rate factors are: for the *ortho* position $o_f^{Me} = 4.5$, for the *meta* $m_f^{Me} = 4.8$, and for the *para* $p_f^{Me} = 749$.[92] This means that toluene is acetylated at the *ortho* position 4.5 times as fast as a single position in benzene, or 0.75 times as fast as the overall rate of acetylation of benzene.[93] A partial rate factor > 1 for a given position indicates that the group in question activates that position for the given reaction. Partial rate factors differ from one reaction to another and are even different, though less so, for the same reaction under different conditions.

Once the partial rate factors are known, the proportions of isomers to be obtained when two or more groups are present on a ring can be predicted, *if the assumption is made that the effect of substituents is independent*. For example, if the two methyl groups in *m*-xylene have the same effect as the methyl group in toluene, the theoretical partial rate factors at each position can be calculated by multiplying those from toluene. It is therefore possible to calculate the overall theoretical rate ratio for acetylation of *m*-xylene relative to benzene, since this is one-sixth the sum of the partial rate factors and the isomer distribution if the reaction is kinetically controlled.[94] The calculated agreement can be fairly good, but many cases are known where the effects are not additive (as in Sec. 11.B.ii).[95] For example, this treatment predicts that for 1,2,3-trimethylbenzene there should be 35% 5 substitution and 65% 4 substitution, but acetylation gave 79% 5 substitution and 21% of the 4 isomer. The treatment is thrown off by steric effects, such as those mentioned earlier (Sec. 11.B.iv), by products arising from ipso attack (Sec. 11.B.ii), and by resonance interaction *between* groups (e.g., **22**), which must make the results deviate from simple additivity of the effects of the groups.



22

Another approach that avoids the problem created by having competing leaving groups present in the same substrate is the use of substrates that contain only one leaving group. This is most easily accomplished by the use of a leaving group other than hydrogen. By this means overall rate ratios can be measured for specific positions.[96] Results obtained in this way[97] give a reactivity order quite consistent with that for hydrogen as leaving group.

[92] Brown, H.C.; Marino, G.; Stock, L.M. *J. Am. Chem. Soc.* ***1959***, *81*, 3310.

[93] For a discussion of *ortho* selective C—H bond activation, see Yang, Q.L.B.; Lin, H.; Aghdassi, N.; Miao, K.; Zhang, J.; Zhang, H.; Li, Y.; Duhm, S.; Fan, J.; Chi, L. *J. Am. Chem. Soc.* ***2016***, *138*, 2809.

[94] Marino, G.; Brown, H.C. *J. Am. Chem. Soc.* ***1959***, *81*, 5929.

[95] See Cook, R.S.; Phillips, R.; Ridd, J.H. *J. Chem. Soc., Perkin Trans. 2* ***1974***, 1166. For a theoretical treatment of why additivity fails, see Godfrey, M. *J. Chem. Soc. B* ***1971***, 1545.

[96] See Eaborn, C. *J. Organomet. Chem.* ***1975***, *100*, 43.

[97] See Eaborn, C.; Jackson, P.M. *J. Chem. Soc. B* **1969**, 21.

A quantitative scale of reactivity for aromatic substrates (fused, heterocyclic, and substituted rings) has been devised, based on the hard–soft acid–base concept (Sec. 8.E).[98] From molecular orbital theory, a quantity called *activation hardness* can be calculated for each position of an aromatic ring. The smaller the activation hardness, the faster the attachment at that position; hence the treatment predicts the most likely orientations for incoming groups.

11.D. A QUANTITATIVE TREATMENT OF REACTIVITY OF THE ELECTROPHILE: THE SELECTIVITY RELATIONSHIP

Not all electrophiles are equally reactive. The nitronium ion is attacked not only by benzene but also by aromatic rings that contain a strongly deactivating group. On the other hand, diazonium ions couple only with rings containing a powerful activating group. Attempts have been made to correlate the influence of substituents with the reactivity of the group being attacked. The most obvious way to do this is with the *Hammett equation* (Sec. 8.G):

$$\log F(k/k_0) = \rho\sigma$$

For aromatic substitution,[99] k_0 is divided by 6 and, for *meta* substitution, k is divided by 2, so that comparisons are made for only one position (consequently, k/k_0 for, say, the methyl group at a *para* position is identical to the partial rate factor p_f^{Me}). It was soon found that, while this approach worked fairly well for electron-withdrawing groups, it failed for those that are electron donating. However, if the equation is modified by the insertion of the Brown σ^+ values instead of the Hammett σ values (because a positive charge develops during the transition state), more satisfactory correlations can be made, even for electron-donating groups.[100] Groups with a negative value of σ_p^+ or σ_m^+ are activating for that position; groups with a positive value are deactivating. The ρ values correspond to the susceptibility of the reaction to stabilization or destabilization by the Z group and to the reactivity of the electrophile. The ρ values vary not only with the electrophile, but also with conditions. A large negative value of ρ means an electrophile of relatively low reactivity. Of course, this approach is completely useless for *ortho* substitution, since the Hammett equation does not apply there.

A modification of the Hammett approach, suggested by Brown, called the *selectivity relationship*,[101] is based on the principle that reactivity of a species varies inversely with selectivity. The selectivity was measured by two indexes: (i) their selectivity in attacking toluene rather than benzene, and (ii) their selectivity between the *meta* and *para* positions in toluene.[101] An electrophile that is more selective in one respect is also more selective in the other. In many cases, electrophiles known to be more stable (hence less reactive) than others show a higher selectivity, as would be expected. For example, the *tert*-butyl cation is more stable and more selective than the isopropyl (Sec. 5.A.ii), and Br_2 is more selective than Br^+. However, deviations from the relationship are known.[102] Selectivity depends not

[98] Zhou, Z.; Parr, R.G. *J. Am. Chem. Soc.* ***1990***, *112*, 5720.
[99] See Exner, O.; Böhm, S. *J. Org. Chem.* ***2002***, *67*, 6320.
[100] See Koptyug, V.A.; Salakhutdinov, N.F.; Detsina, A.N. *J. Org. Chem. USSR* ***1984***, *20*, 1039.
[101] Stock, L.M.; Brown, H.C. *Adv. Phys. Org. Chem.* ***1963***, *1*, 35.
[102] See Olah, G.A.; Olah, J.A.; Ohyama, T. *J. Am. Chem. Soc.* ***1984***, *106*, 5284.

only on the nature of the electrophile but also on the temperature. As expected, it normally decreases with increasing temperature.

Brown assumed that a good measurement of selectivity was the ratio of the *para* and *meta* partial rate factors in toluene. He defined the selectivity S_f of a reaction as

$$S_f = \log F\left(p_f^{\mathrm{Me}}, m_f^{\mathrm{Me}}\right)$$

That is, the more reactive the reactive species, the less preference it has for the *para* position compared to the *meta*. If we combine the Hammett-Brown $\sigma^+\rho$ relationship with the linearity between $\log S_f$ and $\log p_f^{\mathrm{Me}}$ and between $\log S_f$ and $\log m_f^{\mathrm{Me}}$, it is possible to derive the following expressions:

$$\log p_f^{\mathrm{Me}} = \frac{\sigma_p^+}{\sigma_p^+ - \sigma_m^+} S_f$$

$$\log m_f^{\mathrm{Me}} = \frac{\sigma_m^+}{\sigma_p^+ - \sigma_m^+} S_f$$

S_f is related to ρ by $S_f = \rho(\sigma_p^+ - \sigma_m^+)$.

The general validity of these equations is supported by a great deal of experimental data on aromatic substitution reactions of toluene.[103] For other substituents, the treatment works well with groups that, like methyl, are not very polarizable. For more polarizable groups the correlations are sometimes satisfactory and sometimes not, probably because each electrophile in the transition state makes a different demand on the electrons of the substituent group. Not only are there substrates for which the treatment is poor, but it fails with very powerful electrophiles, which is why it is necessary to postulate the encounter complex mentioned in Sec. 11.A.i. For example, relative rates of nitration of *p*-xylene, 1,2,4-trimethylbenzene, and 1,2,3,5-tetramethylbenzene were 1.0, 3.7, and 6.4,[104] though the extra methyl groups should enhance the rates much more (*p*-xylene itself reacted 295 times faster than benzene). The explanation is that with powerful electrophiles the reaction rate is so rapid (reaction taking place at virtually every encounter[105] between an electrophile and substrate molecule)[106] that the presence of additional activating groups can no longer increase the rate.[107]

Given this behavior (little selectivity in distinguishing between different substrate molecules), the selectivity relationship would predict that positional selectivity should also be very small. However, it is not. For example, under conditions where nitration of *p*-xylene and 1,2,4-trimethylbenzene takes place at about equal rates, there was no corresponding lack of selectivity at positions *within* the latter.[108] Although steric effects are about the same

[103] Stock, L.M.; Brown, H.C. *Adv. Phys. Org. Chem.* ***1963***, *1*, 35 presents many tables of these kinds of data. See also, DeHaan, F.P.; Chan, W.H.; Chang, J.; Ferrara, D.M.; Wainschel, L.A. *J. Org. Chem.* ***1986***, *51*, 1591, and other papers in this series.

[104] Olah, G.A.; Lin, H.C. *J. Am. Chem. Soc.* ***1974***, *96*, 2892.

[105] See Moodie, R.B.; Schofield, K.; Thomas, P.N. *J. Chem. Soc., Perkin Trans. 2* ***1978***, 318.

[106] See Ridd, J.H. *Adv. Phys. Org. Chem.* ***1978***, *16*, 1.

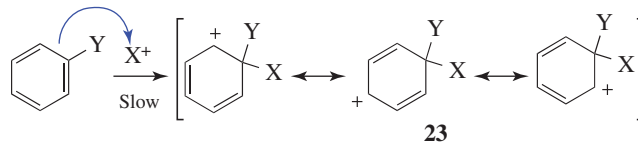
[107] Manglik, A.K.; Moodie, R.B.; Schofield, K.; Dedeoglu, E.; Dutly, A.; Rys, P. *J. Chem. Soc., Perkin Trans. 2* ***1981***, 1358.

[108] Barnett, J.W.; Moodie, R.B.; Schofield, K.; Taylor, P.G.; Weston, J.B. *J. Chem. Soc., Perkin Trans. 2* ***1979***, 747.

at both positions, > 10 times as much 5-nitro product was formed as 6-nitro product. It is clear that the selectivity relationship has broken down and it becomes necessary to explain why such an extremely rapid reaction should occur with positional selectivity. The explanation offered is that the rate-determining step is formation of an encounter complex (**12**, Sec. 11.B.ii).[109] Since the position of attachment is not determined in the rate-determining step, the 5:6 ratio is not related to the reaction rate. Essentially the same idea was suggested earlier[110] and for the same reason (failure of the selectivity relationship in some cases), but the earlier explanation specifically pictured the complex as a π complex, and there is evidence against this (Sec. 11.B.ii).

One interesting proposal[111] is that the encounter pair is a radical pair $NO_2^{\bullet}$ $ArH^{\bullet+}$ formed by an electron transfer (SET), which would explain why the electrophile, once in the encounter complex, can acquire the selectivity that the free NO_2^+ lacked (it is not proposed that a radical pair is present in all aromatic substitutions; only in those that do not obey the selectivity relationship). The radical pair subsequently collapses to the arenium ion. There is evidence both for[112] and against this proposal.[113]

11.E. THE EFFECT OF THE LEAVING GROUP



23

In the vast majority of aromatic electrophilic substitutions, the leaving group is H^+, as indicated above, and very little work has been done on the relative electrofugal ability of other leaving groups. However, the following orders of leaving-group ability have been suggested:[114] (i) for leaving groups that depart without assistance (S_N1 process with respect to the leaving group), NO_2^+[115] < *i*-Pr^+ ~ SO_3 < *t*-Bu^+ ~ArN_2^+ < $ArCHOH^+$ < NO^+ < CO_2; (ii) for leaving groups that depart with assistance from an outside nucleophile (S_N2 process), $Me^+ < Cl^+ < Br^+ < D^+ \sim RCO^+ < H^+ \sim I^+ < Me_3Si^+$. This kind of list can be used to help predict which group, X or Y, will cleave from an arenium ion **23** (see **1**, where Y = H) once it has been formed, and so obtain an idea of which electrophilic substitutions are feasible. However, a potential leaving group can also affect a reaction in another way,

[109] See Sheats, G.F.; Strachan, A.N. *Can. J. Chem.* ***1978***, *56*, 1280. Also see Attinà, M.; Cacace, F.; de Petris, G. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1177.
[110] Olah, G.A. *Acc. Chem. Res.* ***1971***, *4*, 240.
[111] Perrin, C.L. *J. Am. Chem. Soc.* ***1977***, *99*, 5516.
[112] See Sankararaman, S.; Haney, W.A.; Kochi, J.K. *J. Am. Chem. Soc.* ***1987***, *109*, 5235; Keumi, T.; Hamanaka, K.; Hasegawa, K.; Minamide, N.; Inoue, Y.; Kitajima, H. *Chem. Lett.* ***1988***, 1285; Johnston, J.F.; Ridd, J.H.; Sandall, J.P.B. *J. Chem. Soc., Chem. Commun.* ***1989***, 244. For evidence against it, see Eberson, L.; Radner, F. *Acc. Chem. Res.* ***1987***, *20*, 53; Baciocchi, E.; Mandolini, L. *Tetrahedron* ***1987***, *43*, 4035.
[113] See Morkovnik, A.S. *Russ. Chem. Rev.* ***1988***, *57*, 144.
[114] Perrin, C.L. *J. Org. Chem.* ***1971***, *36*, 420.
[115] See Bullen, J.V.; Ridd, J.H.; Sabek, O. *J. Chem. Soc., Perkin Trans. 2* ***1990***, 1681, and other papers in this series.

which is by influencing the rate at which attack of the original electrophile leads to attachment directly at the ipso position. Partial rate factors for electrophilic attack at a position substituted by a group other than hydrogen are called ipso partial rate factors (i_f^X).[114] Such factors for the nitration of *p*-haloanisoles are 0.18, 0.08, and 0.06, for *p*-iodo-, *p*-bromo-, and *p*-chloroanisole, respectively.[116] This means, for example, that attack at the electrophile in this case leads to attachment at the 4 position of 4-iodoanisole 0.18 times as fast as a single position of benzene. Note that this is far slower than attachment at the 4 position resulting from attack of anisole itself so that the presence of the iodo group greatly slows the reaction at that position. A similar experiment on *p*-cresol showed that ipso attack at the methyl position was 6.8 times slower than attack of phenol leading to attachment at the *para* position.[117] Thus, in these cases, both an iodo and a methyl group deactivate the ipso position.[118]

11.F. REACTIONS

The reactions in this chapter are classified according to leaving group. Hydrogen replacements are treated first, and then rearrangements in which the attacking entity is first cleaved from another part of the molecule (hydrogen is also the leaving group in these cases), and finally replacements of other leaving groups.

11.F.i. Hydrogen as the Leaving Group in Simple Substitution Reactions

A. Hydrogen as the Electrophile

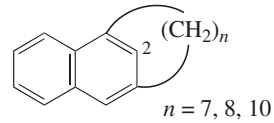
11-1 Hydrogen Exchange

$$ArH + D^+ \rightleftharpoons ArD + H^+$$

Aromatic compounds can exchange hydrogen atoms when treated with acids. The reaction is used chiefly to study mechanistic questions[119] (including substituent effects), but can also be useful to deuterate (add ^2H) or tritiate (add ^3H) aromatic rings selectively. The usual directive effects apply and, for example, phenol treated with D_2O gives slow exchange on heating, with only *ortho* and *para* hydrogen atoms being exchanged.[120] Strong acids, of course, exchange faster with aromatic substrates, and this exchange must be taken into account when studying the mechanism of any aromatic substitution catalyzed by acids. There is evidence that exchange takes place by the ordinary arenium ion mechanism, including the orientation effects noted above and the finding that the reaction is general acid catalyzed, which means that a proton is transferred in the slow

[116] Perrin, C.L.; Skinner, G.A. *J. Am. Chem. Soc.* ***1971***, *93*, 3389. See also, Fischer, P.B.; Zollinger, H. *Helv. Chim. Acta* ***1972***, *55*, 2139.
[117] Tee, O.; Iyengar, N.R.; Bennett, J.M. *J. Org. Chem.* ***1986***, *51*, 2585.
[118] Clemens, A.H.; Hartshorn, M.P.; Richards, K.E.; Wright, G.J. *Aust. J. Chem.* ***1977***, *30*, 103, 113.
[119] See Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 194–277.
[120] Small, P.A.; Wolfenden, J.H. *J. Chem. Soc.* ***1936***, 1811.

step[121] (Sec. 8.D). Furthermore, many examples have been reported of stable solutions of arenium ions formed by attack of a proton on an aromatic ring.[8] Simple aromatic compounds can be extensively deuterated in a convenient fashion by treatment with D_2O and BF_3.[122] It has been shown that tritium exchange takes place readily at the 2 position of **24**, despite the fact that this position is hindered by the bridge, and that the rates were not very different from the comparison compound 1,3-dimethylnaphthalene.[123]



24

Hydrogen exchange can also be effected with strong bases,[124] such as NH_2^-. In these cases the slow step is the proton transfer:[125] so the S_E1 mechanism and not the usual arenium ion mechanism is operating.[126] Aromatic rings can also be deuterated by treatment with D_2O and a rhodium(III) chloride[127] or a Pt[128] catalyst or with C_6D_6 and an alkylaluminum dichloride catalyst,[129] though rearrangements may take place during the latter procedure. Tritium (^3H, abbreviated T) can be introduced by treatment with T_2O and an alkylaluminum dichloride catalyst.[129] Tritiation at specific sites (e.g. >90% *para* in toluene) has been achieved with T_2 gas and a microporous aluminophosphate catalyst.[130]

$$ArH + B \longrightarrow Ar^- + BH^+$$

The mechanisms of hydride abstraction by quinones has been discussed.[131]

B. Nitrogen Electrophiles

11-2 Nitration

$$ArH + HNO_3 \xrightarrow{H_2SO_4} ArNO_2$$

Most aromatic compounds, whether of high or low reactivity, can be nitrated, and a wide variety of nitrating agents are available.[132] For benzene, the simple alkylbenzenes, and less

[121] See Kresge, A.J.; Chiang, Y.; Sato, Y. *J. Am. Chem. Soc.* ***1967***, *89*, 4418; Gruen, L.C.; Long, F.A. *J. Am. Chem. Soc.* ***1967***, *89*, 1287; Butler, A.B.; Hendry, J.B. *J. Chem. Soc. B* ***1970***, 852.
[122] Larsen, J.W.; Chang, L.W. *J. Org. Chem.* ***1978***, *43*, 3602.
[123] Laws, A.P.; Neary, A.P.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* ***1987***, 1033.
[124] See Elvidge, J.A.; Jones, J.R.; O'Brien, C.; Evans, E.A.; Sheppard, H.C. *Adv. Heterocycl. Chem.* ***1974***, *16*, 1.
[125] For a discussion of the aromatic character of this transition state, see Bernasconi, C.F. *Pure Appl. Chem.* ***2009***, *81*, 649.
[126] Shatenshtein, A.I. *Tetrahedron* ***1962***, *18*, 95.
[127] Lockley, W.J.S. *Tetrahedron Lett.* ***1982***, *23*, 3819; *J. Chem. Res. (S)* ***1985***, 178.
[128] See Blake, M.R.; Garnett, J.L.; Gregor, I.K.; Hannan, W.; Hoa, K.; Long, M.A. *J. Chem. Soc., Chem. Commun.* ***1975***, 930. See also, Parshall, G.W. *Acc. Chem. Res.* ***1975***, *8*, 113.
[129] Long, M.A.; Garnett, J.L.; West, J.C. *Tetrahedron Lett.* ***1978***, 4171.
[130] Garnett, J.L.; Kennedy, E.M.; Long, M.A.; Than, C.; Watson, A.J. *J. Chem. Soc., Chem. Commun.* ***1988***, 763.
[131] Guo, X.; Zipse, H.; Mayr, H. *J. Am. Chem. Soc.* ***2014***, *136*, 13863.
[132] See Esteves, P.M.; de M. Carneiro, J.W.; Cardoso, S.P.; Barbosa, A.G.H.; Laali, K.K.; Rasul, G.; Prakash, G.K.S.; Olah, G.A. *J. Am. Chem. Soc.* ***2003***, *125*, 4836; Olah, G.A.; Malhotra, R.; Narang, S.C. *Nitration: Methods*

reactive compounds, the most common reagent is a mixture of concentrated nitric and sulfuric acids,[133] but for active substrates, the reaction can be carried out with nitric acid alone,[134] or in water, acetic acid, acetic anhydride, or chloroform.[135] Milder conditions are necessary for active compounds, such as amines, phenols, and pyrroles, since reaction with mixed nitric and sulfuric acids would oxidize these substrates. With active substrates, such as anilines[136] and phenols,[137] reagents used for nitration include a mixture of dilute nitrous and nitric acids,[138] $NaNO_2$ and trifluoroacetic acid,[139] ceric ammonium nitrate,[140] urea nitrate and nitrourea,[141] NBS/$AgNO_3$,[142] $NaNO_2$, and a hypervalent iodine compound with a Rh catalyst.[143] Phenol can also be nitrated in an ionic liquid.[144] Nitric acid, in the presence of P_2O_5 supported on SiO_2, is useful for the nitration of aromatic compounds under solvent-free conditions.[145] Arylboronic acids have been shown to react with ammonium nitrate and trifluoroacetic acid to give the corresponding nitrobenzene.[146] Arylboronic acids reacted with *t*-butyl nitrite at 8 °C in the air to give the corresponding nitro aryl compound.[147]

Phenols are converted to the 2-pyridinyloxy derivative,[148] then reaction with $Pd(OAc)_2$, $AgNO_2$, and $K_2S_2O_8$ at 110 °C led to the *ortho*-selective nitration, and the 2-pyridinyloxy group was removed by reaction with (i) MeOTf, 100 °C and (ii) 24 equivalents of Na in MeOH at reflux.[149] The reagent NO_2^+ BF_4^- has been used for the nitration of toluene and the dynamics of the reaction were discussed.[150] Green procedures for the nitration of phenol have been reviewed.[151] An alternative route for the nitration of activated aromatic compounds, such as anisole, used a nitrate ester ($RONO_2$) with triflic acid in an ionic liquid for *ortho*-selective nitration.[152] The nitration reaction of 1,2- and 1,4-dimethoxybenzene led

and Mechanisms, VCH, NY, ***1989***; Schofield, K. *Aromatic Nitration*, Cambridge University Press, Cambridge, ***1980***; Hoggett, J.H.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitraton and Aromatic Reactivity*, Cambridge University Press, Cambridge, ***1971***; Weaver, W.M. in Feuer, H. *Chemistry of the Nitro and Nitroso Groups*, pt. 2, Wiley, NY, ***1970***, pp. 1–48. Also see, Bosch, E.; Kochi, J.K. *J. Org. Chem.* ***1994***, *59*, 3314.

[133] Ramana, M.M.V.; Malik, S.S.; Parihar, J.A. *Tetrahedron Lett.* ***2004***, *45*, 8681.

[134] See Parac-Vogt, T.N.; Binnemans, K. *Tetrahedron Lett.* ***2004***, *45*, 3137.

[135] See Tasneem, Ali, M.M.; Rajanna, K.C.; Saiparakash, P.K. *Synth. Commun.* ***2001***, *31*, 1123.

[136] See Yang, X.; Xi, C. *Synth. Commun.* ***2007***, *37*, 3381.

[137] See Bose, A.K.; Ganguly, S.N.; Manhas, M.S.; Rao, S.; Speck, J.; Pekelny, U.; Pombo-Villars, E. *Tetrahedron Lett.* ***2006***, *47*, 1885. Also see Anuradha, V.; Srinivas, P.V.; Aparna, P.; Rao, J.M. *Tetrahedron Lett.* ***2006***, *47*, 4933.

[138] See Ridd, J.H. *Chem. Soc. Rev.* ***1991***, *20*, 149.

[139] Zolfigol, M.A.; Ghaemi, E.; Madrakian, E. *Synth. Commun.* ***2000***, *30*, 1689; Zolfigol, M.A.; Bagherzadeh, M.; Madrakian, E.; Gaemi, E.; Taqian-Nasab, A. *J. Chem. Res. (S)* ***2001***, 140.

[140] Yang, X.; Xi, C.; Jiang, Y. *Tetrahedron Lett.* ***2005***, *46*, 8781.

[141] Almog, J.; Klein, A.; Sokol, A.; Sasson, Y.; Sonenfeld, D.; Tamiri, T. *Tetrahedron Lett.* ***2006***, *47*, 8651.

[142] Nowrouzi, N.; Mehranpour, A.M.; Bashiri, E.; Shayan, Z. *Tetrahedron Lett.* ***2012***, *53*, 4841.

[143] Xie, F.; Qi, Z.; Li, X. *Angew. Chem. Int. Ed.* ***2013***, *52*, 11862.

[144] Rajogopal, R.; Srinivasan, K.V. *Synth. Commun.* ***2004***, *34*, 961.

[145] Hajipour, A.R.; Ruoho, A.E. *Tetrahedron Lett.* ***2005***, *46*, 8307.

[146] Prakash, G.K.S.; Panja, C.; Mathew, T.; Surampudi, V.; Petasis, N.A.; Olah, G.A. *Org. Lett.* ***2004***, *6*, 2205.

[147] Wu, X.-F.; Schranck, J.; Neumann, H.; Beller, M. *Chem. Commun.* ***2011***, *47*, 12462.

[148] Yao, J.; Feng, R.; Wu, Z.; Liu, Z.; Zhang, Y. *Adv. Synth. Catal.* ***2013***, *355*, 1517.

[149] Zhang, W.; Zhang, J.; Ren, S.; Liu, Y. *J. Org. Chem.* ***2014***, *79*, 11508. For a removable directing group involving pyrimidine, see Pawar, G.G.; Brahmanandan, A.; Kapur, M. *Org. Lett.* ***2016***, *18*, 448.

[150] Nieves-Quinones, Y.; Singleton, D.A. *J. Am. Chem. Soc.* ***2016***, *138*, 14167. Molander, G.A.; Cavalcanti, L.N. *J. Org. Chem.* ***2012***, *77*, 4402.

[151] Vekariya, R.H.; Patel, H.D. *Synth. Commun.* ***2014***, *44*, 2313.

[152] Laali, K.K.; Gettwert, V.J. *J. Org. Chem.* ***2001***, *66*, 35.

to the regioselective 1,2-dinitration product or the 1,4-dinitration product.[153] Aromatic, as well as aliphatic, carboxylic acids reacted with NO_2BF_4 in the presence of Ag_2CO_3 at 90 °C to give the aromatic nitro compound or the aliphatic nitro compound.[154] Since the nitro group is deactivating, it is usually easy to stop the reaction after one group has been added, if no activating group is present.

When anilines are nitrated under low-acid conditions, the free amine is nitrated and the orientation is *ortho*/*para*. Under strong-acid conditions, *meta* orientation is generally observed, because the ammonium salt is the species undergoing nitration, which is the conjugate acid of the amine. Although the free base may be present in much smaller amounts than the conjugate acid, it is far more susceptible to aromatic substitution (see also, Sec. 11.B.i). Because of these factors and because they are vulnerable to oxidation by nitric acid, primary aromatic amines are often protected before nitration by treatment with acetyl chloride (**16-71**) or acetic anhydride (**16-72**). *Nitration of the resulting acetanilide derivative avoids all the problems mentioned here.* There is evidence that when the reaction takes place on the free amine, it is the nitrogen that is attacked to give an *N*-nitro compound (Ar—NH—NO_2) which rapidly undergoes rearrangement (see **11-28**) to give the product.[155]

With most of the reagents mentioned, the attacking species is the nitronium ion NO_2^+. There is a great deal of evidence that NO_2^+ is present in most nitration reactions and that it is the attacking entity.[156]

1. Nitric acid has a peak in the Raman spectrum. When nitric acid is dissolved in concentrated sulfuric acid, the peak disappears and two new peaks appear, one at 1400 cm^{-1}, attributable to NO_2^+, and one at 1050 cm^{-1}, due to HSO_4^-.[157]
2. On addition of nitric acid, the freezing point of sulfuric acid is lowered about four times the amount expected if no ionization has taken place.[158] This means that the addition of one molecule of nitric acid results in the production of four particles, which is strong evidence for the ionization reaction between nitric and sulfuric acids given above.
3. Nitronium salts generally nitrate aromatic compounds, which shows that this ion does attack the ring.
4. The rate of the reaction with most reagents is proportional to the concentration of NO_2^+, not to the concentration of other species.[159] When the reagent produces this ion in small amounts, the attack is slow and only active substrates can be nitrated. In concentrated and aqueous mineral acids, the kinetics are second order: first order each in aromatic substrate and in nitric acid (unless pure nitric acid is used in which case there are pseudo-first-order kinetics). But in organic solvents such as nitromethane, acetic acid, and CCl_4, the kinetics are first order in nitric acid alone

[153] Shopsowitz, K.; Lelj, F.; MacLachlan, M.J. *J. Org. Chem.* ***2011***, *76*, 1285. For a Cu-catalyzed reaction, see Sadhu, P.; Alla, S.K.; Punniyamurthy, T. *J. Org. Chem.* ***2015***, *80*, 8245; Zhang, L.; Liu, Z.; Li, H.; Fang, G.; Barry, B.-D.; Belay,T.A.; Bi, X.; Liu, Q. *Org. Lett.* ***2011***, *13*, 6536.

[154] Natarajan, P.; Chaudhary, R.; Venugopalan, P. *J. Org. Chem.* ***2015***, *80*, 10498.

[155] Ridd, J.H.; Scriven, E.F.V. *J. Chem. Soc., Chem. Commun.* ***1972***, 641. See also, Helsby, P.; Ridd, J.H. *J. Chem. Soc., Perkin Trans. 2* ***1983***, 1191.

[156] Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1950***, 2400 and a series of several papers.

[157] Ingold, C.K.; Millen, D.J.; Poole, H.G. *J. Chem. Soc.* ***1950***, 2576.

[158] Gillespie, R.J.; Graham, J.; Hughes, E.D.; Ingold, C.K.; Peeling, E.R.A. *J. Chem. Soc.* ***1950***, 2504.

[159] See Ross, D.S.; Kuhlmann, K.F.; Malhotra, R. *J. Am. Chem. Soc.* ***1983***, *105*, 4299.

and zero order in aromatic substrate, because the rate-determining step is formation of NO_2^+ and the aromatic substrate does not take part in this.

The nitronium ion can be produced by several methods.

1. In concentrated sulfuric acid, it is produced by an acid–base reaction in which nitric acid is the base, and the ionization is essentially complete.

$$HNO_3 + 2\,H_2SO_4 \rightleftharpoons NO_2^+ + H_3O^+ + 2\,HSO_4^-$$

2. In concentrated nitric acid alone,[160] it is produced by a similar acid–base reaction in which one molecule of nitric acid is the acid and another the base. This equilibrium lies to the left (~4% ionization), but enough NO_2^+ is formed for nitration to occur. This equilibrium occurs to a small extent even in organic solvents.

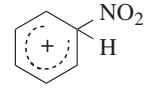
$$2\,HNO_3 \rightleftharpoons NO_2^+ + NO_3^- + H_2O$$

3. With N_2O_5 in CCl_4, there is spontaneous dissociation to NO_2^+ and NO_3^-, but in this case there is evidence that some nitration also takes place with undissociated N_2O_5 as the electrophile.
4. When nitronium salts are used, NO_2^+ is of course present to begin with.
5. Esters and acyl halides of nitric acid ionize to form NO_2^+.

In a few cases, depending on the substrate and solvent, there is evidence that the arenium ion is not formed directly, but via the intermediacy of a radical pair (Sec. 11.D) such as **25**.[161]

$$ArH + NO_2^+ \longrightarrow [\,ArH^{\ddagger}\ NO_2^{\bullet}\,] \longrightarrow$$

25



Functionalized aromatic compounds reacted with $Cu(NO_3)_2.3H_2O$ with a Ru catalyst to give the *meta*-substituted nitro compound.[162] The Cu-catalyzed ipso nitration of haloarenes or heterocyclic haloarenes has been reported.[163] The ipso nitration of arylboronic acids has been reported using bismuth nitrate and perdisulfate,[164] and sodium nitrite and $ClSiMe_3$ has also been used.[165] The nitration of arynes by 2 equivalents of NaNO2 in water/MeCN

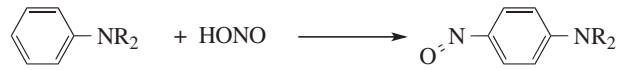
[160] See Belson, D.J.; Strachan, A.N. *J. Chem. Soc., Perkin Trans. 2* ***1989***, 15.
[161] See Ridd, J.H. *Chem. Soc. Rev.* ***1991***, *20*, 149; Kochi, J.K. *Adv. Free Radical Chem. (Greenwich, Conn.)* ***1990***, *1*, 53.
[162] Fan, Z.; Ni, J.; Zhang, A. *J. Am. Chem. Soc.* ***2016***, *138*, 8470.
[163] Joseph, P.J.A.; Priyadarshini, S.; Kantam, M.L.; Maheswaran, H. *Tetrahedron Lett.* ***2012***, *53*, 1511.
[164] Manna, S.; Maity, S.; Rana, S.; Agasti, S.; Maiti, D. *Org. Lett.* ***2012***, *14*, 1736; Yadav, R.R.; Vishwakarma, R.A.; Bharate, S.B. *Tetrahedron Lett.* ***2012***, *53*, 5958.
[165] Surya Prakash, G.K.; Gurung, L.; Schmid, P.C.; Wang, F.; Thomas, T.E.; Panja, C.; Mathew, T.; Olah, G.A. *Tetrahedron Lett.* ***2014***, *55*, 1975. Also see Chatterjee, N.; Bhatt, D.; Goswami, A. *Org. Biomol. Chem.* ***2015***, *13*, 4828; Shen, G.; Zhao, L.; Liu, W.; Huang, X.; Song, H.; Zhang, T. *Synth. Commun.* ***2017***, *47*, 10.

has been developed, giving the nitrobenzene.[166] The Pd-catalyzed, chelation-assisted *ortho*-selective nitration of the oxime derivative of aryl ketones derived from simple arenes, 2-arylquinoxalines, pyridines, quinoline, and pyrazoles have been reported.[167]

Deactivated aromatic compounds, such as acetophenone, were nitrated with N_2O_5 and $Fe(acac)_2$.[168] Even *m*-dinitrobenzene can be nitrated if vigorous conditions are applied, e.g. $NO_2^+ BF_4^-$ in FSO_3H at 150 °C.[169] Deactivated heterocycles such as pyridine are nitrated with N_2O_5 and SO_2.[170]

OS **I**, 372, 396, 408 (see also OS **53**, 129); **II**, 254, 434, 438, 447, 449, 459, 466; **III**, 337, 644, 653, 658, 661, 837; **IV**, 42, 364, 654, 711, 722, 735; **V**, 346, 480, 829, 1029, 1067.

11-3 Nitrosation



Ring nitrosation[171] with nitrous acid is normally carried out only with active substrates, such as amines and phenols. However, primary aromatic amines give diazonium ions (**13-19**) when treated with nitrous acid,[172] and secondary amines tend to give *N*-nitroso rather than *C*-nitroso compounds (**12-49**). Therefore, this reaction is normally limited to phenols and tertiary aromatic amines. Nevertheless, secondary aromatic amines can be *C*-nitrosated in two ways. The *N*-nitroso compound first obtained can be isomerized to a *C*-nitroso compound (**11-29**), or it can be treated with another equivalent of nitrous acid to give an *N*,*C*-dinitroso compound. Also, a successful nitrosation of anisole has been reported, where the solvent was CF_3COOH—CH_2Cl_2.[173]

Much less work has been done on the mechanism of this reaction than on **11-2**.[174] In some cases, the attacking entity is NO^+, but in others it is apparently NOCl, NOBr, N_2O_3, and so on, in each of which there is a carrier of NO^+. Both NOCl and NOBr are formed during the normal process of making nitrous acid (the treatment of sodium nitrite with HCl or HBr). Nitrosation requires active substrates because kinetic studies have shown that NO^+ is at least 10^{14} times less reactive than NO_2^+.[175] A consequence of the relatively high stability of NO^+ is that this species is easily cleaved from the arenium ion, so that k_{-1} competes with k_2 (Sec. 11.A.i) and isotope effects are found.[176] With phenols, there is evidence that nitrosation may first take place at the OH group, after which the nitrite ester thus formed

[166] Dhokale, R.A.; Mhaske, S.B. *Org. Lett.* ***2016***, *18*, 3010.
[167] Zhang, W.; Lou, S.; Liu, Y.; Xu, Z. *J. Org. Chem.* ***2013***, *78*, 5932.
[168] Bak, R.R.; Smallridge, A.J. *Tetrahedron Lett.* ***2001***, *42*, 6767.
[169] Olah, G.A.; Lin, H.C. *Synthesis* ***1974***, 444.
[170] Arnestad, B.; Bakke, J.M.; Hegbom, I.; Ranes, E. *Acta Chem. Scand. B* ***1996***, *50*, 556.
[171] See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 58–76; Atherton, J.H.; Moodie, R.B.; Noble, D.R.; O'Sullivan, B. *J. Chem. Soc., Perkin Trans. 2* ***1997***, 663.
[172] See Hoefnagel, M.A.; Wepster, B.M. *Recl. Trav. Chim. Pays-Bas* ***1989***, *108*, 97.
[173] Radner, F.; Wall, A.; Loncar, M. *Acta Chem. Scand.* ***1990***, *44*, 152.
[174] See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 58–76; Atherton, J.H.; Moodie, R.B.; Noble, D.R.; O'Sullivan, B. *J. Chem. Soc., Perkin Trans. 2* ***1997***, 663.
[175] Challis, B.C.; Higgins, R.J. *J. Chem. Soc., Perkin Trans. 2* ***1972***, 2365.
[176] Challis, B.C.; Higgins, R.J. *J. Chem. Soc., Perkin Trans. 2* ***1973***, 1597.

rearranges to the *C*-nitroso product.[177] Tertiary aromatic amines substituted in the *ortho* position generally do not react with HONO, probably because the *ortho* substituent prevents planarity of the dialkylamino group, without which the ring is no longer activated. This is an example of steric inhibition of resonance (Sec. 2.F).

OS **I**, 214, 411, 511; **II**, 223; **IV**, 247.

11-4 Amination or Phosphination[178] (*N*-Arylation)

$$\mathrm{ArH} + \mathrm{NH_3(RNH_2)} \xrightarrow{\text{Metal catalyst}} \mathrm{ArNH_2(ArNHR)}$$
$$\mathrm{ArX} + \mathrm{NH_3(RNH_2)} \xrightarrow{\text{Metal catalyst}} \mathrm{ArNH_2(ArNHR)}$$

Aromatic compounds can be converted to primary aromatic amines[179] by treatment with hydrazoic acid HN_3 in the presence of $AlCl_3$ or H_2SO_4.[180] Higher yields (>90%) have been reported with trimethylsilyl azide (Me_3SiN_3) and triflic acid (F_3CSO_2OH).[181] Tertiary amines have been prepared by treatment of aromatic hydrocarbons with *N*-chlorodialkylamines, by heating in 96% sulfuric acid, with $AlCl_3$ or $FeCl_3$ in nitroalkane solvents, or by irradiation.[182] Treatment of an aryl halide with an amine and a Pd catalyst leads to the aniline derivative.[183] The ligand-free amination of haloarenes by reaction with an amine and $Pd_2(dba)_3$ as a catalyst, with microwave irradiation, has been reported.[184] Recyclable Pd catalysts for this reaction have been developed.[185]

The Ni-catalyzed reaction of aryl halides and ammonia has been reported.[186] Aryl halides reacted with aqueous ammonia when heated with PG-400 and CuI to give the arylamine.[187] Magnetically separable $CuFe_2O_4$ nanoparticles in PEG have been used for the reaction of aryl halides and ammonia to give the arylamine.[188] Arylzinc reagents react with benzyloxyamines with a Cu catalyst to give the arylamine.[189] A *meta*-selective C—H amination reaction has been reported by the reaction of aniline derivatives with *N*-benzyloxyamines with a Pd catalyst and hydroxypyridine ligands and a modified norbornene mediator.[190]

Diphenyliodonium salts react with amines in the presence of a Cu catalyst. Diphenyliodonium tetrafluoroborate, $Ph_2I^+\ BF_4^-$, reacts with indole in DMF at 150 °C

[177] Gosney, A.P.; Page, M.I. *J. Chem. Soc., Perkin Trans. 2* ***1980***, 1783.
[178] See Kovacic, P. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1493–1506.
[179] See Ghorai, S.K.; Gopalsamuthiram, V.G.; Jawalekar, A.M.; Patre, R.E.; Pal, S. *Tetrahedron* ***2017***, *73*, 1769.
[180] Kovacic, P.; Russell, R.L.; Bennett, R.P. *J. Am. Chem. Soc.* ***1964***, *86*, 1588.
[181] Olah, G.A.; Ernst, T.D. *J. Org. Chem.* ***1989***, *54*, 1203.
[182] Bock, H.; Kompa, K. *Angew. Chem. Int. Ed.* ***1965***, *4*, 783; *Chem. Ber.* ***1966***, *99*, 1347, 1357, 1361.
[183] See Ruiz-Castillo, P.; Buchwald, S.L. *Chem. Rev.* ***2016***, *116*, 12564. See Cai, L.; Qian, X.; Song, W.; Liu, T.; Tao, X.; Li, W.; Xie, X. *Tetrahedron* ***2014***, *70*, 4754; Pompeo, M.; Farmer, J.L.; Froese, D.J.; Organ, M.G. *Angew. Chem. Int. Ed.* ***2014***, *53*, 3223; Park, N.H.; Vinogradova, E.V.; Surry, D.S.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***2015***, *54*, 8259.
[184] Basolo, L.; Bernasconi, A.; Broggini, G.; Gazzola, S.; Beccalli, E.M. *Synthesis* ***2013***, *45*, 3151.
[185] Dumrath, A.; Lübbe, C.; Neumann, H.; Jackstell, R.; Beller, M. *Chem. Eur. J.* ***2011***, *17*, 9599.
[186] Borzenko, A.; Rotta-Loria, N.L.; MacQueen, P.M.; Lavoie, C.M.; McDonald, R.; Stradiotto, M. *Angew. Chem. Int. Ed.* ***2015***, *54*, 3773.
[187] Chen, J.; Yuan, T.; Hao, W.; Cai, M. *Tetrahedron Lett.* ***2011***, *52*, 3710.
[188] Kumar, A.S.; Ramani, T.; Sreedhar, B. *Synlett* ***2013***, *24*, 938.
[189] McDonald, S.L.; Hendrick, C.E.; Wang, Q. *Angew. Chem. Int. Ed.* ***2014***, *53*, 4667.
[190] Wang, P.; Li, G.-C.; Jain, P.; Farmer, M.E.; He, J.; Shen, P.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* ***2016***, *138*, 14092.

with a $Cu(OAc)_2$ catalyst, for example, to give *N*-phenylindole.[191] Aryliodonium compounds reacted directly with amides, without a metal catalyst but with NaH, to give the *N*-arylamide.[192] The amination of arenes with heteroaromatic amines and hypervalent iodine(III) reagents to give a new arylamine has been reported.[193]

Benzoxazoles are converted to the 2-amino compound by reaction with an amine and a NIS catalyst, with 2 equivalents of acetic acid and 2 equivalents of aq. H_2O_2.[194] Aryl halides reacted with NH_4OH in the presence of a CuI catalyst to give the arylamine.[195] The reaction of aryl halides with secondary amines, catalyzed by a Pd catalyst, with heating and an air-stable ligand, provided the arylamine.[196] Aromatic compounds have been converted to the corresponding arylamine via initial treatment with NBS in the presence of $FeCl_3$ in $(bmim)_2NTf_2$ to form the aryl bromide in situ, and subsequent treatment with an amine in the presence of CuI gave the amine.[197] Arylsilanes reacted with amines in the presence of 3 equivalents of CuI, and 2 equivalents each of Na_2CO_3 and NaF, in the presence of air, to give the arylamine.[198] Aryl halides reacted with amides in the presence of a Pd catalyst to give the corresponding *N*-arylamine.[199] Aryl halides also reacted with amines in the presence of a *N*-heterocyclic carbene Pd catalyst to give the arylamine.[200]

The reaction of heteroarenes with butyllithium and then $ClAlEt_2$ gave the heteroaryl-$AlEt_2$ derivative, and reaction with benzyloxyamines and a Pt catalyst gave the heteroarylamine.[201] Aryl boroxines react with *O*-benzoyl amines with heating and 2 equivalents of K_2CO_3 to give *N*-arylamines.[202] The metal-free anodic oxidation of arenes with pyridine and Bu_4NBF_4 gave the corresponding pyridinium salt, which was heated with piperidine to give the arylamine.[203] Aryl halides have also been coupled to *N*-trimethylsilylamines using a Pd catalyst to give arylamines.[204]

Aryl- and heteroaryl compounds were first treated with an iodonium compound and then an amine, in the presence of a Cu catalyst, to give the arylamine or the heteroarylamine.[205] Aryl or heteroaryl chlorides reacted with amines in the presence of CuI and oxalic diamide ligands to give the arylamine or the heteroarylamine.[206] The Cu-catalyzed reaction of arylboronic acids with aminals has been reported.[207] The Cu-catalyzed reaction of boronic acids and amines is known to give the corresponding arylamine.[208] Aromatic compounds reacted

[191] Zhou, T.; Chen, Z.-C. *Synth. Commun.* ***2002***, *32*, 903.
[192] Tinnis, F.; Stridfeldt, E.; Lundberg, H.; Adolfsson, H.; Olofsson, B. *Org. Lett.* ***2015***, *17*, 2688.
[193] Manna, S.; Serebrennikova, P.O.; Utepova, I.A.; Antonchick, A.P.; Chupakhin, O.N. *Org. Lett.* ***2015***, *17*, 4588.
[194] Wagh, Y.S.; Sawant, D.N.; Bhanage, B.M. *Tetrahedron Lett.* ***2012***, *53*, 3482.
[195] Jung, H.S.; Yun, T.; Cho, Y.; Jeon, H.B. *Tetrahedron* ***2016***, *72*, 5988.
[196] Roiban, G.-D.; Mehler, G.; Reetz, M.T. *Eur. J. Org. Chem.* ***2014***, 2070.
[197] Mostafa, M.A.B.; Calder, E.D.D.; Racys, D.T.; Sutherland, A. *Chem. Eur. J.* ***2017***, *23*, 1044.
[198] Morstein, J.; Kalkman, E.D.; Cheng, C.; Hartwig, J.F. *Org. Lett.* ***2016***, *18*, 5244.
[199] Ma, F.; Xie, X.; Zhang, L.; Peng, Z.; Ding, L.; Fu, L.; Zhang, Z. *J. Org. Chem.* ***2012***, *77*, 5279.
[200] See Chen, W.-C.; Shao, L.-X. *J. Org. Chem.* ***2012***, *77*, 9236.
[201] Yoon, H.; Lee, Y. *J. Org. Chem.* ***2015***, *80*, 10244.
[202] Xiao, Q.; Tian, L.; Tan, R.; Xia, Y.; Qiu, D.; Zhang, Y.; Wang, J. *Org. Lett.* ***2012***, *14*, 4230.
[203] Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* ***2013***, *135*, 5000.
[204] Shimizu, K.; Minami, Y.; Goto, O.; Ikehira, H.; Hiyama, T. *Chem. Lett.* ***2014***, *43*, 438.
[205] Sokolovs, I.; Lubriks, D.; Suna, E. *J. Am. Chem. Soc.* ***2014***, *136*, 6920.
[206] Zhou, W.; Fan, M.; Yin, J.; Jiang, Y.; Ma, D. *J. Am. Chem. Soc.* ***2015***, *137*, 11942.
[207] Zhou, Y.; Xie, Y.; Yang, L.; Xie, P.; Huang, H. *Tetrahedron Lett.* ***2013***, *54*, 2713.
[208] Chan, D.M.T.; Monaco, K.L.; Wang, R.P.; Wintes, M.P. *Tetrahedron Lett.* ***1998***, *39*, 2933; Lam, P.Y.S.; Clark, C.G.; Saubern, S.; Adams, J.; Winters, M.P.; Cha, D.M.T.; Combs, A. *Tetrahedron Lett.* ***1998***, *39*, 2941. For a

with NaN_3 and BF_3—H_2O to give the arylamine.[209] Aryl or heteroaryl chlorides or sulfonate esters reacted with amines with a Ni catalyst to give the corresponding aryl or heteroarylamine.[210]

Tertiary (and to a lesser extent, secondary) aromatic amines can also be prepared in moderate to high yields by amination with an *N*-chlorodialkylamine (or an *N*-chloroalkylamine) and a metallic-ion catalyst (e.g., Fe^{2+}, Ti^{3+}, Cu^{+}, Cr^{2+}) in the presence of sulfuric acid.[211] The attacking species in this case is the aminium radical ion $R_2NH\bullet$ formed by reaction of dialkyammnium chloride and the metal.[212] When an alkyl group is present, attack at the benzylic position competes with ring substitution. Aromatic rings containing only *meta*-directing groups do not give the reaction at all. Fused ring systems react well.[213]

Aryl hydrazines have been prepared by the copper-catalyzed cross-coupling of aryl bromides and hydrazine, in water.[214] The reaction with hydrazine has also been done using continuous flow techniques (Sec. 7.D).[215]

Direct *amidation* can be carried out if an aromatic compound is heated with a hydroxamic acid (RCONHOH) in polyphosphoric acid, but the scope is essentially limited to phenolic ethers.[216] Naphthol reacted with a substituted hydrazine to give the 1-amino derivative.[217] Arenes reacted with 2 equivalents of $TsNH_2$ in the presence of $Cu(OAc)_2$ to give the aryl tosylamide when heated to 130 °C.[218] *N*-Arylbenzamides reacted with *O*-benzoyl hydroxylamines using Pd catalysts to give the *ortho*-dialkylamino *N*-arylbenzamide.[219]

Potassium aryltrifluoroborates were converted to the corresponding arylamine by reaction with NH_4OH in the presence of $CuSO_4$ as the catalyst.[220]

Aryl, vinyl, benzylic, and allyl esters react with phosphorus compounds in the presence of a Ni catalyst gave C—O bond cleavage and formation of the organophosphorus compound.[221] The Cu-catalyzed arylation of secondary phosphine oxides with diaryliodonium salts gave tertiary phosphine oxides with good enantioselectivity.[222] The Ni-catalyzed reaction of aryl iodides and H-phosphinates gave the corresponding aryl phosphinate.[223] Aryl

review, see Rao, K.S.; Wu, T.-S. *Tetrahedron* ***2012***, *68*, 7735. See Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* ***2012***, *51*, 3642; Lalic, G.; Rucker, R.P. *Synlett* ***2013***, *24*, 268.

[209] Surya Prakash, G.K.; Gurung, L.; Marinez, E.R.; Mathew, T.; Olah, G.A. *Tetrahedron Lett.* ***2016***, *57*, 288.

[210] Park, N.H.; Teverovskiy, G; Buchwald, S.L. *Org. Lett.* ***2014***, *16*, 220. For a Pd-catalyst amination reaction of heteroaryl halides, see Park, N.H.; Teverovskiy, G.; Buchwald, S.L. *Org. Lett.* ***2014***, *16*, 220.

[211] See Minisci, F. *Top. Curr. Chem.* ***1976***, *62*, 1 (see pp. 6–16), *Synthesis* ***1973***, 1 (see pp. 2–12), Sosnovsky, G.; Rawlinson, D.J. *Adv. Free-Radical Chem.* ***1972***, *4*, 203 (see pp. 213–238).

[212] See Chow, Y.L. *React. Intermed. (Plenum)* ***1980***, *1*, 151.

[213] See Citterio, A.; Gentile, A.; Minisci, F.; Navarrini, V.; Serravalle, M.; Ventura, S. *J. Org. Chem.* ***1984***, *49*, 4479.

[214] Kurandina, D.V.; Eliseenkov, E.V.; Ilyin, P.V.; Boyarskiy, V.P. *Tetrahedron* ***2014***, *70*, 4043.

[215] DeAngelis, A.; Wang, D.-H.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***2013***, *52*, 3434.

[216] March, J.; Engenito Jr., J.S. *J. Org. Chem.* ***1981***, *46*, 4304. Also see, Cablewski, T.; Gurr, P.A.; Rander, K.D.; Strauss, C.R. *J. Org. Chem.* ***1994***, *59*, 5814.

[217] Tang, Q.; Zhang, C.; Luo, M. *J. Am. Chem. Soc.* ***2008***, *130*, 5840.

[218] Zhang, M.; Zhang, A. *Synthesis* ***2012***, *44*, 1.

[219] Yoo, E.J.; Ma, S.; Mei, T.-S.; Chan, K.S.L.; Yu, J.-Q. *J. Am. Chem. Soc.* ***2011***, *133*, 7652.

[220] Liesen, A.P.; Silva, A.T.; Sousa, J.C.; Menezes, P.H.; Oliveira, R.A. *Tetrahedron Lett.* ***2012***, *53*, 4240. Also see Kuik, D.; McCubbin, J.A.; Tranmer, G.K. *Synthesis* ***2017***, *49*, 2555.

[221] Yang, J.; Chen, T.; Han, L.-B. *J. Am. Chem. Soc.* ***2015***, *137*, 1782.

[222] Beaud, R.; Phipps, R.J.; Gaunt, M.J. *J. Am. Chem. Soc.* ***2016***, *138*, 13183. Xu, J.; Zhang, P.; Gao, Y.; Chen, Y.; Tang, G.; Zhao, Y. *J. Org. Chem.* ***2013***, *78*, 8176.

[223] Kinbara, A.; Ito, M.; Abe, T.; Yamagishi, T. *Tetrahedron* ***2015***, *71*, 7614. See Jablokai, E.; Keglevich, G. *Org. Prep. Proceed. Int.* ***2014***, *46*, 281.

iodides reacted with Ph_2PCl using $PdCl_2$ and tetrabutylammonium bromide to give the corresponding arylphosphine.[224] 4-Tosyl or mesyl functionalized aryl derivatives reacted with phosphites in the presence of a Pd catalyst to give the phosphorylated aryl derivative.[225]

Also see, **13-5**, **13-16**.

11-5 Direct Introduction of the Diazonium Group

$$\mathrm{ArH} \xrightarrow[\mathrm{HX}]{2\ \mathrm{HONO}} \mathrm{ArN_2^+\ X^-}$$

Diazonium salts can be prepared directly by replacement of an aromatic hydrogen without the necessity of going through the amino group.[226] The reaction is essentially limited to active substrates (amines and phenols), since otherwise poor yields are obtained. Since the reagents and the substrate are the same as in reaction **11-3**, the first species formed is the nitroso compound. In the presence of excess nitrous acid, this is converted to the diazonium ion.[227] A synthesis of solid aryldiazonium chlorides is now available.[228] Aryldiazomethanes have been prepared using continuous flow synthesis (sec.7.D).[229]

11-6 Diazonium Coupling

$$\mathrm{ArH} + \mathrm{Ar'N_2^+} \longrightarrow \mathrm{Ar{-}N{=}N{-}Ar'}$$

Aromatic diazonium ions normally couple only with active substrates such as amines and phenols.[230] Many of the products of this reaction are used as dyes (*azo dyes*).[231] The mechanism of (*Z/E*)-isomerization in Ar—N=N—Ar systems has been studied.[232] Substitution is mostly *para* to the activating group, unless that position is already occupied, in which case *ortho* substitution takes place. The pH of the solution is important both for phenols and amines. For amines, the solutions may be mildly acidic or neutral. The fact that amines give *ortho* and *para* products shows that even in mildly acidic solution they react in their un-ionized form. If the acidity is too high, the reaction does not occur, because the concentration of free amine becomes too small. Phenols must be coupled in slightly alkaline solution where they are converted to the more reactive phenoxide ions, because phenols themselves are not active enough for the reaction. However, neither phenols nor amines react in moderately alkaline solution, because the diazonium ion is converted to a diazo hydroxide Ar—N=N—OH.

[224] Nowrouzi, N.; Keshtgar, S.; Jahromi, E.B. *Tetrahedron Lett.* ***2016***, *57*, 348.
[225] Fu, W.C.; So, C.M.; Kwong, F.Y. *Org. Lett.* ***2015***, *17*, 5906.
[226] Tedder, J.M. *J. Chem. Soc.* ***1957***, 4003.
[227] Kamalova, F.R.; Nazarova, N.E.; Solodova, K.V.; Yaskova, M.S. *J. Org. Chem. USSR* ***1988***, *24*, 1004.
[228] Mohamed, S.K.; Gomaa, M.A.-M.; El-Din, A.M.N. *J. Chem. Res. (S)* ***1997***, 166.
[229] Lévesque, É.; Laporte, S.T.; Charette, A.B. *Angew. Chem. Int. Ed.* ***2017***, *56*, 837.
[230] See Szele, I.; Zollinger, H. *Top. Curr. Chem.* ***1983***, *112*, 1; Hegarty, A.F. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 2, Wiley, NY, ***1978***, pp. 545–551.
[231] See Zollinger, H. *Color Chemistry*, VCH, NY, ***1987***, pp. 85–148; Gordon, P.F.; Gregory, P. *Organic Chemistry in Colour*, Springer, NY, ***1983***, pp. 95–162.
[232] Asano, T.; Furuta, H.; Hofmann, H.-J.; Cimiraglia, R.; Tsuno, Y.; Fujio, M. *J. Org. Chem.* ***1993***, *58*, 4418.

Primary and secondary amines face competition from attack at the nitrogen.[233] However, the resulting *N*-azo compounds (aryl triazenes) can be isomerized to *C*-azo compounds (**11-30**). In at least some cases, even when the *C*-azo compound is isolated, it is the result of initial *N*-azo compound formation followed by isomerization. It is therefore possible to synthesize the *C*-azo compound directly in one laboratory step.[234] Acylated amines and phenolic ethers and esters are ordinarily not active enough for this reaction, though it is sometimes possible to couple them (as well as such polyalkylated benzenes as mesitylene and pentamethylbenzene) to diazonium ions containing electron-withdrawing groups in the *para* position, since such groups increase the concentration of the positive charge and thus the electrophilicity of the ArN_2^+. Phase-transfer catalysis has also been used.[235]

Coupling of a few aliphatic diazonium compounds to aromatic rings has been reported, involving cyclopropanediazonium ions and bridgehead diazonium ions, in which loss of N_2 would lead to very unstable carbocations.[236]

OS **I**, 49, 374; **II**, 35, 39, 145.

C. Sulfur Electrophiles

11-7 Sulfonation

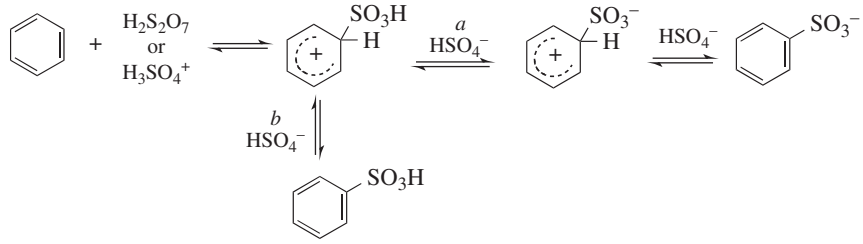
$$ArH + H_2SO_4 \longrightarrow ArSO_2OH$$

Aromatic derivatives are converted to the corresponding aryl sulfonic acid. The sulfonation reaction is very broad in scope and many aromatic hydrocarbons (including fused ring systems), aryl halides, ethers, carboxylic acids, amines,[237] acylated amines, ketones, nitro compounds, and sulfonic acids have been sulfonated.[238] Phenols can also be successfully sulfonated, but attack at oxygen may compete.[239] Sulfonation is often accomplished with concentrated sulfuric acid, but it can also be done with fuming sulfuric acid, SO_3,[240] $ClSO_2OH$, $ClSO_2NMe_2/In(OTf)_3$,[241] or other reagents.[242] A $FeCl_3$-based ionic liquid has been used for the sulfonation of aromatic compounds.[243] Since this is a reversible reaction (see **19-74**), it may be necessary to drive the reaction to completion. However, at low temperatures the reverse reaction is very slow and the forward reaction is practically irreversible.[244] Sulfur trioxide reacts much more rapidly than sulfuric acid with benzene; the reaction is nearly instantaneous. Sulfones are often side products. When sulfonation is carried out on a benzene ring containing four or five alkyl and/or halogen groups, rearrangements usually occur (see **11-36**). The mechanism has been discussed, comparing a concerted mechanism versus

[233] See Penton, J.R.; Zollinger, H. *Helv. Chim. Acta* ***1981***, *64*, 1717, 1728.
[234] Kelly, R.P.; Penton, J.R.; Zollinger, H. *Helv. Chim. Acta* ***1982***, *65*, 122.
[235] Hashida, Y.; Kubota, K.; Sekiguchi, S. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 905.
[236] See Szele, I.; Zollinger, H. *Top. Curr. Chem.* ***1983***, *112*, 1 (see pp. 3–6).
[237] See Khelevin, R.N. *J. Org. Chem. USSR* ***1987***, *23*, 1709; ***1988***, *24*, 535 and references cited therein.
[238] See Nelson, K.L. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1355–1392; Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 62–83, 87–124.
[239] See de Wit, P.; Woldhuis, A.F.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1988***, *107*, 668.
[240] Bisseret, P.; Blanchard, N. *Org. Biomol. Chem.* ***2013***, *11*, 5393.
[241] Frost, C.G.; Hartley, J.P.; Griffin, D. *Synlett* ***2002***, 1928.
[242] See Hajipour, A.R.; Mirjalili, B.B.F.; Zarei, A.; Khazdooz, L.; Ruoho, A.E. *Tetrahedron Lett.* ***2004***, *45*, 6607.
[243] Bahrami, K.; Khodei, M.M.; Shahbazi, F. *Tetrahedron Lett.* ***2008***, *49*, 3931.
[244] Spryskov, A.A. *J. Gen. Chem. USSR* ***1960***, *30*, 2433.

the S_EAr mechanism.[245] Molecular mechanics showed that in nonpolar media and "in the absence of catalysts the mechanism of aromatic sulfonation with a single SO_3 is concerted and does not involve the conventionally depicted 1:1 σ complex (Wheland) intermediate. In polar, higher dielectric SO_3-complexing media, the calculations favor an S_EAr mechanism for the 2:1 reaction involving a Wheland-type arene-$(SO_3)_2$ dimer intermediate."[245]

A great deal of work has been done on the mechanism,[246] chiefly by Cerfontain and co-workers. Mechanistic study is made difficult by the complicated nature of the solutions. Indications are that the electrophile varies with the reagent, though SO_3 is involved in all cases, either free or combined with a carrier. In aqueous H_2SO_4 solutions, the electrophile is thought to be $H_3SO_4^+$ (or a combination of H_2SO_4 and H_3O^+) at concentrations below ~80–85% H_2SO_4, and $H_2S_2O_7$ (or a combination of H_2SO_4 and SO_3) at concentrations higher than this[247] (the changeover point varies with the substrate[248]). Evidence for a change in electrophile is that in both the dilute and the concentrated solutions the rate of the reaction was proportional to the activity of $H_3SO_4^+$ and $H_2S_2O_7$, respectively. Further evidence is that with toluene as substrate the two types of solution gave very different *ortho*/*para* ratios. The mechanism is essentially the same for both electrophiles and may be shown as:[247]



The other product of the first step is HSO_4^- or H_2O from $H_2S_2O_7$ or $H_3SO_4^+$, respectively. Path *a* is the principal route, except at very high H_2SO_4 concentrations, when path *b* becomes important. With $H_3SO_4^+$ the first step is rate determining under all conditions, but with $H_2S_2O_7$ the first step is the slow step only up to ~96% H_2SO_4, when a subsequent proton transfer becomes partially rate determining.[249] The $H_2S_2O_7$ is more reactive than $H_3SO_4^+$. In fuming sulfuric acid (H_2SO_4 containing excess SO_3), the electrophile appears to be dependent on the concentration.[250] Finally, when pure SO_3 is the reagent in aprotic solvents, SO_3 itself is the actual electrophile.[251] Free SO_3 is the most reactive of all these species, so that attack here is generally fast and a subsequent step is usually rate determining, at least in some solvents.

OS **II**, 42, 97, 482, 539; **III**, 288, 824; **IV**, 364; **VI**, 976.

[245] Koleva, G.; Galabov, B.; Kong, J.; Schaefer III, H.F.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***2011***, *133*, 19094.

[246] Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Wiley, NY, ***1968***. See Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1985***, *104*, 153; Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 56–77.

[247] Cerfontain, H.; Lambrechts, H.J.A.; Schaasberg-Nienhuis, Z.R.H.; Coombes, R.G.; Hadjigeorgiou, P.; Tucker, G.P. *J. Chem. Soc., Perkin Trans. 2* ***1985***, 659 and references cited therein.

[248] See Kaandorp, A.W.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1969***, *88*, 725.

[249] Kort, C.W.F.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1967***, *86*, 865.

[250] Koeberg-Telder, A.; Cerfontain, H. *J. Chem. Soc., Perkin Trans. 2* ***1973***, 633.

[251] Lammertsma, K.; Cerfontain, H. *J. Chem. Soc., Perkin Trans. 2* ***1980***, 28 and references cited therein.

11-8 Halosulfonation

$$ArH + ClSO_2OH \longrightarrow ArSO_2Cl$$

Aromatic sulfonyl chlorides can be prepared directly, by treatment of aromatic rings with chlorosulfuric acid.[252] Since sulfonic acids can also be prepared by the same reagent (**11-7**), it is likely that they are intermediates, being converted to the halides by excess chlorosulfuric acid.[253] The reaction has also been effected with bromo- and fluorosulfuric acids. Sulfinyl chlorides (ArSOCl) have been prepared by the reaction of thionyl chloride and an aromatic compound on Montmorillonite K-10 clay.[254]

OS **I**, 8, 85.

11-9 Sulfonylation

$$ArH + SOCl_2 \xrightarrow{TfOH} ArSOAr$$

$$ArH + Ar'SO_2Cl \xrightarrow{AlCl_3} ArSO_2Ar'$$

Diaryl sulfoxides can be prepared by the reaction of aromatic compounds with thionyl chloride and triflic acid.[255] Diaryl sulfones have also been prepared using thionyl chloride with the ionic liquid [bmim]Cl•$AlCl_3$.[256] Diaryl sulfones can be formed by treatment of aromatic compounds with aryl sulfonyl chlorides and a *Friedel-Crafts catalyst.*[257] This reaction is analogous to *Friedel-Crafts acylation* with carboxylic acid halides (**11-17**). In a better procedure, the aromatic compound is treated with an aryl sulfonic acid and P_2O_5 in polyphosphoric acid.[258] Indium *tris*(triflate)[259] and indium trichloride[260] lead to sulfonation of aromatic compounds in the presence of sulfonyl chlorides. Indium bromide was used with indoles.[261] A ferric chloride-catalyzed reaction with microwave irradiation has also been reported,[262] as has the use of zinc metal with microwave irradiation.[263] The reaction can be extended to the preparation of alkyl aryl sulfones by the use of a sulfonyl fluoride.[264]

[252] For a review, see Gilbert, E.E. *Sulfonaton and Related Reactions*, Wiley, NY, ***1965***, pp. 84–87.
[253] See van Albada, M.P.; Cerfontain, H. *J. Chem. Soc., Perkin Trans. 2* ***1977***, 1548, 1557.
[254] Karade, N.N.; Kate, S.S.; Adude, R.N. *Synlett* ***2001***, 1573.
[255] Olah, G.A.; Marinez, E.R.; Prakash, G.K.S. *Synlett* ***1999***, 1397.
[256] See Mohile, S.S.; Potdar, M.K.; Salunkhe, M.M. *Tetrahedron Lett.* ***2003***, *44*, 1255.
[257] See Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 77–83; Jensen, F.R.; Goldman, G. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1319–1347.
[258] Sipe Jr., H.J.; Clary, D.W.; White, S.B. *Synthesis* ***1984***, 283. See also, Ueda, M.; Uchiyama, K.; Kano, T. *Synthesis* ***1984***, 323.
[259] Frost, C.G.; Hartley, J.P.; Whittle, A.J. *Synlett* ***2001***, 830.
[260] Garzya, V.; Forbes, I.T.; Lauru, S.; Maragni, P. *Tetahedron Lett.* ***2004***, *45*, 1499.
[261] Yadav, J.S.; Reddy, B.V.S.; Krishna, A.D.; Swamy, T. *Tetahedron Lett.* ***2003***, *44*, 6055.
[262] Marquié, J.; Laporterie, A.; Dubac, J.; Roques, N.; Desmurs, J.-R. *J. Org. Chem.* ***2001***, *66*, 421.
[263] Bandgar, B.P.; Kasture, S.P. *Synth. Commun.* ***2001***, *31*, 1065.
[264] Hyatt, J.A.; White, A.W. *Synthesis* ***1984***, 214.

Indole-2-sulfones were prepared by reaction of indoles with sodium alkylsufonates in the presence of molecular iodine.[265] 2-Sulfuonyl indoles were also prepared by the reaction of indoles with *N*-sulfonyl hydrazines with an iodine catalyst and 2 equivalents of TBHP.[266] 2-Aryloxypyridines reacted with benzenesulfonyl chloride in the presence of $Pd(OAc)_2$, K_2CO_3, and MS 4Å to give the 2-aryloxypuridin *ortho*-phenylsulfone.[267] 8-Acylamino quinolines reacted with arylsulfonyl chlorides in the presence of a CuBr catalyst and 2 equivalents of K_2CO_3 at 10 °C to give the 5-arylsulfone derivative.[268]

Direct formation of diaryl sulfones from benzenesulfonic acid and benzene used Nafion-H.[269] Aryl halides react with sulfinic acid salts via a proline-promoted CuI-catalyzed coupling reaction.[270] Arylboronic acids (see **10-73**) are sulfonated in ionic liquids, using a Cu catalyst.[271]

It is noted that vinyl sulfones were prepared by the Pd-catalyzed reaction of alkenes with organosulfonyl chlorides.[272]

OS **X**, 147.

D. Halogen Electrophiles

11-10 Halogenation[273]

$$\mathrm{ArH} + \mathrm{X_2} \xrightarrow[\mathrm{X = Cl,\ Br,\ I,\ F}]{\text{Catalyst}} \mathrm{Ar - X}$$

Many halogenation techniques have been reported via a S_EAr mechanism or a transition metal-catalyzed reaction. Ecofriendly halogenation techniques have been reviewed.[274]

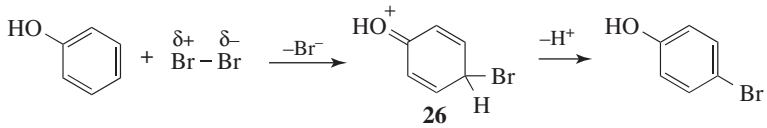
Chlorine[275] and Bromine[276] Aromatic compounds can be brominated or chlorinated by treatment with bromine or chlorine in the presence of a catalyst.[277] For amines and phenols the reaction is so rapid that it is carried out with a dilute solution of Br_2 or Cl_2 in water at room temperature, or with aqueous HBr in DMSO.[278] Typically, it is not possible to stop

[265] Katrun, P.; Mueangkaew, C.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D.; Kuhakarn, C. *J. Org. Chem.* ***2014***, *79*, 1778.
[266] Rahaman, R.; Barman, P. *Synlett* ***2017***, *28*, 684.
[267] Xu, Y.; Liu, P.; Li, S.-L.; Sun, P. *J. Org. Chem.* ***2015***, *80*, 1269.
[268] Wei, J.; Jiang, J.; Xiao, X.; Lin, D.; Deng, Y.; Ke, Z.; Jiang, H.; Zeng, W. *J. Org. Chem.* ***2016***, *81*, 946. Also see Li, J.-M.; Weng, J.; Lu, G.; Chan, A.S.C. *Tetrahedron Lett.* ***2016***, *57*, 2121.
[269] Olah, G.A.; Mathew, T.; Prakash, G.K.S. *Chem. Commun.* ***2001***, 1696.
[270] Zhu, W.; Ma, D. *J. Org. Chem.* ***2005***, *70*, 2696.
[271] Kantam, M.L.; Neelima, B.; Sreedhar, B.; Chakravarti, R. *Synlett* ***2008***, 1455.
[272] Xu, Y.-H.; Wang, M.; Lu, P.; Loh, T.-P. *Tetrahedron* ***2013***, *69*, 4403.
[273] See de la Mare, P.B.D. *Electrophilic Halogenation*, Cambridge University Press, Cambridge, ***1976***; Braendlin, H.P.; McBee, E.T. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1517–1593. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 619–628.
[274] Kandepi, V.V.K.M.; Narender, N. *Synthesis* ***2012***, *44*, 15.
[275] For electrophilicities of chlorinating agents, Duan, X.-H.; Mayr, H. *Org. Lett.* ***2010***, *12*, 2238.
[276] For a computational study of the electrophilie affinity for the bromination of arenes, see Galabov, B.; Koleva, G.; Schaefer III, H.F.; Schleyer, P.v.R. *J. Org. Chem.* ***2010***, *75*, 2813.
[277] For a site-directed bromination using an electrochemical method, see Raju, T.; Kulangiappar, K.; Kulandainathan, M.A.; Malini, U.U.R.; Muthukumaran, A *Tetrahedron Lett.* ***2006***, *47*, 4581.
[278] Srivastava, S.K.; Chauhan, P.M.S.; Bhaduri, A.P. *Chem. Commun.* ***1996***, 2679.

the reaction with anilines before all the available *ortho* and *para* positions are substituted, because the initially formed haloamines are weaker bases than the original amines and are less likely to be protonated by the liberated HX.[279] For this reason, the corresponding anilides (*N*-acylaniline derivatives) are used if monosubstitution is desired. With phenols it is possible to stop after one group has entered.[280] The rapid room-temperature reaction with amines and phenols is often used as a test for these compounds. In general, for active substrates (including anilines, phenols, naphthalene, and polyalkylbenzenes[281] such as mesitylene and isodurene), no catalyst is needed. The overall effectiveness of reagents in aromatic substitution is $Cl_2 > BrCl > Br_2 > ICl > I_2$. A mixture of $ZnBr_2$/diazene has been suggested for the regioselective *para* bromination of activated aromatic substrates.[282]

When chlorination or bromination is carried out at high temperatures (e.g., 300–400 °C), *ortho*/*para*-directing groups direct *meta* and vice versa.[283] A different mechanism operates here, which is not completely understood. It is also possible for bromination to take place by the S_E1 mechanism. An example is the *t*-BuOK-catalyzed bromination of 1,3,5-tribromobenzene.[284]

For reactions in the absence of a catalyst, the reactive species is Br_2 or Cl_2 that has been polarized by the ring (remember that halogens are polarizable).[285] Evidence for molecular chlorine or bromine as the attacking species in these cases is that acids, bases, and other ions, especially chloride ion, accelerate the rate about equally, though if chlorine dissociated into Cl^+ and Cl^-, the addition of chloride should decrease the rate and the addition of acids should increase it. Intermediate **26** has been detected spectrally in the aqueous bromination of phenol.[286]



For less activated aromatic rings, Fe was commonly used at one time for halogenation, but the real catalyst was shown not to be the iron itself, but rather the $FeBr_3$ or $FeCl_3$ formed in small amounts from the reaction between iron and the reagent. Indeed, ferric chloride and other Lewis acids are typically directly used as catalysts, as is iodine. Many Lewis acids can be used, including thallium(III) acetate, which promotes bromination with high regioselectivity *para* to an *ortho*/*para*-directing group.[287]

[279] See Berthelot, J.; Guette, C.; Desbène, P.; Basselier, J.; Chaquin, P.; Masure, D. *Can. J. Chem.* ***1989***, *67*, 2061. For another procedure, see Onaka, M.; Izumi, Y. *Chem. Lett.* ***1984***, 2007.

[280] See Brittain, J.M.; de la Mare, P.B.D. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 1, Wiley, NY, ***1983***, pp. 522–532.

[281] See Baciocchi, E.; Illuminati, G. *Prog. Phys. Org. Chem.* ***1967***, *5*, 1.

[282] Stropnik, T.; Bombek, S.; Kočevar, M.; Polanc, S. *Tetrahedron Lett.* ***2008***, *49*, 1729.

[283] See Kooyman, E.C. *Pure. Appl. Chem.* ***1963***, *7*, 193.

[284] Mach, M.H.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1974***, *96*, 936.

[285] See de la Mare, P.B.D., *Electrophilic Halogenation*, Cambridge University Press, Cambridge, ***1976***; de la Mare, P.B.D.; Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 83–139. See also, Tee, O.S.; Paventi, M.; Bennett, J.M. *J. Am. Chem. Soc.* ***1989***, *111*, 2233.

[286] Tee, O.S.; Iyengar, N.R.; Paventi, M. *J. Org. Chem.* ***1983***, *48*, 759. See also, Tee, O.S.; Iyengar, N.R. *Can. J. Chem.* ***1990***, *68*, 1769.

[287] McKillop, A.; Bromley, D.; Taylor, E.C. *J. Org. Chem.* ***1972***, *37*, 88.

When a Lewis-acid catalyst[288] is used with chlorine or bromine, the attacking entity may be Cl^+ or Br^+, formed by $FeCl_3 + Br_2 \rightarrow FeCl_3Br^- + Br^+$, or it may be Cl_2 or Br_2. With other reagents, the attacking entity in brominations may be Br^+ or a species, such as H_2OBr^+ (the conjugate acid of HOBr), in which H_2O is a carrier of Br^+.[289]

Other reagents can be used to promote chlorination or bromination. The Cu-catalyzed chlorination has been reported using dioxygen as an oxidant.[290] *N*-Bromosuccinimide (NBS) under photochemical conditions[291] brominates aromatic compounds, as does pyridinium bromide perbromide,[292] and NBS in acetic acid with ultrasound is effective.[293] Both NCS and NBS with aqueous BF_3 gave the respective chloride or bromide.[294] NBS in an ionic liquid[295] gave the brominated aromatic, and *para* bromination of aniline was reported by mixing aniline with the ionic liquid, bmim Br_2.[296] Similarly, hmim Br_3,[297] without another reagent, is a brominating agent. Majetich and co-workers reported the use of HBr/DMSO for the remarkably selective bromination of aniline.[298] Highly *para*-selective bromination was accomplished using dioxane dibromide, under solvent-free conditions.[299]

If the substrate contains alkyl groups, side-chain halogenation (**14-1**) is possible with most of the reagents mentioned above, including chlorine and bromine. Since side-chain halogenation is catalyzed by light, the reactions should be run in the absence of light wherever possible. Sulfuryl chloride (SO_2Cl_2) in acetic acid chlorinates anisole derivatives.[300] A mixture of KCl and Oxone chlorinated activated aromatic compounds[301] and *para* bromination of anisole was reported using KBr[302] or NH_4Br.[303] Conversion of aniline to the *N*-$SnMe_3$ derivative allowed *in situ* bromination with bromine, with high *para* selectivity after conversion to the free amine with aqueous KF.[304]

Both bromination[305] and iodination[306] of arenes have been reviewed. Arenes have been converted to *ortho* halo derivatives by reaction with NBS or NIS in the presence of Rh catalyst.[307] Aryl chlorides and aryl bromides are formed by the reaction of aryl triflates

[288] See also, Zhang, Y.; Shibatomi, K.; Yamamoto, H. *Synlett* ***2005***, 2837.
[289] See Rao, T.S.; Mali, S.I.; Dangat, V.T. *Tetrahedron* ***1978***, *34*, 205.
[290] Chen, X.; Hao, X.-S.; Goodhue, C.E.; Yu, J.-Q. *J. Am. Chem. Soc.* ***2006***, *128*, 6790.
[291] Chhattise, P.K.; Ramaswamy, A.V.; Waghmode, S.B. *Tetrahedron Lett.* ***2008***, *49*, 189.
[292] Reeves, W.P.; Lu, C.V.; Schulmeier, B.; Jonas, L.; Hatlevik, O. *Synth. Commun.* ***1998***, *28*, 499. Also see, Bisarya, S.C.; Rao, R. *Synth. Commun.* ***1993***, *23*, 779.
[293] Paul, V.; Sudalai, A.; Daniel, T.; Srinivasan, K.V. *Synth. Commun.* ***1995***, *25*, 2401.
[294] Prakash, G.K.S.; Mathew, T.; Hoole, D.; Esteves, P.M.; Wang, Q.; Rasul, G.; Olah, G.A. *J. Am. Chem. Soc.* ***2004***, *126*, 15770. Also see Andersh, B.; Murphy, D.L.; Olson, R.J. *Synth. Commun.* ***2000***, *30*, 2091.
[295] See Rajagopal R.; Jarikote, D.V.; Lahoti, R.J.; Daniel, T.; Srinivasan, K.V. *Tetrahedron Lett.* ***2003***, *44*, 1815. For a reaction in Bu_4NBr, see Ganguly, N.C.; De, P.; Dutta, S. *Synthesis* ***2005***, 1103.
[296] See Lei, Z.-G.; Chen, Z.-C.; Hu, Y.; Zheng, Q.-G. *Synthesis* ***2004***, 2809.
[297] See Chiappe, C.; Leandri, E.; Pieraccini, D. *Chem. Commun.* ***2004***, 2536.
[298] Majetich, G.; Hicks, R.; Reister, S. *J. Org. Chem.* ***1997***, *62*, 4321.
[299] Chaudhuri, S.K.; Roy, S.; Saha, M.; Bhar, S. *Synth. Commun.* ***2007***, *37*, 581.
[300] Yu, G.; Mason, H.J.; Wu, X.; Endo, M.; Douglas, J.; Macor, J.E. *Tetrahedron Lett.* ***2001***, *42*, 3247.
[301] Narender, N.; Srinivasu, P.; Kulkarni, S.J.; Raghavan, K.V. *Synth. Commun.* ***2002***, *32*, 279.
[302] Tamhankar, B.V.; Desai, U.V.; Mane, R.B.; Wadgaonkar, P.P.; Bedekar, A.V. *Synth. Commun.* ***2001***, *31*, 2021.
[303] Arun Kumar, M.; Rohitha, C.N.; Kulkarni, S.J.; Narender, N. *Synthesis* ***2010***, 1629.
[304] Smith, M.B.; Guo, L.; Okeyo, S.; Stenzel, J.; Yanella, J.; La Chapelle, E. *Org. Lett.* ***2002***, *4*, 2321. A polymeric Sn reagent has been developed for this purpose, see Chrétien, J.-M.; Zammattio, F.; Le Grognec, E.; Paris, M.; Cahingt, B.; Montavon, G.; Quintard, J.-P. *J. Org. Chem.* ***2005***, *70*, 2870.
[305] Voskressensky, L.G.; Golantsov, N.E.; Maharramov, A.M. *Synthesis* ***2016***, *48*, 615.
[306] Sloan, N.L.; Sutherland, A. *Synthesis* ***2016***, *48*, 2869.
[307] Schröder, N.; Delord, J.W.; Frank Glorius, F. *J. Am. Chem. Soc.* ***2012***, *134*, 8298.

with KCl or KBr, with a Pd catalyst and the addition of 0.5 equivalents of KF.[308] Arenes reacted with NBS or NIS to give the corresponding aryl halide with ball milling, without solvent, catalyst, or additives.[309] Arylboronic acids reacted with iodide or bromide to give aryl bromides or aryl iodides with a $CuBr_2$ catalyst in the presence of oxygen.[310]

The Ir-catalyzed borylation of arenes led to *meta* halogenation.[311] Certain alkylated phenols can be brominated in the *meta* positions with Br_2 in the superacid solution SbF_5—HF.[312] It is likely that the *meta* orientation is the result of conversion by the superacid of the OH group to the OH_2^+ group, which should be *meta* directing because of its positive charge. Bromination and the *Sandmeyer reaction* (**13-22**) can be carried out in one laboratory step to give 3,4,5-tribromonitrobenzene by treatment of an aromatic primary amine with $CuBr_2$ and *tert*-butyl nitrite.[313] With deactivated aromatic derivatives, NBS and sulfuric acid is an effective reagent, giving the *meta*-brominated product.[314] Bromination at C-6 of 2-aminopyridine was accomplished with NBS.[315]

Aryl and heteroaryl bromides have been converted to the corresponding chloride with Me_4NCl and a Cu_2O catalyst.[316] The *ortho* chlorination of phenols has been reported by reaction with SO_2Cl_2 in the presence of 2,2,6,6-tetramethylpiperidine.[317] The bromination of arenes was reported using an ionic liquid as both the catalyst and the solvent.[318] The reaction of 2-phenylpyridine with NBS or Br_2, with a Ru catalyst and a catalytic amount of mesitoic acid, gave 1-pyridyl-3-bromobenzene.[319]

Furan and thiophene are known to polymerize in the presence of strong acids, both Brønsted-Lowry and Lewis. For such highly reactive heteroaromatic systems, alternative halogenating reagents are commonly used. Furan was converted to 2-bromofuran with a bromine•dioxane complex, for example, at <0 °C.[320] 3-Butylthiophene reacted with NBS/acetic acid to give 2-bromo-3-butylthiophene.[321] With NBS and a catalytic amount of PBr_3 at −78 °C to −10 °C, *N*-methylpyrrole gave *N*-methyl-3-bromopyrrole.[322]

Iodine Iodine is the least reactive of the halogens in aromatic substitution.[323] Except for active substrates, an oxidizing agent must normally be present to oxidize I_2 to a better electrophile.[324] Examples of such oxidizing agents used with I_2 are HNO_3, hypervalent

[308] Pan, J.; Wang, X.; Zhang, Y.; Buchwald, S.L. *Org. Lett.* ***2011***, *13*, 4974.
[309] Bose, A.; Mal, P. *Tetrahedron Lett.* ***2014***, *55*, 2154.
[310] Zhang, G.; Lv, G.; Li, L.; Chen, F.; Cheng, J. *Tetrahedron Lett.* ***2011***, *52*, 1993.
[311] Murphy, J.M.; Liao, X.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2007***, *129*, 15434.
[312] Jacquesy, J.; Jouannetaud, M.; Makani, S. *J. Chem. Soc., Chem. Commun.* ***1980***, 110.
[313] Doyle, M.P.; van Lente, M.A.; Mowat, R.; Fobare, W.F. *J. Org. Chem.* ***1980***, *45*, 2570.
[314] Rajesh, K.; Somasundaram, M.; Saiganesh, R.; Balasubramanian, K.K. *J. Org. Chem.* ***2007***, *72*, 5867.
[315] Cañibano, V.; Rodríguez, J.F.; Santos, M.; Sanz-Tejedor, A.; Carreño, M.C.; González, G.; García-Ruano, J.L. *Synthesis* ***2001***, 2175.
[316] Feng, X.; Qu, Y.; Han, Y.; Yu, X.; Bao, M.; Yamamoto, Y. *Chem. Commun.* ***2012***, *48*, 9468.
[317] Saper, N.I.; Snider, B.B. *J. Org. Chem.* ***2014***, *79*, 809.
[318] Ren, Y.-L.; Wang, B.; Tian, X.-Z.; Zhao, S.; Wang, J. *Tetrahedron Lett.* ***2015***, *56*, 6452.
[319] Teskey, C.J.; Lui, Y.W.; Greaney, M.F. *Angew. Chem. Int. Ed.* ***2015***, *54*, 11677.
[320] See Baciocchi, E.; Clementi, S.; Sebastiani, G.V. *J. Chem. Soc., Chem. Commun.* ***1975***, 875.
[321] Hoffmann, K.J.; Carlsen, P.H.J. *Synth. Commun.* ***1999***, *29*, 1607.
[322] Dvornikova, E.; Kamienska-Trela, K. *Synlett* ***2002***, 1152.
[323] See Pizey, J.S. in Pizey, J.S. *Synthetic Reagents,* Vol. 3, Wiley, NY, ***1977***, pp. 227–276. For a review of aromatic iodination, see Merkushev, E.B. *Synthesis* ***1988***, 923.
[324] Butler, A.R. *J. Chem. Educ.* ***1971***, *48*, 508.

iodine compounds such as $PhI(OTf)_2$,[325] $NaIO_4$,[326] NH_4I and H_2O_2,[327] and a mixture of $NaIO_4$/KI/NaCl.[328] The reagent ICl is a better iodinating agent than iodine itself.[329] A mixture of $ICl/In(OTf)_3$ has also been used.[330] Iodination can also be accomplished by treatment of the substrate with KI/KIO_3 in aqueous methanol,[331] and NaI with an Fe catalyst.[332]

A solvent-free iodination was accomplished using $NaICl_2$ and an *N*-bromoammonium salt.[333] A solvent-free iodination used I_2 and $AgNO_3$.[334] Another solvent-free iodination used I_2 with $Bi(NO_3)_3$ on silica gel.[335] A mixture of iodine/pyridine/dioxane leads to selective *para* iodination of aniline derivatives.[336] Selective *ortho* cyanation allows the reaction with iodine to give the corresponding aryl iodide.[337] *N*-Iodosuccinimide and *p*-toluenesulfonic acid give regioselective iodination of phenol and related compounds.[338]

The actual attacking species is less clear than with bromine or chlorine. Iodine itself is too unreactive. This is except for active species such as phenols, where there is good evidence that I_2 is the attacking entity.[339] There is evidence that AcOI may be the reactive entity when peroxyacetic acid is the oxidizing agent,[340] and I_3^+ when SO_3 or HIO_3 is the oxidizing agent.[341] The I^+ ion has been implicated in several procedures.[342] For an indirect method for accomplishing aromatic iodination, see **12-30**.

Benzamides and α-arylacetamides reacted with I_2 and CsOAc with a Pd catalyst to give the corresponding *ortho* iodide.[343] Aryl iodides were prepared from arenes by reaction with NIS and $AgNTf_2$ as catalyst.[344] Aromatic compounds have been converted to aryl iodides by reaction with NIS and $FeCl_3$/(bmim)NTf_2.[345] Toluene reacted with iodo-saccharin in (bmim)BF_4 to give 4-iodotoluene.[346] Arylboronic acids were converted to the corresponding aryl iodide by reaction with molecular iodine and KF.[347] Arylboronic acids also reacted

[325] Panunzi, B.; Rotiroti, L.; Tingoli, M. *Tetrahedron Lett.* ***2003***, *44*, 8753.
[326] Lulinski, P.; Skulski, L. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 951.
[327] Narender, N.; Reddy, K.S.R.; Krishna Mohan, K.V.V.; Kulkarni, S.J. *Tetrahedron Lett.* ***2007***, *48*, 6124.
[328] Emmanuvel, L.; Shukla, R.K.; Sudalai, A.; Gurunath, S.; Sivaram, S. *Tetrahedron Lett.* ***2006***, *47*, 4793.
[329] See McCleland, C.W. in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 85–164; Mukaiyama, T.; Kitagawa, H.; Matsuo, J.-i. *Tetrahedron Lett.* ***2000***, *41*, 9383.
[330] Johnsson, R.; Meijer, A.; Ellervik, U. *Tetrahedron* ***2005***, *61*, 11657.
[331] Adimurthy, S.; Ramachandraiah, G.; Ghosh, P.K.; Bedekar, A.V. *Tetrahedron Lett.* ***2003***, *44*, 5099.
[332] Firouzabadi, H.; Iranpoor, N.; Shiri, M. *Tetrahedron Lett.* ***2003***, *44*, 8781.
[333] Hajipour, A.R.; Ruoho, A.E. *Org. Prep. Proceed. Int.* ***2002***, *34*, 647.
[334] Yusubov, M.S.; Tveryakova, E.N.; Krasnokutskaya, E.A.; Perederyna, I.A.; Zhdankin, V.V. *Synth. Commun.* ***2007***, *37*, 1259.
[335] Alexander, V.M.; Khandekar, A.C.; Samant, S.D. *Synlett* ***2003***, 1895.
[336] Monnereau, C.; Blart, E.; Odobel, F. *Tetrahedron Lett.* ***2005***, *46*, 5421.
[337] Usui, S.; Hashimoto, Y.; Morey, J.V.; Wheatley, A.E.H.; Uchiyama, M. *J. Am. Chem. Soc.* ***2007***, *129*, 15102.
[338] Bovonsombat, P.; Leykajarakul, J.; Khan, C.; Pla-on, K.; Krause, M.M.; Khanthapura, P.; Ali, R.; Doowa, N. *Tetrahedron Lett.* ***2009***, *50*, 2664.
[339] Grovenstein Jr., E.; Aprahamian, N.S.; Bryan, C.J.; Gnanapragasam, N.S.; Kilby, D.C.; McKelvey Jr., J.M.; Sullivan, R.J. *J. Am. Chem. Soc.* ***1973***, *95*, 4261.
[340] Ogata, Y.; Urasaki, I. *J. Chem. Soc. C* ***1970***, 1689.
[341] Arotsky, J.; Butler, R.; Darby, A.C. *J. Chem. Soc. C* ***1970***, 1480.
[342] Galli, C. *J. Org. Chem.* ***1991***, *56*, 3238.
[343] Wang, X.-C.; Hu, Y.; Bonacorsi, S.; Hong, Y.; Burrell, R.; Yu, J.-Q. *J. Am. Chem. Soc.* ***2013***, *135*, 10326.
[344] Racys, D.T.; Sharif, S.A.I.; Pimlott, S.L.; Sutherland, A. *J. Org. Chem.* ***2016***, *81*, 772. For a NIS iodination reaction mediated by TFA, see Bergström, M.; Suresh, G.; Naidu, V.R.; Unelius, C.R. *Eur. J. Org. Chem.* ***2017***, 3234.
[345] Racys, D.T.; Warrilow, C.E.; Pimlott, S.L.; Sutherland, A. *Org. Lett.* ***2015***, *17*, 4782.
[346] Bailey, L.; Handy, S.T. *Tetrahedron Lett.* ***2011***, *52*, 2413.
[347] Tramutola, F.; Chiummiento, L.; Funicello, M.; Lupattelli, P. *Tetrahedron Lett.* ***2015***, *56*, 1122.

with iodine in aqueous solution in the presence of cetyltrimethylammonium bromide to give the corresponding aryl iodide.[348] A *meta*-selective iodination of activated arenes was reported using NIS and a gold catalyst.[349] Iodination of deactivated arenes was reported using triiodoisocyanuric acid in concentrated sulfuric acid.[350]

Fluorine Direct fluorination of aromatic rings with F_2 is not feasible at room temperature, because of the extreme reactivity of F_2.[351] It has been accomplished at low temperatures (e.g., −70 to −20 °C, depending on the substrate),[352] but the reaction is not yet of preparative significance. Fluorination has also been reported with acetyl hypofluorite CH_3CO_2F (generated from F_2 and sodium acetate).[353] However, none of these methods seems likely to displace the *Schiemann reaction* (**13-23**; heating diazonium tetrafluoroborates) as the most common method for introducing fluorine into aromatic rings.

Aryl chlorides have been converted to aryl fluorides using CsF and a Ru catalyst at 120–180 °C.[354] Aromatic triflates have been converted to the corresponding aryl fluoride by reaction with 3 equivalents of CsF and a Pd catalyst.[355] Aryltriethoxysilane reacted with 2 equivalents of Selectfluor and 2 equivalents of Ag_2O, with BaO at 90 °C, to give the corresponding aryl fluoride.[356]

Aryl fluorides have been prepared from arylstannanes or aryl trifluoroborates by reaction with *N*-fluoro-2,4,6-trimethylpyridinium triflate.[357] For the conversion of aryltributylstannanes, their reaction with tetrabutylammonium triphenyldifluorosilicate (TBAT) and copper(II) triflate gave the aryl fluoride.[358] Aryl fluorides have been prepared by the Pd-catalyzed reaction from potassium aryltrifluoroborates.[359] The *para*-selective fluorination of anilides has been reported using hypervalent iodine reagents.[360] Aryldiazonium tetrafluoroborates were formed in situ using flow techniques (Sec. 7.D) and then converted to the final product, aryl fluorides.[361] Using continuous flow techniques (Sec. 7.D), aniline derivatives were converted to the corresponding aryl fluoride using TFA, $LiBF_4$, and *t*-BuONO.[362]

OS **I**, 111, 121, 123, 128, 207, 323; **II**, 95, 97, 100, 173, 196, 343, 347, 349, 357, 592; **III**, 132, 134, 138, 262, 267, 575, 796; **IV**, 114, 166, 256, 545, 547, 872, 947; **V**, 117, 147, 206, 346; **VI**, 181, 700; **VIII**, 167; **IX**, 121, 356. Also see OS **II**, 128.

[348] Tale, R.H.; Toradmal, G.K.; Gopula, V.B.; Rodge, A.H.; Pawar, R.P.; Patil, K.M. *Tetrahedron Lett.* ***2015***, *56*, 2699.
[349] Leboeuf, D.; Ciesielski, J.; Frontier, A.J. *Synlett* ***2014***, *25*, 399.
[350] da Ribeiro, R.S.; Esteves, P.M.; de Mattos, M.C.S. *Synthesis* ***2011***, *43*, 739.
[351] See German, L.; Zemskov, S. *New Fluorinating Agents in Organic Synthesis*, Springer, NY, ***1989***; Purrington, S.T.; Kagen, B.S.; Patrick, T.B. *Chem. Rev.* ***1986***, *86*, 997.
[352] Stavber, S.; Zupan, M. *J. Org. Chem.* ***1983***, *48*, 2223. See also, Purrington, S.T.; Woodard, D.L. *J. Org. Chem.* ***1991***, *56*, 142.
[353] See Visser, G.W.M.; Bakker, C.N.M.; van Halteren, B.W.; Herscheid, J.D.M.; Brinkman, G.A.; Hoekstra, A. *J. Org. Chem.* ***1986***, *51*, 1886.
[354] Konovalov, A.I.; Gorbacheva, E.O.; Milserdov, F.M.; Grushin, V.V. *Chem. Commun.* ***2015***, *51*, 13527.
[355] Lee, H.G.; Milner, P.J.; Buchwald, S.L. *Org. Lett.* ***2013***, *15*, 5602.
[356] Tang, P.; Ritter, T. *Tetrahedron* ***2011***, *67*, 4449. For the Ag-mediated reaction of potassium aryltrifluoroborates with Selectfluor, see Dubbaka, S.R.; Narreddula, V.R.; Gadde, S.; Mathew, T. *Tetrahedron* ***2014***, *70*, 9676.
[357] Ye, Y.; Sanford, M.S. *J. Am. Chem. Soc.* ***2013***, *135*, 4648.
[358] Gamache, R.F.; Waldmann, C.; Murphy, J.M. *Org. Lett.* ***2016***, *18*, 4522.
[359] Mazzotti, A.R.; Campbell, M.G.; Tang, P.; Murphy, J.M.; Ritter, T. *J. Am. Chem. Soc.* ***2013***, *135*, 14012.
[360] Tian, T.; Zhong, W.-H.; Meng, S.; Meng, X.-B.; Li, Z.-L. *J. Org. Chem.* ***2013***, *78*, 728.
[361] Yu, Z.-q.; Lv, W.-w.; Yu, C.-m.; Su, W.-k. *Tetrahedron Lett.* ***2013***, *54*, 1261.
[362] Park, N.H.; Senter, T.J.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***2016***, *55*, 11907.

E. Carbon Electrophiles

In the reactions in this section, a new carbon–carbon bond is formed. With respect to the aromatic ring, such reactions are electrophilic substitutions, because a positive species is attacked by the electron-rich ring.

11-11 Friedel-Crafts Alkylation

$$\mathrm{ArH + RCl \xrightarrow{AlCl_3} Ar\text{-}R}$$

The alkylation of aromatic rings, called *Friedel-Crafts alkylation*, is a reaction of very broad scope.[363] The most important reagents are alkyl halides, alkenes, and alcohols, but other types of reagent have also been employed.[363] Tertiary halides are particularly good substrates since they form relatively stable tertiary carbocations. When alkyl halides are used, the reactivity order is F > Cl > Br > I.[364]

Di- and trihalides, when all the halogens are the same, usually react with more than one molecule of an aromatic compound, and it is usually not possible to stop the reaction earlier.[365] Thus, benzene with CH_2Cl_2 gives Ph_2CH_2, not $PhCH_2Cl$, and benzene with $CHCl_3$ gives Ph_3CH. With CCl_4, however, the reaction stops when only three rings have been substituted to give Ph_3CCl.

In most cases, electron-withdrawing groups on the aromatic ring, *meta*-directing groups, make the ring too inactive for alkylation. In other words, a general observation is that benzene rings with a strong deactivating substituent do not undergo the Friedel-Crafts reaction. Nitrobenzene cannot be alkylated, and there are only a few reports of successful Friedel-Crafts alkylations when electron-withdrawing groups are present.[366] The difficulty in many cases is caused by the fact that, with inactive substrates, degradation and polymerization of the electrophile occurs before it can attack the ring. However, if an activating and a deactivating group are both present on a ring, Friedel-Crafts alkylation can be accomplished.[367] It is noted that aromatic nitro compounds can be methylated by a nucleophilic mechanism (**13-12**).

Heterocyclic rings tend to be poor substrates for the Friedel-Crafts reaction. Although some furans and thiophenes have been alkylated, polymerization is quite common, and a true alkylation of a pyridine or a quinoline may not be possible.[368] The reaction of isoquinoline with $ClCO_2Ph$ and AgOTf, followed by reaction with an allylic silane, led to a 2-allylic dihydroisoquinoline.[369]

A catalyst is nearly always required.[370] Lewis acid catalysts such as $AlCl_3$ and boron BF_3 are the most common, but many other Lewis acids have been used.[371] Protonic acids,

[363] See Roberts, R.M.; Khalaf, A.A. *Friedel-Crafts Alkylation Chemistry*, Marcel Dekker, NY, ***1984***. For a treatise on Friedel-Crafts reactions in general, see Olah, G.A. *Friedel-Crafts and Related Reactions*, Wiley, NY, ***1963–1965***. See Olah, G.A. *Friedel-Crafts Chemistry*, Wiley, NY, ***1973***.

[364] See Brown, H.C.; Jungk, H. *J. Am. Chem. Soc.* ***1955***, *77*, 5584.

[365] See Belen'kii, L.I.; Brokhovetsky, D.B.; Krayushkin, M.M. *Chem. Scr.* ***1989***, *29*, 81.

[366] Shen, Y.; Liu, H.; Chen, Y. *J. Org. Chem.* ***1990***, *55*, 3961.

[367] Olah, G.A. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, p. 34.

[368] Drahowzal, F.A. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, p. 433.

[369] Yamaguchi, R.; Nakayasu, T.; Hatano, B.; Nagura, T.; Kozima, S.; Fujita, K.-i. *Tetrahedron* ***2001***, *57*, 109.

[370] See Stang, P.J.; Anderson, A.G. *J. Am. Chem. Soc.* ***1978***, *100*, 1520.

[371] See Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* ***2004***, *44*, 238. Also see Bunce, R.A.; Cain, N.R.; Cooper J.G. *Org. Prep. Proceed. Int.* ***2013***, *45*, 28.

such as HF and H_2SO_4 are commonly used.[372] For active halides a trace of a less-active catalyst, such as $ZnCl_2$, may be enough. For an unreactive halide, such as chloromethane, a more powerful catalyst such as $AlCl_3$ is needed, and in larger amounts. In some cases, especially with alkenes, a Lewis acid catalyst causes reaction only if a small amount of proton-donating co-catalyst is present. Catalysts have been arranged in the following order of overall reactivity: $AlBr_3 > AlCl_3 > GaCl_3 > FeCl_3 > SbCl_5$[373] $> ZrCl_4$, $SnCl_4 > BCl_3$, BF_3, $SbCl_3$;[374] but the reactivity order in each case depends on the substrate, reagent, and conditions. Calcium has been used to catalyze Friedel-Crafts alkylation reactions, at room temperature.[375]

In Friedel-Crafts alkylation reactions, the product is more reactive than the starting aromatic substrate, and di- and polyalkylation are frequently observed. However, the activating effect of simple alkyl groups (e.g., ethyl, isopropyl) is only ~1.5–3 times as fast as benzene for Friedel-Crafts alkylations,[376] so it is often possible to obtain high yields of monoalkyl product.[377] Actually, the fact that di- and polyalkyl derivatives are frequently obtained is not due to the small difference in reactivity but to the circumstance that alkylbenzenes are preferentially soluble in the catalyst layer, where the reaction actually takes place.[378] This factor can be removed by the use of a suitable solvent, by high temperatures, or by high-speed stirring. It is important to note that the OH, OR, NH_2, and so on, groups do not facilitate the reaction, since most Lewis acid catalysts coordinate with these basic groups. Although phenols give the usual Friedel-Crafts reactions, orienting *ortho* and *para*, the reaction is very poor for aniline derivatives.

Alcohols are more active than alkyl halides, but if a Lewis acid catalyst is used more catalyst is required, since the catalyst complexes with the OH group. However, proton acids such as H_2SO_4 are often used to catalyze alkylation with alcohols. An intramolecular cyclization was reported from an allylic alcohol, using P_2O_5, to give indene derivatives.[379] Secondary alcohols are coupled to aromatic compounds using a heterobimetallic Ir–Sn complex.[380] Molecular iodine has been used to catalyze benzylation of arenes with benzylic alcohols.[381] A "contra Friedel-Crafts" *tert*-butylation has been reported.[382] Allylic alcohols reacted with anisole derivatives in the presence of an iron(III) porphyrin catalyst to give the *para* allylic-substituted anisole derivative.[383] Aromatic compounds reacted with benzylic alcohols in the presence of triphenylphosphine ditriflate (Ph_3P^+ OTf $^-$OTf) to give the benzylic substituted arene.[384] 1,1-Diaryl compounds were prepared by the graphene oxide-mediated reaction of

[372] See Olah, G.A. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, pp. 201–366, 853–881. A reusable catalyst derived from a heteropoly acid has been reported; see Okumura, K.; Yamashita, K.; Hirano, M.; Niwa, M. *Chem. Lett.* ***2005***, *34*, 716.
[373] See Yakobson, G.G.; Furin, G.G. *Synthesis* ***1980***, 345.
[374] Russell, G.A. *J. Am. Chem. Soc.* ***1959***, *81*, 4834.
[375] Niggemann, M.; Meel, M.J. *Angew. Chem. Int. Ed.* ***2010***, *49*, 3684.
[376] Olah, G.A.; Kuhn, S.J.; Flood, S.H. *J. Am. Chem. Soc.* ***1962***, *84*, 1688.
[377] See Davister, M.; Laszlo, P. *Tetrahedron Lett.* ***1993***, *34*, 533 for examples of paradoxical selectivity in Friedel-Crafts alkylation.
[378] Francis, A.W. *Chem. Rev.* ***1948***, *43*, 257.
[379] Nishibayashi, Y.; Joshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* ***2002***, *124*, 11846.
[380] Podder, S.; Choudhury, J.; Roy, S. *J. Org. Chem.* ***2007***, *72*, 3129.
[381] Sun, G.; Wang, Z. *Tetrahedron Lett.* ***2008***, *49*, 4929.
[382] Clayden, J.; Stimson, C.C.; Keenan, M. *Chem. Commun.* ***2006***, 1393.
[383] Teranishi, S.; Kurahashi, T.; Matsubara, S. *Synlett* ***2013***, *24*, 2148.
[384] Khodaei, M.M.; Nazari, E. *Tetrahedron Lett.* ***2012***, *53*, 5131.

arenes with benzylic alcohols.[385] Cycloalkanols reacted with aromatic compounds in the presence of $FeCl_3/AgSbF_6$ to give the arylcycloalkane.[386]

When carboxylic esters are the reagents, there is competition between alkylation and Friedel-Crafts acylation (**11-17**). This competition can often be controlled by choice of catalyst, and alkylation is usually favored, but carboxylic esters are not often employed in Friedel-Crafts reactions. Other alkylating agents are ethers,[387] thiols, sulfates, sulfonates, alkyl nitro compounds,[388] and even alkanes and cycloalkanes, under conditions where these are converted to carbocations. Notable are oxirane, which puts the CH_2CH_2OH group onto the ring,[389] and cyclopropyl[390] units. Arenes reacted with cycloalkanes in the presence of a Ru catalyst and 2 equivalents of *tert*-butylperoxide to give the arylcycloalkane.[391] Arylboronic acids reacted with cycloalkanes in the presence of a Ni catalyst to give the arylcycloalkane. For all types of reagent the reactivity order is allylic ≈ benzylic > tertiary > secondary > primary.

Benzylic halides reacted with arylboronic acids in the presence of $CsCO_3$ in aqueous benzotrifluoride to give the benzylic substituted arene.[392] Benzene, toluene, or chlorobenzene reacted with bromoalkanes in the presence of $AlCl_3$ and microwave irradiation to give the arene.[393] Alkyl iodides reacted with arenes to give the alkylated aryl compounds with *meta* selectivity using a Pd catalyst and a functionalized norbornene compound.[394] It is noted that tertiary alkylbenzenes, which are generally not available via Friedel-Crafts reactions due to rearrangement of the intermediate cation, are available via a two-step process: (i) react with $SOCl_2$ and (ii) reaction with 2 equivalents of Me_3Al.[395]

Alkyl mesylates undergo alkylation reaction with benzene rings in the presence of $Sc(OTf)_3$.[396] Arenes reacted with alkylcarboxylic acids in the presence of $Pd(OAc)_2$ and $PhI(OAc)_2$; heating led to decarboxylative alkylation to give the alkylated aromatic compound.[397] 1-Functionalized naphthalenes reacted with Me_3Al or the Me_3Al diamine complex with 2,3-dichlorobutane and an Fe complex to give the 8-methyl 1-functionalized naphthalene.[398] *N*-Pyrimidylindoles reacted with alkylarenes in the presence of a Cu

[385] Hu, F.; Patel, M.; Luo, F.; Flach, C.; Mendelsohn, R.; Garfunkel, E.; He, H.; Szostak, M. *J. Am. Chem. Soc.* ***2015***, *137*, 14473. For a $SnBr_4$-mediated reaction, see Suzuki, N.; Tsuchihashi, S.; Nakata, K. *Tetrahedron Lett.* ***2016***, *57*, 1456.

[386] Jefferies, L.R.; Cook, S.P. *Org. Lett.* ***2014***, *16*, 2026.

[387] See Podder, S.; Roy, S. *Tetrahedron* ***2007***, *63*, 9146.

[388] Bonvino, V.; Casini, G.; Ferappi, M.; Cingolani, G.M.; Pietroni, B.R. *Tetrahedron* ***1981***, *37*, 615.

[389] Taylor, S.K.; Dickinson, M.G.; May, S.A.; Pickering, D.A.; Sadek, P.C. *Synthesis* ***1998***, 1133. See also, Brandänge, S.; Bäckvall, J.-E.; Leijonmarck, H. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 2051.

[390] Patra, P.K.; Patro, B.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* ***1993***, *34*, 3951.

[391] Guo, X.; Li, C.-J. *Org. Lett.* ***2011***, *13*, 4977.

[392] Ueda, M.; Nakakoji, D.; Kuwahara, Y.; Nishimura, K.; Ryu, I. *Tetrahedron Lett.* ***2016***, *57*, 4142. Also see Ricardo, C.L.; Mo, X.; McCubbin, J.A.; Hall, D.G. *Chem. Eur. J.* ***2015***, *21*, 4218.

[393] Zupp, L.R.; Campanella,V.L.; Rudzinski, D.M.; Beland, F.; Priefer, R. *Tetrahedron Lett.* ***2012***, *53*, 5343.

[394] Shen, P.-X.; Wang, X.-C.; Wang, P.; Zhu. R.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* ***2015***, *137*, 11574. For an alkylation of arenes catalyzed by a Ru compound using alkylboron reagents, see Wang, H.; Yu, S.; Qi, Z.; Li, X. *Org. Lett.* ***2015***, *17*, 2812.

[395] Hartsel, J.A.; Craft, D.T.; Chen, Q.-H.; Ma, M.; Carlier, P.R. *J. Org. Chem.* ***2012***, *77*, 3127.

[396] Singh, R.P.; Kamble, R.M.; Chandra, K.L.; Saravanani, P.; Singh, V.K. *Tetrahedron* ***2001***, *57*, 241.

[397] Premi, C.; Dixit, A.; Jain, N. *Org. Lett.* ***2015***, *17*, 598.

[398] Shang, R.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* ***2015***, *137*, 7660. Also see Bunce, R.A.; Cain, N.R.; Cooper, J.G. *Org. Prep. Proceed. Int.* ***2012***, *44*, 131; Liu, D.; Li, Y.; Qi, X.; Liu, C.; Lan, Y.; Lei, A. *Org. Lett.* ***2015***, *17*, 998.

catalyst and with 2 equivalents of di-*tert*-butylbenzoyl peroxide to give the 2-benzylic indole derivative.[399]

An important use of the Friedel-Crafts alkylation reaction is to effect ring closure,[400] via an intramolecular process.[401] The most common method is to heat an aromatic compound having a halogen, hydroxy, or alkene group in the proper position with aluminum chloride. Another way of effecting ring closure through Friedel-Crafts alkylation is to use a reagent containing two halogens. These reactions are most successful for the preparation of six-membered rings,[402] though five- and seven-membered rings have also been closed in this manner. For other Friedel-Crafts ring-closure reactions, see **11-15**, **11-13**, and **11-17**.

The electrophile in Friedel-Crafts alkylation is a carbocation, at least in most cases.[403] The cation is formed from the attacking reagent and the catalyst. For the three most important types of reagent these reactions are: (i) the reaction of alkyl halides with Lewis acids, such as $AlCl_3$, (ii) the protonation and loss of water from alcohols to form a carbocation, (iii) the reaction of alcohols with Lewis acids, and (iv) the reaction of alkenes with an acid to form a carbocation.[404] Rearrangement of the alkyl substrate occurs frequently and is an important synthetic limitation of Friedel-Crafts alkylation. Rearrangement is usually in the order primary → secondary → tertiary and usually occurs by migration of the smaller group on the adjacent carbon. In the absence of special electronic or resonance influences on the migrating group (such as phenyl), H migrates before methyl, which migrates before ethyl, and so on (see discussion of rearrangement mechanisms in Chapter 18). It is therefore *not* usually possible to put a primary alkyl group (other than methyl[405] and ethyl) onto an aromatic ring by Friedel-Crafts alkylation. Because of these rearrangements, *n*-alkylbenzenes are often prepared by acylation (**11-17**), followed by reduction (**19-66**).

Rearrangement is possible even with a non-carbocation mechanism. The rearrangement could occur *before* the attack on the ring takes place. It has been shown that treatment of $CH_3{}^{14}CH_2Br$ with $AlBr_3$ in the absence of any aromatic compound gave a mixture of the starting material and $^{14}CH_3CH_2Br$.[406] Similar results were obtained with $PhCH_2{}^{14}CH_2Br$, in which case the rearrangement was so fast that the rate could be measured only below −0 °C.[407] Rearrangement could also occur *after* formation of the product, since alkylation is reversible (see **11-33**).[408]

There is direct evidence, from IR and NMR spectra, that the *tert*-butyl cation is quantitatively formed when *tert*-butyl chloride reacts with $AlCl_3$ in anhydrous liquid HCl.[409] In the case of alkenes, the more stable carbocation (*Markovnikov's rule*, Sec. 15.B.ii) is formed. Carbocation formation is particularly easy from some reagents, because of the

[399] Zhang, H.-J.; Su, F.; Wen, T.-B. *J. Org. Chem.* ***2015***, *80*, 1322.
[400] See Barclay, L.R.C. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, pp. 785–977.
[401] See Stashenko, E.E.; Martínez, J.R.; Tafurt-García, G.; Palma, A.; Bofill, J.M. *Tetrahedron* ***2008***, *64*, 7407.
[402] See Khalaf, A.A.; Roberts, R.M. *J. Org. Chem.* ***1966***, *31*, 89.
[403] See Taylor, R. *Electrophilic Aromatic Substitution*, Wiley, NY, ***1990***, pp. 188–213.
[404] For a Se-promoted intermolecular reaction see Tang, E.; Zhao, Y.; Li, W.; Wang, W.; Zhang, M.; Dai, X. *Org. Lett.* ***2016***, *18*, 912.
[405] See Gelman, D.; Schumann, H.; Blum, J. *Tetrahedron Lett.* ***2000***, *41*, 7555.
[406] Adema, E.H.; Sixma, F.L.J. *Recl. Trav. Chim. Pays-Bas* ***1962***, *81*, 323, 336.
[407] See Roberts, R.M.; Gibson, T.L. *Isot. Org. Chem.* ***1980***, *5*, 103.
[408] See Lee, C.C.; Hamblin, M.C.; Uthe, J.F. *Can. J. Chem.* ***1964***, *42*, 1771.
[409] Kalchschmid, F.; Mayer, E. *Angew. Chem. Int. Ed.* ***1976***, *15*, 773.

stability of the cations. Triphenylmethyl chloride[410] and 1-chloroadamantane[411] require no catalyst or solvent to react with activated aromatic rings (e.g., phenols, amines). Ions as stable as this are less reactive than other carbocations and often attack only active substrates. The tropylium ion, for example, alkylates anisole, but not benzene.[412] It was noted in Sec. 10.F that relatively stable vinylic cations can be generated from certain vinylic compounds. These have been used to introduce vinylic groups into aryl substrates.[413] Lewis acids, such as BF_3[414] or $AlEt_3$,[415] can also be used to alkylate aromatic rings with alkene units.

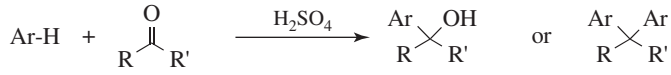
There is considerable evidence that many Friedel-Crafts alkylations, especially with primary reagents, do not go through a completely free carbocation. The ion may exist as a tight ion pair with, say, $AlCl_4^-$ as the counterion or as a complex. Among the evidence is the result that methylation of toluene by methyl bromide and methyl iodide gave different *ortho*/*para*/*meta* ratios,[416] although the same ratios are expected if the same species attacked in each case. Other evidence is that, in some cases, the reaction kinetics are third order; first order each in aromatic substrate, attacking reagent, and catalyst.[417] In these instances a mechanism in which the carbocation is slowly formed and then rapidly attacked by the aromatic ring is ruled out since, in such a mechanism, the substrate would not appear in the rate expression. Since it is known that free carbocations, once formed, are rapidly attacked by the ring (acting as a nucleophile), there are no free carbocations here. Another possibility (with alkyl halides) is that some alkylations take place by an S_N2 mechanism (with respect to the halide), in which case no carbocations would be involved at all. However, a formal S_N2 mechanism requires inversion of configuration. Most investigations of Friedel-Crafts stereochemistry, even where an S_N2 mechanism might most be expected, have resulted in total racemization, or at best a few percent inversion. A few exceptions have been found,[418] most notably where the reagent was optically active propylene oxide, in which case 100% inversion was reported.[419]

Diastereoselective alkylation is possible from alcohol precursors, and high facial diastereoselectivity was reported with "chiral benzylic cations," for example.[420] Catalytic asymmetric Friedel-Crafts alkylation reactions are known.[421] An asymmetric Friedel-Crafts alkylation of indoles has been reported.[422] *N*-Methylpyrrole reacted with the C=C unit of methacrolein in the presence of a chiral catalyst to give the 2-alkylated pyrrole, with good enantioselectivity.[423]

[410] See Chuchani, G.; Zabicky, J. *J. Chem. Soc. C* ***1966***, 297.
[411] Takaku, M.; Taniguchi, M.; Inamoto, Y. *Synth. Commun.* ***1971***, *1*, 141.
[412] Bryce-Smith, D.; Perkins, N.A. *J. Chem. Soc.* ***1962***, 5295.
[413] Kitamura, T.; Kobayashi, S.; Taniguchi, H.; Rappoport, Z. *J. Org. Chem.* ***1982***, *47*, 5503.
[414] Majetich, G.; Liu, S.; Siesel, D. *Tetrahedron Lett.* ***1995***, *36*, 4749.
[415] Majetich, G.; Zhang, Y.; Liu, S. *Tetrahedron Lett.* ***1994***, *35*, 4887.
[416] Brown, H.C.; Jungk, H. *J. Am. Chem. Soc.* ***1956***, *78*, 2182.
[417] See Choi, S.U.; Brown, H.C. *J. Am. Chem. Soc.* ***1963***, *85*, 2596.
[418] Some instances of retention of configuration have been reported; a neighboring-group mechanism is likely in these cases: see Effenberger, F.; Weber, T. *Angew. Chem. Int. Ed.* ***1987***, *26*, 142.
[419] Nakajima, T.; Suga, S.; Sugita, T.; Ichikawa, K. *Tetrahedron* ***1969***, *25*, 1807. For cases of almost complete inversion, with acyclic reagents, see Piccolo, O.; Azzena, U.; Melloni, G.; Delogu, G.; Valoti, E. *J. Org. Chem.* ***1991***, *56*, 183.
[420] Mühlthau, F.; Schuster, O.; Bach, T. *J. Am. Chem. Soc.* ***2005***, *127*, 9348.
[421] Poulsen, T.B.; Jørgensen, K.A. *Chem. Rev.* ***2008***, *108*, 2903; Adachi, S.; Tanaka, F.; Watanabe, K.; Watada, A.; Harada, T. *Synthesis* ***2010***, 2652; Faita, G.; Mella, M.; Toscanini, M.; Desimoni, G. *Tetrahedron* ***2010***, *66*, 3024.
[422] Wu, J.; Li, X.; Wu, F.; Wan, B. *Org. Lett.* ***2011***, *13*, 4834. Also see Wu, H.; Sheng, W.-J.; Chen, B.; Liu, R.-R.; Gao, J.-R.; Jia, Y.-X. *Synlett* ***2015***, *26*, 2817.
[423] Paras, N.A.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2001***, *123*, 4370.

OS **I**, 95, 548; **II**, 151, 229, 232, 236, 248; **III**, 343, 347, 504, 842; **IV**, 47, 520, 620, 665, 702, 898, 960; **V**, 130, 654; **VI**, 109, 744.

11-12 Hydroxyalkylation: Cyclodehydration of Carbonyl-Containing Compounds



When an aldehyde, ketone, or other carbonyl-containing substrate is treated with a protonic or Lewis acid, an oxygen-stabilized cation is generated. In the presence of an aromatic ring, *Friedel-Crafts-type alkylation* occurs. The condensation of aromatic rings with aldehydes or ketones is called *hydroxyalkylation*.[424] The reaction can be used to prepare alcohols,[425] though more often the alcohol initially produced reacts with another molecule of aromatic compound (**11-11**) to give diarylation. The diarylation reaction is especially common with phenols (the diaryl product here is called a bisphenol). The reaction is normally carried out in alkaline solution on the phenolate ion.[426] Another variation involved Friedel-Crafts coupling of an aldehyde to an activated aromatic compound (an aniline derivative) to give diaryl carbinols that exhibited atropisomerism (Sec. 4.C, category 5).[427] The attacking species is the carbocation, $R_2(OH)C^+$, formed from the aldehyde or ketone and the acid catalyst, except when the reaction is carried out in basic solution. When the reaction was done with a chiral aluminum complex, modest enantioselectivity was observed.

The hydroxymethylation of phenols with formaldehyde is called the *Lederer-Manasse reaction*. This reaction must be carefully controlled,[428] since it is possible for the *para* and both *ortho* positions to be substituted and for each of these to be rearylated, so that a polymeric structure is produced. However, such polymers, which are of the Bakelite type (phenol–formaldehyde resins), are of considerable commercial importance.[429]

Two methods, both involving boron-containing reagents, have been devised for the regioselective *ortho* hydroxymethylation of phenols or aromatic amines.[430] Conjugated aldehydes undergo Friedel-Crafts alkylation with aryltrifluoroborate salts, in the presence of a catalytic amount of an imidazolidinone.[431]

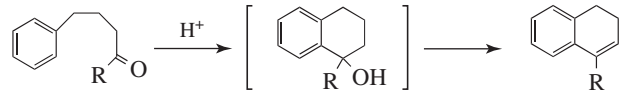
OS **III**, 326; **V**, 422; **VI**, 471, 856; **VIII**, 75, 77, 80. Also see OS **I**, 214.

11-13 Cyclodehydration of Carbonyl-Containing Compounds

The reaction of a carbonyl and an aromatic ring can be carried out intramolecularly. When reaction with a Lewis acid leads to an oxygen-stabilized carbocation, *Friedel-Crafts alkylation* occurs to give an alcohol or an alkene, if dehydration occurs under the reaction

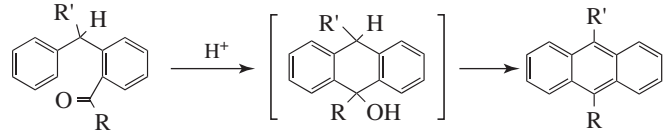
[424] See Hofmann, J.E.; Schriesheim, A. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1963***, pp. 597–640.
[425] See Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G. *Synthesis* ***1980***, 124.
[426] For a review, see Schnell, H.; Krimm, H. *Angew. Chem. Int. Ed.* ***1963***, *2*, 373.
[427] Gothelf, A.S.; Hansen, T.; Jørgensen, K.A. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 854.
[428] Casiraghi, G.; Casnati, G.; Pochini, A.; Puglia, G.; Ungaro, R.; Sartori, G. *Synthesis* ***1981***, 143.
[429] Gardziella, A.; Pilato, L.A.; Knop, A. *Phenolic Resins: Chemistry, Applications, Standardization, Safety and Ecology*, 2nd ed., Springer, ***2000***; Hesse, W. "Phenolic Resins" in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, ***2002***.
[430] Sugasawa, T.; Toyoda, T.; Adachi, M.; Sasakura, K. *J. Am. Chem. Soc.* ***1978***, *100*, 4842; Nagata, W.; Okada, K.; Aoki, T. *Synthesis* ***1979***, 365.
[431] Lee, S.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2007***, *129*, 15438.

conditions. When the ring is formed the alcohol moiety is benzylic and treatment with acid results in cyclodehydration to form the alkene. Dehydration almost always takes place to give a double bond conjugated with the aromatic ring.[432] The method is very general and is widely used to close both carbocyclic and heterocyclic rings.[433] Polyphosphoric acid is a common reagent, but other acids have also been used.



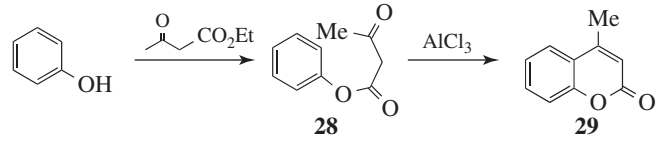
An intramolecular cyclization of an aryl ether to the carbonyl of a pendant aryl ketone, on clay with microwave irradiation, led to a benzofuran via *Friedel-Crafts cyclization* and elimination of water.[434]

In a variation known as the *Bradsher reaction*,[435] diarylmethanes containing a carbonyl group in the *ortho* position can be cyclized to anthracene derivatives, **27**, and in this case 1,4-dehydration takes place, at least formally.



27

A variation of this reaction involves acylation of a β-keto ester to give **28**, followed by *Friedel-Crafts cyclization* of the ketone moiety. The product is a coumarin, **29**, in what is known as the *Pechmann condensation*.[436] Isolation of esters, such as **28**, is not always necessary, and protonic acids can be used rather than Lewis acids.



28 **29**

The Pechmann condensation is facilitated by the presence of hydroxyl (OH), dimethylamino (NMe_2), and alkyl groups *meta* to the hydroxyl of the phenol.[437] The reaction has been accomplished using microwave irradiation on graphite/Montmorillonite K-10.[438] Pechmann condensation in an ionic liquid using ethyl acetate has also been reported.[439]

[432] See Bonnet-Delpon, D.; Charpentier-Morize, M.; Jacquot, R. *J. Org. Chem.* ***1988***, *53*, 759.
[433] See Bradsher, C.K. *Chem. Rev.* ***1987***, *87*, 1277.
[434] Meshram, H.M.; Sekhar, K.C.; Ganesh, Y.S.S.; Yadav, J.S. *Synlett* ***2000***, 1273.
[435] Bradsher, C.K. *Chem. Rev.* ***1987***, *87*, 1277 (pp. 1287–1294).
[436] von Pechmann, H.; Duisberg, C. *Ber.* ***1883***, *16*, 2119; Sethna, S.; Phadke, R. *Org. React.* ***1953***, *7*, 1. For a Pechmann condensation in ionic liquids, see Kumar, V.; Tomar, S.; Patel, R.; Yousaf, A.; Parmar, V.S.; Malhotra, S.V. *Synth. Commun.* ***2008***, *38*, 2646.
[437] Miyano, M.; Dorn, C.R. *J. Org. Chem.* ***1972***, *37*, 259.
[438] Frère, S.; Thiéry, V.; Besson, T. *Tetrahedron Lett.* ***2001***, *42*, 2791.
[439] See Potdar, M.K.; Mohile, S.S.; Salunkhe, M.M. *Tetrahedron Lett.* ***2001***, *42*, 9285.

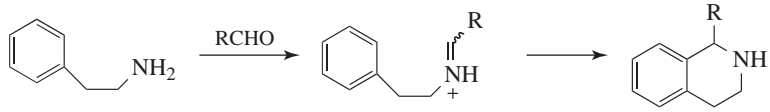
The reaction of resorcinol with ethyl 4,4,4-trifluoroacetoacetate and trifluorotoluene with heating led to a Pechmann condensation and formation of the 4-trifluoromethylcomarin.[440]

The carbonyl unit involved in the cyclization process is not restricted to aldehydes and ketones. The carbonyl of acid derivatives, such as amides, can also be utilized. One of the more important cyclodehydration reactions is applied to the formation of heterocyclic systems via cyclization of β-aryl amides, in what is called the *Bischler-Napieralski reaction*.[441] In this reaction amides of the type **30** are cyclized by reaction with phosphorus oxychloride or other reagents, including polyphosphoric acid, sulfuric acid, or phosphorus pentoxide, to give a dihydroisoquinoline, **31**.

30 **31**

The Bischler-Napieralski reaction has been done in ionic liquids using $POCl_3$.[442] The reaction has also been done using solid phase (Sec. 9.D.iv) techniques.[443] If the starting compound contains a hydroxyl group in the α position, an additional dehydration takes place and the product is an isoquinoline.[444]

Another useful variation is the *Pictet-Spengler isoquinoline synthesis*, also known as the *Pictet-Spengler reaction*.[445] When a β-arylamine reacts with an aldehyde, the product is an iminium salt, which cyclizes with an aromatic ring to complete the reaction and generate a tetrahydroisoquinoline.[446] The reactive intermediate is an iminium ion **32** rather than an oxygen-stabilized cation, but attack at the electrophilic carbon of the C=N unit (see **16-31**) leads to an isoquinoline derivative, **33**.



32 **33**

Metal-catalyzed reactions are known, including the use of $AuCl_3$/AgOTf.[447] A variety of aldehydes can be used, and substitution on the aromatic ring leads to many derivatives. When the reaction is done in the presence of a chiral catalyst, good enantioselectivity was observed.[448] An organocatalyst, (*R*)-3,3′-bis(2,4,6-triisopropylphenyl)-BINOL-phosphoric acid, has been used for a Pictet-Spengler approach to the synthesis of several

[440] Tyndall, S.; Wong, K.F.; VanAlstine-Parris, M.A. *J. Org. Chem.* ***2015***, *80*, 8951.
[441] See Fodor, G.; Nagubandi, S. *Tetrahedron* ***1980***, *36*, 1279.
[442] See Judeh, Z.M.A.; Ching, C.B.; Bu, J.; McCluskey, A. *Tetrahedron Lett.* ***2002***, *43*, 5089.
[443] Chern, M.-S.; Li, W.R. *Tetrahedron Lett.* ***2004***, *45*, 8323.
[444] Wang, X.-j.; Tan, J.; Grozinger, K. *Tetrahedron Lett.* ***1998***, *39*, 6609.
[445] Pictet, A.; Spengler, T. *Ber.* ***1911***, *44*, 2030; Cox, E.D.; Cook, J.M. *Chem. Rev.* ***1995***, *95*, 1797. See also, Whaley, W.M.; Govindachari, T.R. *Org. React.* ***1951***, *6*, 74; Youn, S.W. *Org. Prep. Proceed. Int.* ***2006***, *38*, 505. For an alternative strategy, see Henderson, L.; Knight, D.W.; Williams, A.C. *Tetrahedron Lett.* ***2012***, *53*, 4657.
[446] Ong, H.H.; May, E.L. *J. Heterocycl. Chem.* ***1971***, *8*, 1007.
[447] Youn, S.W. *J. Org. Chem.* ***2006***, *71*, 2521.
[448] See Sewgobind, N.V.; Wanner, M.J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J.H.; Hiemstra, H. *J. Org. Chem.* ***2008***, *73*, 6405.

natural products.[449] An $In(OTf)_3$-catalyzed intramolecular reaction has been reported.[450] 3-Hydroxyethylindole derivatives were treated with an aldehyde with a dual catalyst composed of a secondary amine derivatives that contain thiourea unit, in the presence of MS 4Å, that generated an oxocarbenium ion for an enantioselective oxa-Pictet-Spengler reaction.[451] An oxa-Pictet-Spengler reaction was reported using a nitrated confined imidodiphosphoric acid catalyst.[452]

Another variation in this basic procedure leads to tetrahydroisoquinolines. When phenethylamine was treated with *N*-hydroxymethylbenzotriazole and then $AlCl_3$ in chloroform, cyclization occurred. Reduction with sodium borohydride gave the 1,2,3,4-tetrahydro-*N*-methylisoquinoline.[453]

OS **I**, 360, 478; **II**, 62, 194; **III**, 281, 300, 329, 568, 580, 581; **IV**, 590; **V**, 550; **VI**, 1. Also see OS **I**, 54.

11-14 Haloalkylation

$$ArH + HCHO + HCl \xrightarrow{ZnCl_2} ArCH_2Cl$$

When certain aromatic compounds are treated with formaldehyde and HCl, the CH_2Cl group is introduced into the ring in a reaction called *chloromethylation*. The reaction has also been carried out with other aldehydes and with HBr and HI. The more general term *haloalkylation* covers these cases.[454] The reaction is successful for benzene, and alkyl-, alkoxy-, and halobenzenes, but is greatly hindered by *meta*-directing groups, which reduce yields or completely prevent the reactions. Amines and phenols are too reactive and usually give polymers unless deactivating groups are also present, but phenolic ethers and esters successfully undergo the reaction. Compounds of lesser reactivity can often be chloromethylated with chloromethyl methyl ether ($ClCH_2OMe$), or methoxyacetyl chloride $MeOCH_2COCl$.[455] Zinc chloride is the most common catalyst, but other Friedel-Crafts catalysts are also employed. As with reaction **11-12**, and for the same reason, an important side product is the diaryl compound Ar_2CH_2 (from formaldehyde).

Apparently, the initial step involves reaction of the aromatic compound with the aldehyde to form the hydroxyalkyl compound, exactly as in **11-12**, and then the HCl converts this to the chloroalkyl compound.[456] The acceleration of the reaction by $ZnCl_2$ has been attributed[457] to the raising of the acidity of the medium, causing an increase in the concentration of $HOCH_2^+$ ions.

OS **III**, 195, 197, 468, 557; **IV**, 980.

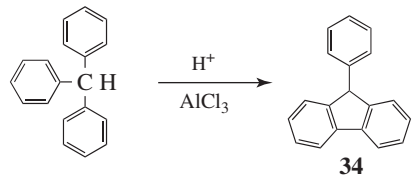
[449] Ruiz-Olalla, A.; Würdemann, M.A.; Wanner, M.J.; Ingemann, S.; van Maarseveen, J.H.; Hiemstra, H. *J. Org. Chem.* ***2015***, *80*, 5125.
[450] Kuninobu, Y.; Tatsuzaki, T.; Matsuki, T.; Takai, K. *J. Org. Chem.* ***2011***, *76*, 7005.
[451] Zhao, C.; Chen, S.B.; Seidel, D. *J. Am. Chem. Soc.* ***2016***, *138*, 9053.
[452] Das, S.; Liu, L.; Zheng, Y.; Alachraf, M.W.; Thiel, W.; De, C.K.; List, B. *J. Am. Chem. Soc.* ***2016***, *138*, 9429.
[453] Locher, C.; Peerzada, N. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 179.
[454] See Belen'kii, L.I.; Vol'kenshtein, Yu.B.; Karmanova, I.B. *Russ. Chem. Rev.* ***1977***, *46*, 891; Olah, G.A.; Tolgyesi, W.S. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1963***, pp. 659–784.
[455] McKillop, A.; Madjdabadi, F.A.; Long, D.A. *Tetrahedron Lett.* ***1983***, *24*, 1933.
[456] Ogata, Y.; Okano, M. *J. Am. Chem. Soc.* ***1956***, *78*, 5423. See also, Olah, G.A.; Yu, S.H. *J. Am. Chem. Soc.* ***1975***, *97*, 2293.
[457] Lyushin, M.M.; Mekhtiev, S.D.; Guseinova, S.N. *J. Org. Chem. USSR* ***1970***, *6*, 1445.

11-15 Friedel-Crafts Arylation

$$2\text{ArH} \xrightarrow[\text{H}^+]{\text{AlCl}_3} \text{Ar—Ar} + \text{H}_2$$

The coupling of two aromatic molecules by treatment with a Lewis acid and a proton acid is called the *Scholl reaction*.[458] Yields are low and the synthesis is seldom useful. High temperatures and strong-acid catalysts are required, and the reaction fails for substrates that are destroyed by these conditions. The reaction becomes important with large fused ring systems, so ordinary *Friedel-Crafts reactions* (**11-11**) on these systems are rare. Yields can be increased by the addition of a salt such as $CuCl_2$ or $FeCl_3$, which acts as an oxidant.[459] Rhodium[460] and Ru catalysts[461] have also been used. Twisted polycyclic arenes have been prepared by intramolecular Scholl reactions.[462]

Intramolecular Scholl reactions, such as formation of **34** from triphenylmethane, are much more successful than the intermolecular reaction. The mechanism is not clear, but it may involve attack by a proton to give an arenium ion of the type **13** (Sec. 11.A.i, category 2), which would be the electrophile that attacks the other ring.[463] An "intramolecular Scholl reaction of 1-benzoylpyrene gave 8*H*-dibenzo[*def*,*qr*]chrysen-8-one and 11*H*-indeno[2,1-*a*]pyren-11-one in a 1:2 ratio."[464] A molecular modeling study indicated that the arenium–cation mechanism predicted the regioselectivity and that the reaction was under kinetic control.[464]



34

OS **IV**, 482; **X**, 359. Also see OS **V**, 102, 952.

11-16 Arylation of Aromatic Compounds By Metalated Aryls

$$\text{Ar-M} \xrightarrow{\text{Ar'-H}} \text{Ar—Ar'}$$

Many metalated aryl compounds are known to couple with aromatic compounds. Aniline derivatives react with $ArPb(OAc)_3$, for example, to give the 2-arylaniline.[465] Phenolic anions also react to form biaryls, with modest enantioselectivity, in the presence of

[458] See Kovacic, P.; Jones, M.B. *Chem. Rev.* ***1987***, *87*, 357; Balaban, A.T.; Nenitzescu, C.D. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, pp. 979–1047.

[459] For examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 77–84; Sartori, G.; Maggi, R.; Bigi, F.; Grandi, M. *J. Org. Chem.* ***1993***, *58*, 7271.

[460] Barrett, A.G.M.; Itoh, T.; Wallace, E.M. *Tetrahedron Lett.* ***1993***, *34*, 2233. For a microwave-promoted reaction, see Lewis, J.C.; Wu, J.Y.; Bergman, R.G.; Ellman, J.A. *Angew. Chem. Int. Ed.* ***2006***, *45*, 1589.

[461] Matsushita, M.; Kamata, K.; Yamaguchi, K.; Mizuno, N. *J. Am. Chem. Soc.* ***2005***, *127*, 6632. For a coupling reaction of pyridines, see Kawashima, T.; Takao, T.; Suzuki, H. *J. Am. Chem. Soc.* ***2007***, *129*, 11006.

[462] Pradhan, A.; Dechambenoi, P.; Bock, H.; Durola, F. *J. Org. Chem.* ***2013***, *78*, 2266.

[463] See Clowes, G.A. *J. Chem. Soc. C* ***1968***, 2519.

[464] Oded, Y.N.; Pogodin, S.; Agranat, I. *J. Org. Chem.* ***2016***, *81*, 11389.

[465] Saito, S.; Kano, T.; Ohyabu, Y.; Yamamoto, H. *Synlett* ***2000***, 1676.

brucine.[466] A Mn(III)-mediated synthesis of biaryls used microwave irradiation for the coupling reaction.[467] The homocoupling reaction of aryl Grignard reagents in the presence of TEMPO is known.[468] A Cu-catalyzed coupling reaction with hypervalent arylated iodine derivatives is known.[469]

Heating benzene with arylpalladium(II) carboxylate and K_2CO_3 led to the biaryl.[470] A fluorocation surrogate such as Selectfluor mediates the coupling of arenes with *N*-arylbenzamide derivatives to give the corresponding biaryl with heating and a Pd catalyst.[471] Biaryls were prepared by the electrochemical coupling of phenol derivatives with arenes in a methanol/fluorinated alcohol solvent.[472]

Phenols reacted with aryl iodides in the presence of a Pd catalyst and CO_2 to give the *meta* aryl phenol.[473] Functionalized aromatic compounds reacted with aryl iodides in the presence of $Pd(Ac)_2$ and a 2-hydroxypyridine compound as ligand, and mediated by norbornene, to give the *meta* aryl compound.[474]

Heteroaromatic compounds reacted with bromoheteroarenes with a Pd catalyst and 30% of pivalic acid, with microwave irradiation, to give the heteroaryl–heteroaryl compound.[475] Heteroaromatic compounds reacted with diaryliodinium salts in the presence of NaOH to give the aryl-substituted heteroaromatic compound.[476]

See reactions **13-9**, **13-10**, **13-11**.

11-17 Aryl Ketone Formation: Friedel-Crafts Acylation

$$\mathrm{ArH + RCOCl \xrightarrow{AlCl_3} ArCOR}$$

A traditional method for the preparation of aryl ketones is known as *Friedel-Crafts acylation*.[477] Reagents other than acyl halides can be used,[478] including carboxylic acids,[479] anhydrides, and ketenes. Oxalyl chloride has been used to give diaryl 1,2-diketones.[480] Carboxylic esters usually give alkylation as the predominant product (see **11-11**).[481]

[466] Kano, T.; Ohyabu, Y.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* ***2002***, *124*, 5365.
[467] Demir, A.S.; Findik, H.; Saygili, N.; Subasi, N.T. Te*trahedron* ***2010***, *66*, 1308.
[468] Maji, M.S.; Studer, A. *Synthesis* ***2009***, 2467.
[469] Phipps, R.J.; Grimster, N.P.; Gaunt, M.J. *J. Am. Chem. Soc.* ***2008***, *130*, 8172.
[470] Tan, Y.; Hartwig, J.P. *J. Am. Chem. Soc.* ***2011***, *133*, 3308.
[471] Wang, X.; Leow, D.; Yu, J.-Q. *J. Am. Chem. Soc.* ***2011***, *133*, 13864.
[472] Kirste, A.; Elsler, B.; Schnakenburg, G.; Waldvogel, S.R. *J. Am. Chem. Soc.* ***2012***, *134*, 3571.
[473] Luo, J.; Preciado, S.; Larrosa, I. *J. Am. Chem. Soc.* ***2014***, *136*, 4109.
[474] Wang, P.; Farmer, M.E.; Huo, X.; Jain, P.; Shen, P.-X.; Ishoey, M.; Bradner, J.E.; Wisniewski, S.R.; Eastgate, M.D.; Yu, J.-Q. *J. Am. Chem. Soc.* ***2016***, *138*, 9269.
[475] Baghbanzadeh, M.; Pilger, C.; Kappe, C.O. *J. Org. Chem.* ***2011***, *76*, 8138.
[476] Wen, J.; Zhang, R.-Y.; Chen, S.-Y.; Zhang, J.; Yu, X.-Q. *J. Org. Chem.* ***2012***, *77*, 766.
[477] See Olah, G.A. *Friedel-Crafts and Related Reactions*, Wiley, NY, ***1963–1964***, as follows: Vol. 1, Olah, G.A., pp. 91–115; Vol. 3, Gore, P.H., pp. 1–381; Peto, A.G., pp. 535–910; Sethna, S., pp. 911–1002; Jensen, F.R.; Goldman, G., pp. 1003–1032. Also see *Advances in Friedel-Crafts Acylation Reactions: Catalytic and Green Processes*, Sartori, G.; Maggi, R., CRC Press, Boca Raton, FL. ***2009***.
[478] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1423–1426.
[479] Kawamura, M.; Cui, D.-M.; Hayashi, T.; Shimada, S. *Tetrahedron Lett.* ***2003***, *44*, 7715. See Kaur, J.; Kozhevnikov, I.V. *Chem.Commun.* ***2002***, 2508.
[480] Taber, D.F.; Sethuraman, M.R. *J. Org. Chem.* ***2000***, *65*, 254.
[481] See Hwang, J.P.; Prakash, G.K.S.; Olah, G.A. *Tetrahedron* ***2000***, *56*, 7199.

The alkyl group (R in RCOCl) may be aryl as well as alkyl.[482] The major disadvantages of Friedel-Crafts alkylation, which are polyalkylation and rearrangement of the intermediate carbocation, are not a problem in Friedel-Crafts acylation because (i) the intermediate is an acylium ion (an acylium ion, $RC{\equiv}O^+$) that is stabilized by resonance and (ii) the RCO group is deactivating (the carbonyl is electron withdrawing), so the reaction stops cleanly after one group is introduced because the ketone product is less reactive than the aromatic precursor. All four acyl halides can be used, and the order of activity is usually, but not always, I > Br > Cl > F.[483] However, acyl chlorides are most commonly employed because they are usually the easiest and cheapest to prepare, but primarily because they are sufficiently reactive in most cases. With active substrates (e.g., aryl ethers, fused ring systems, thiophenes), Friedel-Crafts acylation can be carried out with very small amounts of catalyst, often just a trace, or even sometimes with no catalyst at all.

Protonic acids can be used as catalysts when the reagent is a carboxylic acid.[484] Other catalysts can be used. Triflic anhydride promotes dehydrative acylation of carboxylic acids,[485] as does P_2O_5/SiO_2.[486] The mixed carboxylic sulfonic anhydrides $RCOOSO_2CF_3$ are extremely reactive acylating agents and can smoothly acylate benzene without a catalyst.[487] A solvent-free method is also available using tosic acid/graphite.[488] Acyl halides are coupled to arylboronic acids under microwave irradiation.[489] Friedel-Crafts acylation using a carboxylic acid with a catalyst called Envirocat-EPIC (an acid-treated clay-based material was reported.[490] Acylation has been accomplished in carbon disulfide.[491] An interesting variation couples a conjugated acid chloride with benzene, in the presence of $AlCl_3$ and microwave irradiation, to give an indanone.[492] Potassium iodide or lithium iodide has been used as an activating agent for the reaction of acid chlorides with arenes.[493]

The reaction is quite successful for many types of substrate, including fused ring systems which give poor results in **11-11**. Compounds containing electron-donating (*ortho*/*para*-directing) groups, including alkyl, hydroxy, alkoxy, halogen, and acetamido groups, are easily acylated and give mainly or exclusively the *para* products, because of the relatively large size of the acyl group. However, aromatic amines give poor results. With amines and phenols there may be competition from *N*- or *O*-acylation, and the Fries rearrangement may compete with *O*-acylated phenols. *Friedel-Crafts acylation is usually not possible for aromatic rings with only deactivating (meta-directing) groups.* Indeed, nitrobenzene is often used as a solvent for the reaction. Most five-membered ring heterocyclic systems, including

[482] For a discussion of the relationship between electrophilicity of the substituting agents and substrate selectivity, see Meneses, L.; Fuentealba, P.; Contreras, R. *Tetrahedron* ***2005***, *61*, 831.
[483] Yamase, Y. *Bull. Chem. Soc. Jpn.* ***1961***, *34*, 480; Corriu, R. *Bull. Soc. Chim. Fr.* ***1965***, 821.
[484] See Kawamura, M.; Cui, D.-M.; Shimada, S. *Tetrahedron* ***2006***, *62*, 9201. Also see Posternak, A.G.; Garlyauskayte, R.Yu.; Yagupol'ski, L.M. *Tetrahedron Lett.* ***2009***, *50*, 446.
[485] Khodaei, M.M.; Alizadeh, A.; Nazari, E. *Tetrahedron Lett.* ***2007***, *48*, 4199.
[486] Zarei, A.; Hajipour, A.R.; Khazdooz, L. *Tetrahedron Lett.* ***2008***, *49*, 6715.
[487] Effenberger, F.; Sohn, E.; Epple, G. *Chem. Ber.* ***1983***, *116*, 1195. See also, Keumi, T.; Yoshimura, K.; Shimada, M.; Kitajima, H. *Bull. Chem. Soc. Jpn.* ***1988***, *44*, 455.
[488] Sarvari, M.H.; Sharghi, H. *Helv. Chim. Acta* ***2005***, *88*, 2282.
[489] Poláčková, V.; Toma, Š.; Augustínová, I. *Tetrahedron* ***2006***, *62*, 11675.
[490] Bandgar, B.P.; Sadavarte, V.S. *Synth. Commun.* ***1999***, *29*, 2587.
[491] Georgakilas, V.; Perdikomatis, G.P.; Triantafyllou, A.S.; Siskos, M.G.; Zarkadis, A.K. *Tetrahedron* ***2002***, *58*, 2441.
[492] Yin, W.; Ma, Y.; Xu, J.; Zhao, Y. *J. Org. Chem.* ***2006***, *71*, 4312.
[493] Wakeham, R.J.; Taylor, J.E.; Bull, S.D.; Morris, J.A.; Williams, J.M.J. *Org. Lett.* ***2013***, *15*, 702.

furans, thiophenes, and pyrroles,[494] can be acylated in good yield, but not six-membered ring heterocycles, such as pyridines or quinolines. Initial reaction of indole with Et_2AlCl[495] or $SnCl_4$,[496] followed by acetyl chloride, leads to 3-acetylindole; the reaction is in the more active five-membered ring. When an electron-withdrawing group is on the nitrogen, as in *N*-acetylindole, reaction with acetic anhydride and $AlCl_3$ gave *N*,6-diacetylindole.[497] Gore presents an extensive summary of the substrates to which acylation has been applied.[498]

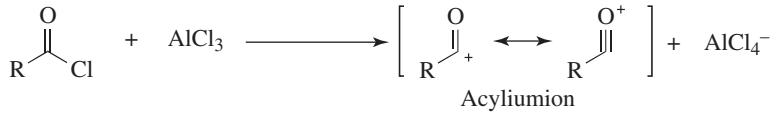
Friedel-Crafts acylation can be carried out with cyclic anhydrides,[499] in which case the product contains a carboxyl group in the side chain. When succinic anhydride is used, the product is $ArCOCH_2CH_2CO_2H$. This product can be reduced (**19-66**) to $ArCH_2CH_2CH_2CO_2H$, and then be cyclized by an internal Friedel-Crafts acylation to give a tetralone. The total process is called the *Haworth reaction*.[500] When a mixed anhydride RCOOCOR′ is the reagent, two products are possible: ArCOR and ArCOR′. Which product predominates depends on two factors. If R contains electron-withdrawing groups, then ArCOR′ is chiefly formed, but if this factor is approximately constant in R and R′, the ketone with the larger R group predominantly forms.[501] This means that *formylations* of the ring do not occur with mixed anhydrides of formic acid HCOOCOR.

As noted, an important use of the Friedel-Crafts acylation is to effect ring closure.[502] This closure can be accomplished if an acyl halide, anhydride, or carboxylic acid[503] group is in the proper position. An example is the conversion of 3-phenylpropanoyl chloride to indanone. The reaction is used mostly to close six-membered rings. Even large rings can be closed by high-dilution techniques.[504] Tricyclic and larger systems are often made by using substrates containing one of the acyl groups on a ring, and many fused ring systems are made in this manner. If the bridging group is CO, the product is a quinone.[505] One of the most common catalysts for intramolecular Friedel-Crafts acylation is polyphosphoric acid[506] (because of its high potency), but $AlCl_3$, H_2SO_4, and other Lewis and proton acids are also used, though acylations with acyl halides are not generally catalyzed by proton acids.

The mechanism of Friedel-Crafts acylation has been studied,[507] and at least two mechanisms probably operate, depending on the conditions.[508]

[494] Yadav, J.S.; Reddy, B.V.S.; Kondaji, G.; Rao, R.S.; Kumar, S.P. *Tetrahedron Lett.* ***2002***, *43*, 8133.
[495] Zhang, Z.; Yang, Z.; Wong, H.; Zhu, J.; Meanwell, N.A.; Kadow, J.F.; Wang, T. *J. Org. Chem.* ***2002***, *67*, 6226.
[496] Ottoni, O.; de V.F. Neder, A.; Dias, A.K.B.; Cruz, R.P.A.; Aquino, L.B. *Org. Lett.* ***2001***, *3*, 1005.
[497] Cruz, R.P.A.; Ottoni, O.; Abella, C.A.M.; Aquino, L.B. *Tetrahedron Lett.* ***2001***, *42*, 1467. See Pal, M.; Dakarapu, R.; Padakanti, S. *J. Org. Chem.* ***2004***, *69*, 2913.
[498] Gore, P.H. *Chem. Ind. (London)* ***1974***, pp. 36–100; with tables, pp. 105–321.
[499] Peto, A.G. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, p. 535.
[500] See Agranat, I.; Shih, Y. *J. Chem. Educ.* ***1976***, *53*, 488.
[501] Edwards Jr., W.R.; Sibelle, E.C. *J. Org. Chem.* ***1963***, *28*, 674.
[502] See Sethna, S. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 911–1002. For examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1427–1431.
[503] See Cui, D.-M.; Zhang, C.; Kawamura, M.; Shimada, S. *Tetrahedron Lett.* ***2004***, *45*, 1741.
[504] See Schubert, W.M.; Sweeney, W.A.; Latourette, H.K. *J. Am. Chem. Soc.* ***1954***, *76*, 5462.
[505] See Naruta, Y.; Maruyama, K. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 1, Wiley, NY, ***1988***, pp. 325–332; Thomson, R.H. in Patai, S. *The Chemistry of the Quinonoid Compounds*, Vol. 1, pt. 1, Wiley, NY, ***1974***, pp. 136–139.
[506] See Rowlands, D.A. in Pizey, J.S. *Synthetic Reagents*, Vol. 6, Wiley, NY, ***1985***, pp. 156–414.
[507] See Effenberger, F.; Eberhard, J.K.; Maier, A.H. *J. Am. Chem. Soc.* ***1996***, *118*, 12572.
[508] See Taylor, R. *Electrophilic Aromatic Substitution*, Wiley, NY, ***1990***, pp. 222–237.

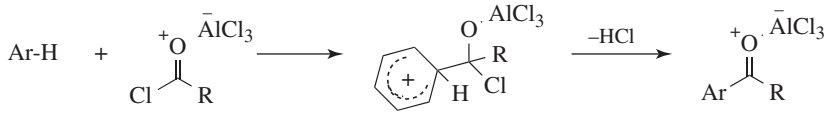
1. In most cases the species attacked by benzene is the acyl cation, the resonance-stabilized *acyliun ion*, either free or as an ion pair, formed by the chlorine atom of an acid chloride reacting as a Lewis base, attacking the aluminum of the Lewis acid, $AlCl_3$.[509]



Acyliumion

If R is tertiary, RCO^+ may lose CO to give R^+, and the alkyl arene ArR is often a side product or even the main product. Such cleavage is much more likely with relatively unreactive substrates, where the acylium ion has time to break down. For example, pivaloyl chloride (Me_3CCOCl) gives the normal acyl product with anisole but gives the alkyl product Me_3CPh with benzene.

2. In the other mechanism, an acyl cation is not involved, but the 1:1 complex (**35**) is formed and reacts with benzene directly to give **36**.[510] Loss of HCl leads to **37**, the complexed ketone product.



Free-ion attack is more likely for sterically hindered R.[511] The ion CH_3CO^+ has been detected (by IR spectroscopy) in the liquid complex between acetyl chloride and aluminum chloride, and in polar solvents, such as nitrobenzene; but in nonpolar solvents, such as chloroform, only the complex and not the free ion is present.[512] In any event, 1 molar equivalent of catalyst certainly remains complexed to the product at the end of the reaction. When the reaction is performed with RCO^+ SbF_6^- no catalyst is required and the free ion[513] (or ion pair) is undoubtedly the attacking entity.[514] The use of $LiClO_4$ on the metal triflate-catalyzed Friedel-Crafts acylation of methoxynaphthalene derivatives has been examined, and the presence of the lithium salt leads to acylation in the ring containing the methoxy unit, whereas reaction occurs in the other ring in the absence of lithium salts.[515]

[509] After 2 min, exchange between PhCOCl and $Al(^{36}Cl)_3$ is complete: Oulevey, G.; Susz, P.B. *Helv. Chim. Acta* ***1964***, *47*, 1828.
[510] See Tan, L.K.; Brownstein, S. *J. Org. Chem.* ***1983***, *48*, 302.
[511] Gore, P.H. *Bull. Chem. Soc. Jpn.* ***1962***, *35*, 1627; Satchell, D.P.N. *J. Chem. Soc.* ***1961***, 5404.
[512] Cassimatis, D.; Bonnin, J.P.; Theophanides, T. *Can. J. Chem.* ***1970***, *48*, 3860.
[513] See Chevrier, B.; Le Carpentier, J.; Weiss, R. *Acta Crystallogr., Sect. B* ***1972***, *28*, 2673; *J. Am. Chem. Soc.* ***1972***, *94*, 5718.
[514] Olah, G.A.; Lin, H.C.; Germain, A. *Synthesis* ***1974***, 895. Also see Al-Talib, M.; Tashtoush, H. *Org. Prep. Proced. Int.* ***1990***, *22*, 1.
[515] Kobayashi, S.; Komoto, I. *Tetrahedron* ***2000***, *56*, 6463.

In most Friedel-Crafts acylation reactions, the catalyst is a Lewis acid,[516] similar to those in reaction **11-11**. In acylation a little more than 1 equivalent of catalyst is required per mole of reagent, because the first equivalent coordinates with the oxygen of the reagent [as in $R(Cl)C{=}O^{+}{}^{-}AlCl_3$].[517] A reusable catalyst [$Ln(OTf)_3{-}LiClO_4$] has been developed.[518] Ferric chloride in an ionic liquid has also been used.[519] Work continues using myriad catalysts for Friedel-Crafts acylation. Aryl iodides reacted with aldehydes, with $Pd(OAc)_2$ and Ag_2O, in the presence of TBHP, to give the acyl ketone.[520] Aryl methyl ketones have been prepared by the cross coupling of aryl bromides or heteroaryl bromides and acetyltrimethylsilane, in the presence of a Pd catalyst.[521] The erbium trifluoromethanesulfonate-catalyzed acylation using aromatic carboxylic acids has been reported, using microwave irradiation.[522] Aryl methyl ketones reacted with aryl halide to give diaryl ketones using a Pd catalyst and then exposure to oxygen.[523] Arylthio esters reacted with arylzinc chlorides (ArZnCl) to give the diaryl ketone using a Pd catalyst.[524] Triphenylbismuth reacted with 3 equivalents of benzoyl chloride to give 3 equivalents of benzophenone using a Pd catalyst on a mobile crystalline material.[525] Aromatic compounds reacted with acyl chlorides in the presence of $AgNO_3$ to give the aryl ketone.[526] Friedel-Crafts acylation has been accomplished with arenes and acyl halides using $Bi(OTf)_3$ in $(bmi)PF_6$ with microwave irradiation or with heating.[527] A catalytic, regioselective Friedel-Crafts acylation has been reported, using nanopowder $CuFe_2O_4$ catalyst that is moisture insensitive. Note that the magnetic properties of the catalyst render it magnetically separable.[528] Biaryl-2-tosylamines reacted with aryl aldehydes in the presence of a Pd catalyst and 2 equivalents each of TBHP and acetic acid give the 2′-aryl ketone 2-tosylaminebiaryl.[529] Functionalized arenes treated with acetamide and SO_2Cl_2 gave the Friedel-Crafts acylation product including using sonication or microwave irradiation.[530] 4-Fluorobenzoic acid

[516] See Pearson, D.E.; Buehler, C.A. *Synthesis* ***1972***, 533. Metals used include **Bi**: Répichet, S.; Le Roux, C.; Roques, N.; Dubac, J. *Tetrahedron Lett.* ***2003***, *44*, 2037. **Ga**: Matsu, J.-i.; Odashima, K.; Kobayashi, S. *Synlett* ***2000***, 403. **In**: Choudhary, V.R.; Jana, S.K.; Patil, N.S. *Tetrahedron Lett.* ***2002***, *43*, 1105. **Sc**: Kawada, A.; Mitamura, S.; Matsuo, J.-i.; Tsuchiya, T.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 2325. **Pd**: Fürstner, A.; Voigtländer, D.; Schrader, W.; Giebel, D.; Reetz, M.T. *Org. Lett.* ***2001***, *3*, 417. **Sm**: Soueidan, M.; Collin, J.; Gil, R. *Tetrahedron Lett.* ***2006***, *47*, 5467. **Ti**: Bensari, A.; Zaveri, N.T. *Synthesis* ***2003***, 267. **Yb**: Barrett, A.G.M.; Bouloc, N.; Braddock, D.C.; Chadwick, D.; Henderson, D.A. *Synlett* ***2002***, 1653. **Zn**: See Sarvari, M.H.; Sharghi, H. *J. Org. Chem.* ***2004***, *69*, 6953.

[517] See Chevrier, B.; Weiss, R. *Angew. Chem. Int. Ed.* ***1974***, *13*, 1. For a discussion of the acylium ion formed by $AlCl_3$, see Huang, Z.; Lin, L.; Han, H.; Lei, A. *Org. Biomol. Chem.* ***2013***, *11*, 1810. For a review of solid catalysts see Sartori, G.; Maggi, R. *Chem. Rev.* ***2011***, *111*, PR181.

[518] See Kawada, A.; Mitamura, S.; Kobayashi, S. *Chem. Commun.* ***1996***, 183.

[519] Khodaei, M.M.; Bahrami, K.; Shahbazi, F. *Chem. Lett.* ***2008***, *37*, 844. Also see Gmouth, S.; Yang, H.; Vaultier, M. *Org. Lett.* ***2003***, *5*, 2219.

[520] Suchand, B.; Satyanarayana, G. *J. Org. Chem.* ***2016***, *81*, 6409.

[521] Ramgren, S.D.; Garg, N.K. *Org. Lett.* ***2014***, *16*, 824.

[522] Tran, P.H.; Hansen, P.E.; Nguyen, H.T.; Le, T.N. *Tetrahedron Lett.* ***2015***, *56*, 612.

[523] Wang, X.; Liu, F.-D.; Tu, H.-Y.; Zhang, A.-D. *J. Org. Chem.* ***2014***, *79*, 6554.

[524] Kunchithapatham, K.; Eichman, C.C.; Stambuli, J.P. *Chem. Commun.* ***2011***, *47*, 12679.

[525] Zhao, H.; Yin, L.; Cai, M. *Eur. J. Org. Chem.* ***2013***, 1337.

[526] Rai, K.M.L.; Musad, E.A. Jagadish, L.; Shivakumar, K.N. *Synth. Commun.* ***2010–2011***, *41*, 953.

[527] Tran, P.H.; Duus, F.; Le, T.N. *Tetrahedron Lett.* ***2012***, *53*, 222; Tran, P.H.; Do, N.B.L.; Le, T.N. *Tetrahedron Lett.* ***2014***, *55*, 205. For an indium triflate-catalyzed reaction and ionic solvent, see Tran, P.H.; Hansen, P.E.; Hoang, H.M.; Chau, D.-K.N.C.; Le, T.N. *Tetrahedron Lett.* ***2015***, *56*, 2187.

[528] Parella, R.; Naveen, Kumar, A.; Babu, S.A. *Tetrahedron Lett.* ***2013***, *54*, 1738.

[529] Cai, Z.-J.; Yang, C.; Wang, S.-Y.; Ji, S.-J. *J. Org. Chem.* ***2015***, *80*, 7928.

[530] Kumar, M.S.; Rajanna, K.C.; Venkanna, P.; Venkateswarlu, M. *Tetrahedron Lett.* ***2014***, *55*, 1756.

reacted with toluene in the presence of methanesulfonic anhydride to give the corresponding diaryl ketone.[531]

An aza-Friedel-Crafts reaction of a phenol derivative, sesamol, with an aldimine in the presence of a Sc catalyst and 3-bromobenzoic acid led to the benzylic amide derivative.[532] Indoles reacted with acyl chlorides in the presence of $ZrCl_4$ to give the 3-acylindole.[533] 2-Alkylindoles reacted first with DBU and then with acyl halides to give the 3-acylindole.[534] Aryl iodides reacted with aryl acid chlorides and CuCN, in the presence of a catalytic amount of $PdCl_2$ and mediated by norbornene, to give the *ortho* cyano diaryl ketone.[535] An intramolecular Friedel-Crafts reaction of an arylalkyl acid chloride gave an indanone or a tetralone product, promoted by a 1,1,1,3,3,3-hexafluoropropan-2-ol solvent.[536]

An intramolecular phospha-Friedel-Crafts reaction has been reported.[537]

OS **I**, 109, 353, 476, 517; **II**, 3, 8, 15, 81, 156, 169, 304, 520, 569; **III**, 6, 14, 23, 53, 109, 183, 248, 272, 593, 637, 761, 798; **IV**, 8, 34, 88, 898, 900; **V**, 111; **VI**, 34, 618, 625 **X**, 125.

11-18 Aromatic Aldehyde Formation: Formylation

$$\text{Ar-H} \longrightarrow \text{Ar-CHO}$$

Direct formylation of an aromatic ring leads to an aldehyde.[538] Reaction **11-17** has not been used for formylation, since neither formic anhydride nor formyl chloride is stable at ordinary temperatures. Formyl chloride has been shown to be stable in chloroform solution for 1 h at −60 °C,[539] but it is not useful for formylating aromatic rings under these conditions. Formic anhydride has been prepared in solution, but has not been isolated.[540] Mixed anhydrides of formic and other acids are known[541] and can be used to formylate amines (see **16-72**) and alcohols, but no formylation takes place when they are applied to aromatic rings. See **13-12** for a nucleophilic method for the formylation of aromatic rings.

The reaction with disubstituted formamides $R_2N{-}CHO$ and phosphorus oxychloride, called the *Vilsmeier* or the *Vilsmeier-Haack reaction*,[542] is the most common method for the

[531] Wilkinson, C. *Org. Lett.* ***2011***, *13*, 2232.

[532] Bai, S.; Liao, Y.; Lin, L.; Luo, W.; Liu, X.; Feng, X. *J. Org. Chem.* ***2014***, *79*, 10662. See Jaratjaroonphong, J.; Krajangsri, S.; Reutrakul, V. *Tetrahedron Lett.* ***2012***, *53*, 2476.

[533] Guchhait, S.K.; Kashyap, M.; Kamble, H. *J. Org. Chem.* ***2011***, *76*, 4753. Also see Barbosa, J.d.S.; da Silva, G.V.; Constantino, M.G. *Tetrahedron Lett.* ***2015***, *56*, 4649.

[534] Johansson, H.; Urruticoechea, A.; Larsen, I.; Pedersen, D.S. *J. Org. Chem.* ***2015***, *80*, 471.

[535] Pan, S.; Wu, F.; Yu, R.; Chen, W. *J. Org. Chem.* ***2016***, *81*, 1558.

[536] Motiwala, H.F.; Vekariya, R.H.; Aubé, J. *Org. Lett.* ***2015***, *17*, 5484. For an intermolecular reaction, see Vekariya, R.H.; Aubé, J. *Org. Lett.* ***2016***, *18*, 3534–3537. Also see Champagne, P.A.; Benhassine, Y.; Desroches, J.; Paquin, J.-F. *Angew. Chem. Int. Ed.* ***2014***, *53*, 13835; Winter, D.K.; Endoma-Arias, M.A.; Hudlicky, T.; Beutler, J.A.; Porco, J.A. *J. Org. Chem.* ***2013***, *78*, 7617.

[537] Wu, B.; Chopra, R.; Yoshikai, N. *Org. Lett.* ***2015***, *17*, 5666.

[538] See Olah, G.A.; Kuhn, S.J.; Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1153–1256; Olah, G.A.; Ohannesian, L.; Arvanaghi, M. *Chem. Rev.* ***1987***, *87*, 671. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1423–1426.

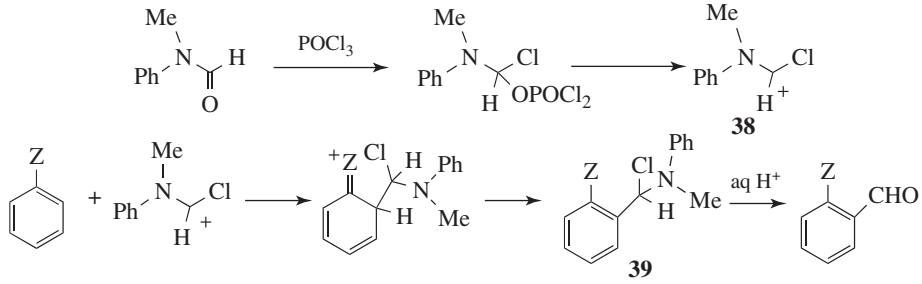
[539] Staab, H.A.; Datta, A.P. *Angew. Chem. Int. Ed.* ***1964***, *3*, 132.

[540] Olah, G.A.; Vankar, Y.D.; Arvanaghi, M.; Sommer, J. *Angew. Chem. Int. Ed.* ***1979***, *18*, 614.

[541] Stevens, W.; van Es, A. *Recl. Trav. Chim. Pays-Bas* ***1964***, *83*, 863.

[542] Reichardt, C. *J. Prakt. Chem.* ***1999***, *341*, 609; Arnold, Z.; Holy, A. *Collect. Czech. Chem. Commun.* ***1962***, *27*, 2886.

formylation of aromatic rings.[543] However, it is applicable only to active substrates, such as amines and phenols. An intramolecular version is also known.[544] Aromatic hydrocarbons and heterocycles can also be formylated, but only if they are much more active than benzene (e.g., azulenes, ferrocenes). Although *N*-phenyl-*N*-methylformamide is a common reagent, other arylalkyl amides and dialkyl amides are also used.[545] Phosgene ($COCl_2$) has been used in place of $POCl_3$. The reaction has also been carried out with other amides to give ketones (actually an example of **11-17**), but not often. The reactive species[546] is **38**,[547] and the mechanism is probably that shown to give **39**, which is unstable and easily hydrolyzes to the product. Either formation of **38** or the reaction of **38** with the substrate can be rate determining, depending on the reactivity of the substrate.[548]



In a related reaction, paraformaldehyde can be used, with $MgCl_2/NEt_3$, to convert phenol to phenol 2-carbaldehyde.[549] Another variation treated acetanilide with $POCl_3$/DMF and generated 2-chloroquinoline-3-carboxaldehyde.[550] Used in conjunction with conjugated hydroxylamines, a tandem *Vilsmeier-Beckman reaction* (see **18-17** for the *Beckman rearrangement*) leads to pyridines (2-chloro-3-carbaldehyde).[551] A chain-extension variation has been reported in which an aryl alkyl ketone is treated with $POCl_3$/DMF on silica with microwave irradiation to give a conjugated aldehyde:[552]

$$ArC(=O)R \rightarrow ArC(Cl)=CHCHO$$

When $(CF_3SO_2)_2O$ was used instead of $POCl_3$, the reaction was extended to some less-active compounds, including naphthalene and phenanthrene.[553] The reaction of aryl ethers, phenol, and also arenes with 3 equivalents of AgOTf and 3 equivalents of Cl_2CHOMe

[543] Jutz, C. *Adv. Org. Chem.* ***1976***, *9*, pt. 1, 225.
[544] Meth-Cohn, O.; Goon, S. *J. Chem. Soc., Perkin Trans. 1* ***1997***, 85.
[545] See Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 1–99.
[546] For a review of such species, see Kantlehner, W. *Adv. Org. Chem.* ***1979***, *9*, pt. 2, 5.
[547] See Arnold, Z.; Holy, A. *Collect. Czech. Chem. Commun.* ***1962***, *27*, 2886; Jugie, G.; Smith, J.A.S.; Martin, G.J. *J. Chem. Soc., Perkin Trans. 2* ***1975***, 925.
[548] Alunni, S.; Linda, P.; Marino, G.; Santini, S.; Savelli, G. *J. Chem. Soc., Perkin Trans. 2* ***1972***, 2070.
[549] Hofsløkken, N.U.; Skattebøl, L. *Acta Chem. Scand.* ***1999***, *53*, 258.
[550] Ali, M.M.; Tasneem, Rajanna, K.C.; Prakash, P.K.S. *Synlett* ***2001***, 251. Also see Akila, S.; Selvi, S.; Balasubramanian, K. *Tetrahedron* ***2001***, *57*, 3465.
[551] Amaresh, R.R.; Perumal, P.T. *Synth. Commun.* ***2000***, *30*, 2269.
[552] Paul, S.; Gupta, M.; Gupta, R. *Synlett* ***2000***, 1115.
[553] Martínez, A.G.; Alvarez, R.M.; Barcina, J.O.; Cerero, S. de la M.; Vilar, E.T.; Fraile, A.G.; Hanack, M.; Subramanian, L.R. *J. Chem. Soc., Chem. Commun.* ***1990***, 1571.

gave the *ortho* formyl derivative.[554] Aryl halides reacted with *t*-BuNC and Et_3SiH in DMF, with $Pd(OAc)_2$ and JohnPhos, to give the aryl aldehyde.[555] Aryl iodides reacted with CO and H_2 with a Pd catalyst to give the aryl carbaldehyde.[556] Aryl bromides reacted with paraformaldehyde and Et_3SiH with a Pd catalyst gave the aryl carbaldehyde.[557] Aryl iodides reacted with CO, base, and a Pd catalyst in PEG-400 to give the aryl carbaldehyde.[558] The Pd-catalyzed formylation of aryl iodides used formic acid.[559] Arylzinc halides reacted with *S*-phenylthioformate and a Pd catalyst to give the corresponding aryl carbaldehyde.[560] Aromatic iodides are formylated using CO_2 with a Pd catalyst on nanoparticles grafted onto amino-functionalized nanostarch. The reaction of aryl halides with CO_2 and PMHS, in the presence of a Pd catalyst and DBU, gave aryl aldehydes.[561]

Indoles reacted with *N*-methylaniline and TBHP with a $RuCl_3$ catalyst to give the 3-formylindole.[562] Indoles reacted with DMSO and 4 equivalents of ammonium acetate in water, at 150 °C, to give the 3-formylindole.[563] Indoles and quinolines reacted with formic acid and a Pd/C catalyst to give the formyl derivative.[564] Hexamethylenetetramine and air was used for the iodine-catalyzed C3-formylation of indole derivatives.[565] *N*-Alkyldihydropyrroles reacted with DMSO in air, with 60% $FeCl_3$, to give the corresponding 2-formylpyrrole.[566]

OS **I**, 217; **III**, 98, **IV**, 331, 539, 831, 915.

$$ArH + Cl_2CHOMe \xrightarrow{AlCl_3} ArCHO$$

Several other formylation methods are known.[567] Dichloromethyl methyl ether formylates aromatic rings with *Friedel-Crafts catalysts*, giving the aldehyde.[568] The ArCHClOMe compound is probably an intermediate. Orthoformates have also been used.[569] In another method, aromatic rings are formylated with formyl fluoride (HCOF) and BF_3.[570] Unlike formyl chloride, formyl fluoride is stable enough for this purpose. This reaction was successful for benzene, alkylbenzenes, PhCl, PhBr, and naphthalene. Phenols can be regioselectively formylated in the *ortho* position in high yields by treatment with 2 molar equivalents of paraformaldehyde in aprotic solvents in the presence of $SnCl_4$ and a tertiary amine.[571]

[554] Ohsawa, K.; Yoshida, M.; Doi, T. *J. Org. Chem.* ***2013***, *78*, 3438.
[555] Jiang, X.; Wang, J.-M.; Zhang, Y.; Chen, Z.; Zhu, Y.-M.; Ji, S.-J. *Org. Lett.* ***2014***, *16*, 3492.
[556] Singh, A.S.; Bhanage, B.M.; Nagarkar, J.M. *Tetrahedron Lett.* ***2011***, *52*, 2383. Also see Neumann, H.; Kadyrov, R.; Wu, X.-F.; Beller, M. *Chem. Asian J.* ***2012***, *7*, 2213.
[557] Kumar, S.; Verma, S.; Jain, S.L. *Tetrahedron Lett.* ***2015***, *56*, 2430.
[558] Han, W.; Liu, B.; Chen, J.; Zhou, Q. *Synlett* ***2017***, *28*, 835.
[559] Sun, G.; Lv, X.; Zhang, Y.; Lei, M.; Hu, L. *Org. Lett.* ***2017***, *19*, 4235.
[560] Haraguchi, R.; Tanazawa, S.-g.; Tokunaga, N.; Fukuzawa, S.-i. *Org. Lett.* ***2017***, *19*, 1646.
[561] Yu, B.; Yang, Z.; Zhao, Y.; Hao, L.; Zhang, H.; Gao, X.; Han, B.; Liu, Z. *Chem. Eur. J.* ***2016***, *22*, 1097.
[562] Wu, W.; Su, W. *J. Am. Chem. Soc.* ***2011***, *133*, 11924.
[563] Fei, H.; Yu, J.; Jiang, Y.; Guo, H.; Cheng, J. *Org. Biomol. Chem.* ***2013***, *11*, 7092.
[564] Kulkarni, A.; Gianatassio, R.; Török, B. *Synthesis* ***2011***, *43*, 1227.
[565] Wang, Q.-D.; Yang, J.-M.; Fang, D.; Ren, J.; Zeng, B.-B. *Tetrahedron. Lett.* ***2017***, *58*, 2877.
[566] Zhang, Z.; Tian, Q.; Qian, J.; Liu, Q.; Liu, T.; Shi, L.; Zhang, G. *J. Org. Chem.* ***2014***, *79*, 8182.
[567] See Nishino, H.; Tsunoda, K.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 545.
[568] Lewin, A.H.; Parker, S.R.; Fleming, N.B.; Carroll, F.I. *Org. Prep. Proceed. Int.* ***1978***, *10*, 201.
[569] Gross, H.; Rieche, A.; Matthey, G. *Chem. Ber.* ***1963***, *96*, 308.
[570] Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* ***1960***, *82*, 2380.
[571] Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G.; Terenghi, G. *J. Chem. Soc., Perkin Trans. 1* ***1980***, 1862.

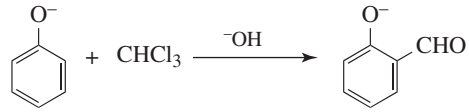
OS **V**, 49; **VII**, 162.

$$ArH + Zn(CN)_2 \xrightarrow{HCl} ArCH{=}NH_2^+\,Cl^- \xrightarrow{H_2O} ArCHO$$

Formylation with $Zn(CN)_2$ and HCl is called the *Gatterman reaction*.[572] It can be applied to alkylbenzenes, phenols and their ethers, and many heterocyclic compounds. However, it cannot be applied to aromatic amines. In the original version of this reaction the substrate was treated with HCN, HCl, and $ZnCl_2$, but the use of $Zn(CN)_2$ and HCl (HCN and $ZnCl_2$ are generated *in situ*) makes the reaction more convenient to carry out and yields are not diminished. The mechanism of the Gatterman reaction has not been investigated very much, but it is known that an initially formed but not isolated nitrogen-containing product is hydrolyzed to aldehyde. This product is presumed to be $ArCH{=}NH_2^+\,Cl^-$, as shown. When benzene was treated with NaCN under superacid conditions ($F_3CSO_2OH{-}SbF_5$, Sec. 5.A.ii), a good yield of product was obtained, leading to the conclusion that the electrophile in this case was $^+C(H){=}N^+H_2$.[573] The Gatterman reaction may be regarded as a special case of **11-24**.

Another method, formylation with CO and HCl in the presence of $AlCl_3$ and CuCl[574] (the *Gatterman-Koch reaction*), is limited to benzene and alkylbenzenes.[575] Aryl halides are converted to aryl aldehydes with CO/H_2 in the presence of a Pd catalyst.[576]

OS **II**, 583; **III**, 549.



In the *Reimer-Tiemann reaction*, aromatic rings are formylated by reaction with chloroform and hydroxide ion.[577] The method is useful only for phenols and certain heterocyclic compounds such as pyrroles and indoles. Unlike the previous formylation methods (in this section), this one is conducted in basic solution. Yields are generally low, seldom rising above 50%.[578] The incoming group is directed *ortho*, unless both *ortho* positions are filled, in which case the attack is *para*.[579] Certain substrates have been shown to give abnormal products instead of or in addition to the normal ones.[580]

A method closely related to the Reimer-Tiemann reaction is the *Duff reaction*, in which hexamethylenetetramine $(CH_2)_6N_4$ is used instead of chloroform. This reaction can be applied only to phenols and amines; *ortho* substitution is generally observed and yields

[572] See Truce, W.E. *Org. React.* ***1957***, *9*, 37; Tanaka, M.; Fujiwara, M.; Ando, H. *J. Org. Chem.* ***1995***, *60*, 2106 for rate studies.
[573] Yato, M.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* ***1991***, *113*, 691.
[574] See, however, Toniolo, L.; Graziani, M. *J. Organomet. Chem.* ***1980***, *194*, 221.
[575] See Crounse, N.N. *Org. React.* ***1949***, *5*, 290.
[576] Sergeev, A.G.; Spannenberg, A.; Beller, M. *J. Am. Chem. Soc.* ***2008***, *130*, 15549.
[577] See Wynberg, H.; Meijer, E.W. *Org. React.* ***1982***, *28*, 1.
[578] See Cochran, J.C.; Melville, M.G. *Synth. Commun.* ***1990***, *20*, 609.
[579] See, however, Neumann, R.; Sasson, Y. *Synthesis* ***1986***, 569.
[580] See Kulinkovich, O.G. *Russ. Chem. Rev.* ***1989***, *58*, 711. See Robinson, E.A. *J. Chem. Soc.* ***1961***, 1663. See also, Langlois, B.R. *Tetrahedron Lett.* ***1991***, *32*, 3691.

are low. A mechanism[581] has been proposed that involves initial aminoalkylation (**11-22**) to give $ArCH_2NH_2$, followed by dehydrogenation to ArCH=NH and hydrolysis of this to the aldehyde product. When $(CH_2)_6N_4$ is used in conjunction with F_3CCO_2H, the reaction can be applied to simple alkylbenzenes; yields are much higher and a high degree of regioselective *para* substitution is found.[582] In this case too an imine seems to be an intermediate. Reaction **11-19** is the direct carboxylation[583] of aromatic rings.[584]

OS **III**, 463; **IV**, 866.

11-19 Aryl Carboxylic Acid Formation

$$ArH + COCl_2 \xrightarrow{AlCl_3} ArCOOH$$

Phosgene, in the presence of *Friedel-Crafts catalysts*, can carboxylate the ring. This process is analogous to **11-17**, but the ArCOCl product initially produced hydrolyzes to the carboxylic acid. However, in most cases the reaction does not take this course, but instead the ArCOCl is attacked by another ring to give a ketone ArCOAr. A number of other reagents have been used to get around this difficulty, including oxalyl chloride, urea hydrochloride, chloral (Cl_3CCHO),[585] carbamoyl chloride (H_2NCOCl), and *N*,*N*-diethylcarbamoyl chloride.[586] With carbamoyl chloride the reaction is called the *Gatterman amide synthesis* and the product is an amide. Among compounds carboxylated by one or another of these reagents are benzene, alkylbenzenes, and fused ring systems.[587]

Although mechanistically different, other methods are available to convert aromatic compounds to aromatic carboxylic acids. The Pd-catalyzed reaction of aromatic compounds and formic acid leads to benzoic acid derivatives.[588] Diphenyliodonium tetrafluoroborate, $Ph_2I^+ BF_4^-$ reacts with CO and indium in DMF, with a Pd catalyst, to give benzophenone.[589] The Ni-catalyzed reaction of CO_2 with aryl bromides and aryl triflates led to carboxylation.[590] 2-Phenylpyridine reacted with CO_2 and 2 equivalents of $AlMe_2(OMe)$, in the presence of a Rh catalyst, to give the 2-pyridylbenzoic acid.[591] Aryl or vinyl chlorides reacted with CO_2 and a Ni catalyst, mediated by Mn, to give the corresponding carboxylic acid.[592] Aryl iodides reacted with CO and K_2CO_3 with a Pd catalyst to give the benzoic acid derivative.[593] Aryl bromides reacted with epoxides and an alcohol in the presence of

[581] Ogata, Y.; Kawasaki, A.; Sugiura, F. *Tetrahedron* ***1968***, *24*, 5001.
[582] Smith, W.E. *J. Org. Chem.* ***1972***, *37*, 3972.
[583] See Fujiwara, Y.; Kawata, I.; Kawauchi, T.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* ***1982***, 132.
[584] See Olah, G.A.; Olah, J.A. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1257–1273.
[585] Menegheli, P.; Rezende, M.C.; Zucco, C. *Synth. Commun.* ***1987***, *17*, 457.
[586] Naumov, Yu.A.; Isakova, A.P.; Kost, A.N.; Zakharov, V.P.; Zvolinskii, V.P.; Moiseikina, N.F.; Nikeryasova, S.V. *J. Org. Chem. USSR* ***1975***, *11*, 362.
[587] See Sartori, G.; Casnati, G.; Bigi, F.; Bonini, G. *Synthesis* ***1988***, 763.
[588] Shibahara, F.; Kinoshita, S.; Nozaki, K. *Org. Lett.* ***2004***, *6*, 2437.
[589] Zhou, T.; Chen, Z.-C. *Synth. Commun.* ***2002***, *32*, 3431.
[590] Meng, Q.-Y.; Wang, S.; König, B. *Angew. Chem. Int. Ed.* ***2017***, *56*, 13426.
[591] Mizuno, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* ***2011***, *133*, 1251.
[592] Fujihara, T.; Nogi, K.; Xu, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* ***2012***, *134*, 9106.
[593] Han, W.; Jin, F.; Zhou, Q. *Synthesis* ***2015***, *47*, 1861.

Pd/C at 150 °C to give the corresponding aryl ester.[594] Arylboronic esters reacted with CO_2 and a Ag catalyst to give the aryl carboxylic acid.[595]

The reaction of indoles with CO_2 and 5 equivalents of LiOtBu in DMF at 100 °C gave the indole 3-carbxylic acid.[596] Indole 3-carbxylate esters were prepared from indoles and CO and an alcohol in the presence of $K_2S_2O_8$ and a Rh catalyst.[597]

OS **V**, 706; **VII**, 420.

Sodium phenoxides can be carboxylated, mostly in the *ortho* position, by carbon dioxide (the *Kolbe-Schmitt reaction*). The mechanism is not clearly understood, but apparently some kind of a complex is formed between the reactants (Ar—O••••Na••••O═C═O),[598] making the carbon of the CO_2 more positive and putting it in a good position to attack the ring. Potassium phenoxide, which is less likely to form such a complex, chiefly reacts at the *para* position. There is evidence that, in the complex formed from potassium salts, the bonding is between the aromatic compound and the carbon atom of CO_2.[599] Carbon tetrachloride can be used instead of CO_2, under *Reimer-Tiemann* (**11-18**) conditions.

A Pd-catalyzed reaction has been used to directly prepare acyl fluorides.[600] Molybdovanadophosphates have been used for the carboxylation of anisole in the presence of CO and O_2.[601] Sodium or potassium phenoxide can be carboxylated regioselectively in the *para* position in high yield by treatment with Na_2CO_3 or K_2CO_3 and CO.[602] ^{14}C labeling showed that it is the carbonate carbon that appears in the *p*-hydroxybenzoic acid product.[603] The CO is converted to sodium formate or potassium formate. Carbon monoxide has also been used to carboxylate aromatic rings with Pd compounds as catalysts.[604] A Pd-catalyzed carboxylation has been reported using Ag_2CO_3 and CO.[605]

An enzymatic carboxylation was reported, in supercritical CO_2 (Sec. 9.D.ii), in which exposure of pyrrole to *Bacillus megaterium* PYR2910 and $KHCO_3$ gave the potassium salt of pyrrole 2-carboxylic acid.[606]

OS **II**, 557.

[594] Min, B.-H.; Kim, D.-S.; Park, H.-S.; Jun, C.-H. *Chem. Eur. J.* ***2016***, *22*, 6234.
[595] Zhang, X.; Zhang, W.-Z.; Shi, L.-L. Guo, C.-X.; Zhang, L.-L.; Lu, X.-B. *Chem. Commun.* ***2012***, *48*, 6292.
[596] Yoo, W.-J.; Capdevila, M.G.; Du, X.; Kobayashi, S. *Org. Lett.* ***2012***, *14*, 5326.
[597] Lang, R.; Wu, J.; Shi, K.; Xia, C.; Li, F. *Chem. Commun.* ***2011***, *47*, 12553.
[598] Hales J.L.; Jones, J.I.; Lindsey, A.S. *J. Chem. Soc.* ***1954***, 3145.
[599] See Hirao, I.; Kito, T. *Bull. Chem. Soc. Jpn.* ***1973***, *46*, 3470.
[600] Sakajura, T.; Chaisakitsin, M.; Hayashi, T.; Tanaka, M. *J. Organometal. Chem.* ***1987***, *334*, 205.
[601] Ohashi, S.; Sakaguchi, S.; Ishii, Y. *Chem. Commun* ***2005***, 486.
[602] Yasuhara, Y.; Nogi, T. *J. Org. Chem.* ***1968***, *33*, 4512; *Chem. Ind. (London)* ***1969***, 77.
[603] Yasuhara, Y.; Nogi, T.; Saisho, H. *Bull. Chem. Soc. Jpn.* ***1969***, *42*, 2070.
[604] See Jintoku, T.; Taniguchi, H.; Fujiwara, Y. *Chem. Lett.* ***1987***, 1159; Ugo, R.; Chiesa, A. *J. Chem. Soc., Perkin Trans. 1* ***1987***, 2625.
[605] Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* ***2008***, *130*, 14082. See also, Sakakibara, K.; Yamashita, M.; Nozaki, K. *Tetrahedron Lett.* ***2005***, *46*, 959.
[606] Matsuda, T.; Ohashi, Y.; Harada, T.; Yanagihara, R.; Nagasawa, T.; Nakamura, K. *Chem. Commun.* ***2001***, 2194.

11-20 Carboxylation: Amidation

$$\mathrm{ArH + RNCO \xrightarrow{AlCl_3} ArCONHR}$$

N-Substituted amides can be prepared by direct attack of isocyanates on aromatic rings.[607] The R group may be alkyl or aryl but, if the latter, dimers and trimers are also obtained. Isothiocyanates similarly give thioamides.[608] The reaction has been carried out intramolecularly both with aralkyl isothiocyanates and acyl isothiocyanates.[609] In the latter case, the product is easily hydrolyzable to a dicarboxylic acid; this is a way of putting a carboxyl group on a ring *ortho* to one already there. The reaction gives better yields with substrates such as $ArCH_2CONCS$, where six-membered rings are formed.

There are interesting transition metal-catalyzed reactions that lead to aryl amides.[610] The use of $POCl_3$ and DMF, with a Pd catalyst, converts aryl iodides to benzamides.[611] Carbonylation is another method that generates amides. Aminocarbonylation is accomplished with microwave irradiation using hydroxylamine as an ammonia equivalent.[612]

Benzamide derivatives and heteroaryl carboxamide derivatives reacted with $TsNH_2$ and $Cu(OAc)_2$ in the air to give the *ortho N*-anilide derivative.[613] Arenes reacted with formamides and $POCl_3$ and $Pd(OAc)_2$/Xantiphos to give the corresponding benzamide derivative.[614] An indole reacted with *N*-phenylacetamide to give the *N*-phenyl-*N*-acetylindole using 2 equivalents of *t*-butyl peroxide and 20% CuBr.[615] Phenol derivatives reacted with CO, ammonia, DBU, and $C_4H_9SO_2F$, with a Pd catalyst, to give the benzamide derivative.[616] The reaction of aryl bromides, CO, and ammonium carbamate gave benzamide derivatives in the presence of a Pd catalyst.[617]

Arylboronic acids reacted with benzonitrile and with KO*t*-Bu and a Cu catalyst to give the *N*-arylbenzamide derivative.[618] Aryl halides reacted with alkyl isonitriles in the presence of Cu_2O and Cs_2CO_3 in 80% aqueous DMSO to give the *N*-alkylbenzamide derivative.[619] Aryl halides also reacted with isocyanides using a polymer-supported Pd/*N*-heterocyclic carbene complex to give the benzamide derivative.[620] Aryl iodides reacted with primary amines in the presence of CO and a Pd catalyst to give the corresponding benzamide

[607] Piccolo, O.; Filippini, L.; Tinucci, L.; Valoti, E.; Citterio, A. *Tetrahedron* ***1986***, *42*, 885.
[608] Jagodzinski, T. *Synthesis* ***1988***, 717.
[609] Smith, P.A.S.; Kan, R.O. *J. Org. Chem.* ***1964***, *29*, 2261.
[610] For review, see Roy, S.; Roy, S.; Gribble, G.W. *Tetrahedron* ***2012***, *68*, 9867.
[611] Hosoi, K.; Nozaki, K.; Hiyama, T. *Org. Lett.* ***2002***, *4*, 2849. See also, Schnyder, A.; Indolese, A.F. *J. Org. Chem.* ***2002***, *67*, 594.
[612] Wu, X.; Wannberg, J.; Larhed, M. *Tetrahedron* ***2006***, *62*, 4665.
[613] Shang, M.; Sun, S.-Z.; Dai, H.X.; Yu, J.-Q. *J. Am. Chem. Soc.* ***2014***, *136*, 3254.
[614] Sawant, D.N.; Wagh, Y.S.; Bhatte, K.D.; Bhanage, B.M. *J. Org. Chem.* ***2011***, *76*, 5489.
[615] Santoro, S.; Liao, R.-Z.; Himo, F. *J. Org. Chem.* ***2011***, *76*, 9246.
[616] Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Eur. J.* ***2012***, *18*, 419.
[617] Nielsen, D.U.; Taaning, R.H.; Lindhardt, A.T.; Gøgsig, T.M.; Skrydstrup, T. *Org. Lett.* ***2011***, *13*, 4454.
[618] Qiao, Y.; Li, G.; Liu, S.; Yangkai, Y.; Tu, J.; Xu, F. *Synthesis* ***2017***, *49*, 1834.
[619] Yavari, I.; Darjani, M.G.; Bayat, M.J. *Tetrahedron Lett.* ***2014***, *55*, 4981. For the use of a nanodomain cubic copper(I) oxide catalyst, see Sarkar, S.; Pal, R.; Roy, M.; Chatterjee, N.; Sarkar, S.; Sen, A.K. *Tetrahedron Lett.* ***2015***, *56*, 623.
[620] Khairnar, B.J.; Bhanage, B.M. *Synthesis* ***2014***, *46*, 1236.

derivative.[621] Arylboronic acids reacted with NH_2CHO with a Cu catalyst to give the aryl formamide.[622,623]

OS **V**, 1051; **VI**, 465.

11-21 Carbonylation: Formation of Aryl Ketones

When a nucleophile adds to the carbonyl of carboxylic acid derivatives such as acid chlorides and esters, the resulting tetrahedral intermediate has the leaving groups Cl and OR. Loss of Cl^- or RO^- regenerates the C=O unit and the overall result of this process is a substitution reaction in which the nucleophile replaces chlorine or alkoxy on the carbonyl. This reaction with carboxylic acid derivatives (acid chlorides, esters, anhydrides, amides) is therefore called *nucleophilic acyl substitution*. Grignard reagents react with acid derivatives to give a ketone. However, ketones are slightly more reactive than the ester, so there is a competition for reaction with the Grignard reagent. In a typical reaction, all of the ester and Grignard reagent will be consumed, and there will be a mixture of the ketone and alcohol products. Esters, anhydrides, and amides give similar products via acyl substitution. The best leaving group is chloride, followed closely by carboxylate (acid chlorides and anhydrides, respectively), and then the alkoxy group from an ester. Organolithium reagents generally behave similarly. Organometallics other than Grignard reagents or organolithium reagents have been used that give the ketone directly.

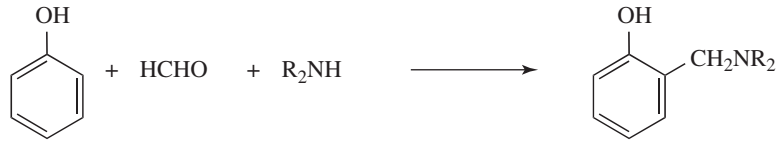
Gilman and co-workers[624] discovered that a Grignard reagent reacts with cadmium chloride ($CdCl_2$) to give a dialkylcadmium reagent (R_2Cd), and this less reactive organometallic is more selective in its reactions with carbonyl derivatives.[625] Apart from the reaction of organocadmium reagents, organocuprates react with acid chlorides to give the ketone, and this reaction is discussed as reaction **16-29**. The reaction of organometallic compounds with carboxylic acid derivatives or with aryl halides and CO[626] leads to the corresponding ketone, and alternative methods for the preparation of aryl ketones have been reported.

Heteroaryl iodides reacted with heteroarenes and CO, in the presence of a Pd catalyst, to give the diaryl ketone.[627] Aryl halides reacted with potassium monoethyl malonate in the presence of $Pd(OAc)_2$, imidazole, $MgCl_2/NEt_3$, and $Co_2(CO)_8$, with microwave irradiation, to give the corresponding β-keto ester.[628] 4-Aminophenyl zinc iodide and 3-aminophenyl zinc iodide were generated from the corresponding aryl iodide by reaction with zinc metal, and reaction with acid chlorides gave the diaryl ketone.[629] Aryl halides reacted with phenylboronic acids and benzene-1,3,5-triyl triformate as the CO source, with a Pd catalyst, to give the diaryl ketone.[630] Functionalized aromatic compounds reacted with aryl aldehydes in air, with a Pd catalyst, to give the diaryl ketone.[631] Aryl aldehydes reacted with aryl iodonium

[621] Marosvölgyi-Haskó, D.; Kégl, T.; Kollár, L. *Tetrahedron* ***2016***, *72*, 7509.
[622] Srivastava, V.P.; Yadav, D.K.; Yadav, A.K.; Watal, G.; Yadav, L.D.S. *Synlett* ***2013***, *24*, 1423.
[623] Kim, J.Y.; Park, S.H.; Ryu, J.; Cho, S.H.; Kim, S.H.; Chang, S. *J. Am. Chem. Soc.* ***2012***, *134*, 9110.
[624] Gilman, H.; Nelson, J.F. *Rec. Trav. Chim.* ***1936***, *55*, 518; Cason, J. *J. Org. Chem.* ***1948***, *13*, 227; See Le Guilly, L.; Tatibouët, F. *Compt. Rend. Ser. C* ***1966***, *262*, 217.
[625] Cason, J. *Chem. Rev.* ***1947***, *40*, 15; Shirley, D.A. *Org. React.* ***1954***, *8*, 28 (see pp. 35–38).
[626] Fang, W.; Zhu, H.; Deng, Q.; Liu, S.; Liu, X.; Shen, Y.; Tu, T. *Synthesis* ***2014***, *46*, 1689.
[627] Tjutrins, J.; Arndtsen, B.A. *J. Am. Chem. Soc.* ***2015***, *137*, 12050. Also see Lang, R.; Xia, C.; Li, F. *New J. Chem.* ***2014***, 2732.
[628] Baburajan, P.; Elango, K.P. *Tetrahedron Lett.* ***2014***, *55*, 3525.
[629] Jung, H.-S.; Kim, S.-H. *Tetrahedron Lett.* ***2015***, *56*, 1004.
[630] Jiang, L.-B.; Qi, X.; Wu, X.-F. *Tetrahedron Lett.* ***2016***, *57*, 3368.
[631] Pan, C.; Jia, X.; Cheng, J. *Synthesis* ***2012***, *44*, 677. Also see Wu, X.-F. *Chem. Eur. J.* ***2015***, *21*, 12252.

compounds, in the presence of a Rh or Ir catalyst, to give the diaryl ketone.[632] Aryl iodides reacted with CO and a nucleophile to give the 1,2-diketone derivative in the presence of a Pd catalyst.[633]

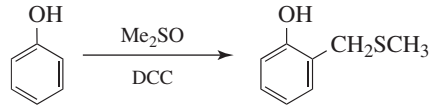
11-22 Aminoalkylation and Amidoalkylation



Phenols, secondary and tertiary aromatic amines,[634] pyrroles, and indoles can be aminomethylated by treatment with formaldehyde and a secondary amine. Other aldehydes have sometimes been employed. Aminoalkylation is a special case of the *Mannich reaction* (**16-17**). When phenols and other activated aromatic compounds are treated with *N*-hydroxymethylchloroacetamide, *amidomethylation* takes place[635] to give the aminomethyl derivative, which is often hydrolyzed *in situ* to the aminoalkylated product. Other *N*-hydroxyalkyl and *N*-chlorinated compounds have also been used.[417] Nitroethane in polyphosphoric acid can be used for the acetamidation of aromatic compounds.[636] Aldimines reacted with pyridine derivatives in the presence of a secondary amine and a lanthanum complex that resulted in the *ortho* aminomethyl pyridine.[637] Aryl halides are aminomethylated with potassium organotrifluoroborates.[638]

OS **I**, 381; **IV**, 626; **V**, 434; **VI**, 965; **VII**, 162.

11-23 Thioalkylation



A methylthiomethyl group can be inserted into the *ortho* position of phenols by heating with dimethyl sulfoxide and 1,3-dicyclohexylcarbodiimide (DCC).[639] Other reagents can be used instead of DCC, among them $SOCl_2$[640] or acetic anhydride.[641] Alternatively, the phenol can be treated with dimethyl sulfide and *N*-chlorosuccinimide (NCS), followed by triethylamine.[642]

OS **VI**, 581, 601.

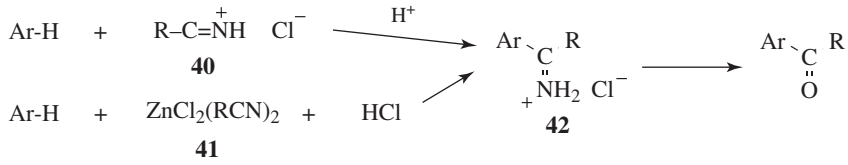
[632] Yang, X.; Wang, H.; Zhou, X.; Li, X. *Org. Biomol. Chem.* ***2016***, *14*, 5233.
[633] de la Fuente, V.; Godard, C.; Zangrando, E.; Claver, C.; Castillón, S. *Chem. Commun.* ***2012***, *48*, 1695. Also see Schranck, J.; Wu, X.-F.; Tlili, A.; Neumann, H.; Beller, M. *Chem. Eur. J.* ***2013***, *19*, 12959.
[634] Miocque, M.; Vierfond, J. *Bull. Soc. Chim. Fr.* ***1970***, 1896, 1901, 1907.
[635] For a review, see Zaugg, H.E. *Synthesis* ***1984***, 85.
[636] Aksenov, A.V.; Aksenov, N.A.; Nadein, O.N.; Aksenova, I.V. *Synlett* ***2010***, 2628.
[637] Nagae, H.; Shibata, Y.; Tsurugi, H.; Mashima, K. *J. Am. Chem. Soc.* ***2015***, *137*, 640.
[638] Molander, G.A.; Sandrock, D.L. *Org. Lett.* ***2007***, *9*, 1597.
[639] Olofson, R.A.; Marino, J.P. *Tetrahedron* ***1971***, *27*, 4195.
[640] Sato, K.; Inoue, S.; Ozawa, K.; Tazaki, M. *J. Chem. Soc., Perkin Trans. 1* ***1984***, 2715.
[641] See Pettit, G.H.; Brown, T.H. *Can. J. Chem.* ***1967***, *45*, 1306; Claus, P. *Monatsh. Chem.* ***1968***, *99*, 1034.
[642] Gassman, P.G.; Amick, D.R. *J. Am. Chem. Soc.* ***1978***, *100*, 7611.

11-24 Acylation with Nitriles: The Hoesch Reaction

$$ArH + RCN \xrightarrow[ZnCl_2]{HCl} ArCOR$$

Friedel-Crafts acylation with nitriles and HCl is called the *Hoesch* or the *Houben-Hoesch reaction*.[643] In most cases, a Lewis acid is necessary, and zinc chloride is the most common. The reaction is generally useful only with phenols, phenolic ethers, and some reactive heterocyclic compounds such as pyrrole, but it can be extended to aromatic amines by the use of BCl_3.[644] Acylation in the case of aniline derivatives is regioselectively *ortho*. Monohydric phenols, however, generally do not give ketones[645] but are attacked at the oxygen to produce imino esters. Many nitriles have been used. Even aryl nitriles give good yields if they are first treated with HCl and $ZnCl_2$ and then the substrate added at 0 °C.[646] In fact, this procedure increases yields with any nitrile. If thiocyanates RSCN are used, thiol esters ArCOSR can be obtained. The *Gatterman reaction* (**11-18**) is a special case of the Hoesch synthesis.

The reaction mechanism is complex and not completely settled.[647] The first stage consists of an attack on the substrate by a species containing the nitrile and HCl (and the Lewis acid, if present) to give an imine salt (an imino ester, **42**). Among the possible reactive species are **40** and **41**. In the second stage, the salts are hydrolyzed to the products, first the iminium salt, and then the ketone.



Ketones can also be obtained by treating phenols or phenolic ethers with a nitrile in the presence of F_3CSO_2OH.[648] The mechanism in this case is different.

OS **II**, 522.

11-25 Cyanation

$$ArH + Cl_3CCN \xrightarrow{HCl} Ar{-}C(CCl_3)=NH_2^+\ Cl^- \xrightarrow{NaOH} ArCN$$

Aromatic hydrocarbons (including benzene), phenols, and phenolic ethers can be cyanated with trichloroacetonitrile, BrCN, or mercury fulminate $Hg(ONC)_2$.[649] In the case of

[643] See Ruske, W. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 383–497.
[644] Sugasawa, T.; Adachi, M.; Sasakura, K.; Kitagawa, A. *J. Org. Chem.* ***1979***, *44*, 578.
[645] For an exception, see Toyoda, T.; Sasakura, K.; Sugasawa, T. *J. Org. Chem.* ***1981***, *46*, 189.
[646] Zil'berman, E.N.; Rybakova, N.A. *J. Gen. Chem. USSR* ***1960***, *30*, 1972.
[647] See Ruske, W. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, p. 383; Jeffery, E.A.; Satchell, D.P.N. *J. Chem. Soc. B* ***1966***, 579.
[648] Amer, M.I.; Booth, B.L.; Noori, G.F.M.; Proença, M.F.J.R.P. *J. Chem. Soc., Perkin Trans. 1* ***1983***, 1075.
[649] Olah, G.A. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, pp. 119–120.

Cl_3CCN, the actual attacking entity is probably $Cl_3C{-}C^{+}{=}NH$, formed by addition of a proton to the cyano nitrogen. Secondary aromatic amines ArNHR, as well as phenols, can be cyanated in the *ortho* position with Cl_3CCN and BCl_3.[650]

Benzoate esters have reacted with aminoacetonitriles in the presence of a Ni catalyst to give the aryl nitrile.[651] Benzamide derivatives reacted with *N*-cyano-*N*-tosylaniline with 20% of $AgSbF_6$ and of NaOAc, with a Ru catalyst, and gave the *ortho* cyanobenzamide derivative.[652] Methylarenes, with an AIBN or benzoyl peroxide catalyst, reacted with NBS or 1,3-dibromo-5,5-dimethylhydantoin; subsequent reaction with molecular iodine in aqueous NH_3 gave the aryl nitrile.[653] Electron-rich arenes were converted to the corresponding aromatic nitriles by reaction with $ZnBr_2$ and dichloromethyl methyl ether, followed by reaction with I_2 and aqueous ammonia.[654] The Cu-catalyzed reaction of benzylic alcohols with aqueous ammonia, O_2, and TEMPO gave the aryl nitrile.[655] Aromatic compounds reacted with CuCN in the presence of air or $PhI(OAc)_2$ and 30% of FeI_2 to give the aryl nitrile.[656] Aromatic compounds reacted with BrCN with a $GaCl_3$ catalyst to give aryl nitriles.[657] Aryl iodides reacted with 0.3 equivalents of $K_4[Fe(CN)_6]$ and 3 equivalents of K_2PO_4, with a Pd catalyst, at 120 °C to give the aryl nitrile.[658] Aryl iodides reacted with acetonitrile and Ph_3PO, with a Cu catalyst and AgOAc as an additive, to give the arylnitrile.[659] Arylmagnesium halides or aryllithium reagents reacted with malononitrile to give the aryl nitrile.[660]

Indole derivatives reacted with *N*-cyano-*N*-tosylaniline, with a $AgSbF_6$ catalyst and a Rh catalyst, to give the 2-cyanoindole.[661] 2-Phenylpyridine reacted with *N*-cyano-*N*-tosylaniline, and a Co catalyst and $AgSbF_6$, to give the 2-pyridiylbenzonitrile.[662] Indoles reacted with acetonitrile, via C—CN bond cleavage, with NIS, base, and a Cu/Si/TEMPO catalyst, at 150 °C, under oxygen, to give the 3-cyanoindole.[663] Indoles reacted with *t*-BuNC and a Pd catalyst to give the cyanoindole.[664]

OS **III**, 293.

F. Oxygen Electrophiles

Oxygen electrophiles are very rare, since oxygen does not bear a positive charge very well. However, there is one reaction that can be mentioned.

[650] Adachi, M.; Sugasawa, T. *Synth. Commun.* ***1990***, *20*, 71.
[651] Takise, R.; Itami, K.; Yamaguchi, J. *Org. Lett.* ***2016***, *18*, 4428.
[652] Liu, W.; Ackermann, L. *Chem. Commun.* ***2014***, *50*, 1878.
[653] Tsuchiya, D.; Kawagoe, Y.; Moriyama, K.; Togo, H. *Org. Lett.* ***2013***, *15*, 4194.
[654] Tamura, T.; Moriyama, K.; Togo, H. *Eur. J. Org. Chem.* ***2015***, 2023.
[655] Tao, C.; Liu, F.; Zh, Y.; Li, W.; Cao, Z. *Org. Biomol. Chem.* ***2013***, *11*, 3349.
[656] Zhang, G.; Lv, G.; Pan, C.; Cheng, J.; Chen, F. *Synlett* ***2011***, *22*, 2991.
[657] Okamoto, K.; Watnadabe, M.; Murai, M.; Hatano, R. Ohe, K. *Chem. Commun.* ***2012***, *48*, 3127.
[658] Ganapathy, D.; Kotha, S.S.; Sekar, G. *Tetrahedron Lett.* ***2015***, *56*, 175.
[659] Song, R.-J.; Wu, J.-C.; Liu, Y.; Deng, G.-B.; Wu, C.-Y.; Wei, W.-T.; Li, J.-H. *Synlett* ***2012***, *23*, 2491.
[660] Reeves, J.T.; Malapit, C.A.; Buono, F.G.; Sidhu, K.P.; Marsini, M.A.; Sader, C.A.; Fandrick, K.R.; Busacca, C.A.; Senanayake, C.H. *J. Am. Chem. Soc.* ***2015***, *137*, 9481.
[661] Chaitanya, M.; Anbarasan, P. *J. Org. Chem.* ***2015***, *80*, 3695.
[662] Li, J.; Ackermann, L. *Angew. Chem. Int. Ed.* ***2015***, *54*, 3635.
[663] Zhao, M.; Zhang, W.; Shen, Z. *J. Org. Chem.* ***2015***, *80*, 8868; Zhu, Y.; Zhao, M.; Lu, W.; Li, L.; Shen, Z. *Org. Lett.* ***2015***, *17*, 2602.
[664] Xu, S.; Huang, X.; Hong, X.; Xu, B. *Org. Lett.* ***2012***, *14*, 4614; Peng, J.; Zhao, J.; Hu, Z.; Liang, D.; Huang, J.; Zhu, Q. *Org. Lett.* ***2012***, *14*, 4966.

11-26 Hydroxylation

There have been only a few reports of direct hydroxylation[665] by an electrophilic process (see, however, **14-4**).[666] In general, poor results are obtained, partly because the introduction of an OH group activates the ring, which suppresses further reaction, and quinone formation is common. However, alkyl-substituted benzenes, such as mesitylene or durene, can be hydroxylated in good yield with CF_3CO_3H and BF_3.[667] In the case of mesitylene, the product, 2,4,6-trimethylphenol, is not subject to further attack. In a related procedure, even benzene and substituted benzenes (e.g., PhMe, PhCl, xylenes) can be converted to phenols in good yields with sodium perborate/F_3CSO_2OH.[668] Aromatic amines, *N*-acyl amines, and phenols were hydroxylated with H_2O_2 in SbF_5/HF.[669]

Another hydroxylation reaction is the *Elbs reaction*.[670] In this method phenols can be oxidized to *p*-diphenols with $K_2S_2O_8$ in alkaline solution.[671] Primary, secondary, or tertiary aromatic amines give predominant or exclusive *ortho* substitution unless both *ortho* positions are blocked, in which case *para* substitution is found. The reaction with amines is called the *Boyland-Sims oxidation*. Yields are low with either phenols or amines, generally <50%. The mechanisms are not clear[672] but have been reviewed.[673]

Electrolysis of benzene, in the presence of trifluoroacetic acid and triethylamine, leads to a 73% yield of phenol.[674] Photolytic hydroxylation of benzene has been reported in the presence of mesoporous TiO_2.[675] Nitrous oxide has been used as an oxidant, in the presence of FeAlPO catalysts.[676]

G. Metal Electrophiles

Reactions in which a metal replaces the hydrogen of an aromatic ring are considered along with their aliphatic counterparts in reactions **12-22** and **12-23**.

[665] For a list of hydroxylation reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 977–978. Also see Asaka, M.; Fujii, H. *J. Am. Chem. Soc.* ***2016***, *138*, 8048.

[666] See Jacquesy, J.; Gesson, J.; Jouannetaud, M. *Rev. Chem. Intermed.* ***1988***, *9*, 1, see pp. 5–10; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1985***, pp. 173–176, 347–350.

[667] See Hart, H. *Acc. Chem. Res.* ***1971***, *4*, 337.

[668] Prakash, G.K.S.; Krass, N.; Wang, Q.; Olah, G.A. *Synlett* ***1991***, 39.

[669] Berrier, C.; Carreyre, H.; Jacquesy, J.; Joannetaud, M. *New J. Chem.* ***1990***, *14*, 283, and references cited therein.

[670] Behrman, E.J. *Org. React.* ***1988***, *35*, 421; Behrman, E.J. *Beil. J. Org. Chem.* ***2006***, *2*, 22.

[671] See Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* ***1982***, *23*, 1573, 1577.

[672] Walling, C.; Camaioni, D.M.; Kim, S.S. *J. Am. Chem. Soc.* ***1978***, *100*, 4814.

[673] Behrman, E.J. *Beil. J. Org. Chem.* ***2006***, *2*, 22.

[674] Fujimoto, K.; Tokuda, Y.; Maekawa, H.; Matsubara, Y.; Mizuno, T.; Nishiguchi, I. *Tetrahedron* ***1996***, *52*, 3889.

[675] Shiraishi, Y.; Saito, N.; Hirai, T. *J. Am. Chem. Soc.* ***2005***, *127*, 12820. Also see Mita, S.; Sakamoto, T.; Yamada, S.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* ***2005***, *46*, 7729.

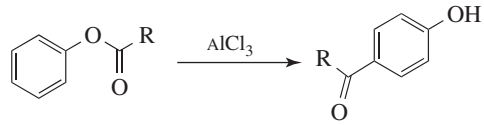
[676] Shiju, N.R.; Fiddy, S.; Sonntag, O.; Stockenhuber, M.; Sankar, G. *Chem. Commun.* ***2006***, 4955.

11.F.ii. Hydrogen as the Leaving Group In Rearrangement Reactions

In these reactions a group is detached from a *side chain* and then reattached the ring, but in other aspects they resemble the reactions already treated in this chapter.[677] Since a group moves from one position to another in a molecule, these are rearrangements (also see Chapter 18). When considering if a given rearrangement is intermolecular or intramolecular, there is evidence that, at least in some cases, an intermolecular mechanism can still result in a high degree of *ortho* migration.[678]

A. Groups Cleaving from Oxygen

11-27 The Fries Rearrangement



Phenolic esters can be rearranged by heating with *Friedel-Crafts catalyst*s in a synthetically useful reaction known as the *Fries rearrangement*.[679] Both *o*- and *p*-acylphenols can be produced, and it is often possible to select conditions so that one predominates. The *ortho*/*para* ratio is dependent on the temperature, solvent, and amount of catalyst used. Exceptions are known, but low temperatures generally favor the *para* product and high temperatures the *ortho* product. The R group may be aliphatic or aromatic. Any *meta*-directing substituent on the ring interferes with the reactions, as might be expected for a Friedel-Crafts process. In the case of aryl benzoates treated with F_3CSO_2OH, the Fries rearrangement was shown to be reversible and an equilibrium was established.[680] Transition metal-catalyzed Fries rearrangements have been reported.[681] Methanesulfonic acid has been used to initiate a Fries rearrangement of aryl phenylacetate to hydroxy aryl ketones.[682]

Questions remain about the exact mechanism.[683] Opinions have been expressed that it is completely intermolecular,[684] completely intramolecular,[685] and partially inter- and intramolecular.[686] One way to decide between inter- and intramolecular processes is to

[677] See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***; Williams, D.L.H.; Buncel, I.M. *Isot. Org. Chem.* ***1980***, *5*, 147; Williams, D.L.H. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 433–486.

[678] See Dawson, I.M.; Hart, L.S.; Littler, J.S. *J. Chem. Soc., Perkin Trans. 2* ***1985***, 1601.

[679] See Shine, H.J. *Aromatic Rearrangments*, Elsevier, NY, ***1967***, pp. 72–82, 365–368; Gerecs, A. in Olah, G.A. in Olah, G. *Friedel-Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 499–533. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 1310.

[680] Effenberger, F.; Gutmann, R. *Chem. Ber.* ***1982***, *115*, 1089.

[681] With $Hf(OTf)_4$, see Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Tetrahedron Lett.* ***1996***, *37*, 2053; with $Sc(OTf)_3$, see Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Tetrahedron Lett.* ***1996***, *37*, 4183; with $ZrCl_4$, see Harrowven, D.C.; Dainty, R.F. *Tetrahedron Lett.* ***1996***, *37*, 7659.

[682] Jeon, I.; Mangion, I.K. *Synlett* ***2012***, *23*, 1927.

[683] See Sharghi, H.; Eshghi, H. *Bull. Chem. Soc. Jpn.* ***1993***, *66*, 135.

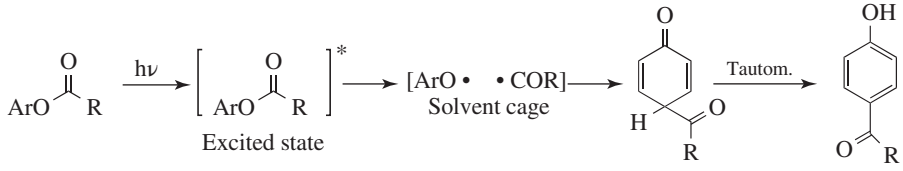
[684] Martin, R.; Gavard, J.; Delfly, M.; Demerseman, P.; Tromelin, A. *Bull. Soc. Chim. Fr.* ***1986***, 659 and references citied therein.

[685] Ogata, Y.; Tabuchi, H. *Tetrahedron* ***1964***, *20*, 1661.

[686] Dawson, I.M.; Hart, L.S.; Littler, J.S. *J. Chem. Soc., Perkin Trans. 2* ***1985***, 1601.

run the reaction of the phenolic ester in the presence of another aromatic compound, say, toluene. If some of the toluene is acylated, the reaction must be, at least in part, intermolecular. If the toluene is not acylated, the presumption is that the reaction is intramolecular, although this is not certain, for it may be that the toluene is not attacked because it is less active than the first reactant. A number of such experiments (called *crossover experiments*) have been carried out; sometimes crossover products have been found and sometimes not. As in **11-17**, an initial complex ($ArO(R)C{=}O^{+}{-}AlCl_3^{-}$) is formed between the substrate and the catalyst, so that a catalyst/substrate molar ratio of at least 1:1 is required. In the presence of aluminum chloride, the Fries rearrangement can be induced with microwave irradiation,[687] but simply heating phenyl acetate with microwave irradiation gives the Fries rearrangement.[688] The Fries rearrangement has been carried out in ionic melts.[689]

The Fries rearrangement can also be carried out with UV light, in the absence of a catalyst.[690] This reaction, called the *photo-Fries rearrangement*,[691] is predominantly an intramolecular free-radical process. Both *ortho* and *para* migration are observed.[692] Unlike the Lewis acid-catalyzed Fries rearrangement, the photo-Fries reaction can be accomplished, though often in low yields, when *meta*-directing groups are on the ring. The available evidence strongly suggests the following mechanism involving formation of the excited state ester followed by dissociation to a radical pair in a solvent cage[693] for the photo-Fries rearrangement[694] (illustrated for formation of the *para* product).



The phenol ArOH is always a side product, resulting from some ArO• that leaks from the solvent cage and abstracts a hydrogen atom from a neighboring molecule. When the reaction was performed on phenyl acetate in the gas phase, where there are no solvent molecules to form a cage (but in the presence of isobutane as a source of abstractable hydrogen atoms), phenol was the chief product and virtually no *o*- or *p*-hydroxyacetophenone was found.[695] Other evidence[696] for the mechanism is that CIDNP has been observed during the course

[687] Khadilkar, B.M.; Madyar, V.R. *Synth. Commun.* ***1999***, *29*, 1195.
[688] Paul, S.; Gupta, M. *Synthesis* ***2004***, 1789.
[689] Harjani, J.R.; Nara, S.J.; Salunkhe, M.M. *Tetrahedron Lett.* ***2001***, *42*, 1979.
[690] Finnegan, R.A.; Matice, J.J. *Tetrahedron* ***1965***, *21*, 1015.
[691] See Bellus, D. *Adv. Photochem.* ***1971***, *8*, 109; Bellus, D.; Hrdlovic, P. *Chem. Rev.* ***1967***, *67*, 599. See Cui, C.; Wang, X.; Weiss, R.G. *J. Org. Chem.* ***1996***, *61*, 1962.
[692] The migration can be made almost entirely *ortho* by cyclodextrin encapsulation (Sec. 3.C.iv): Syamala, M.S.; Rao, B.N.; Ramamurthy, V. *Tetrahedron* ***1988***, *44*, 7234. See also, Veglia, A.V.; Sanchez, A.M.; de Rossi, R.H. *J. Org. Chem.* ***1990***, *55*, 4083.
[693] Proposed by Kobsa, H. *J. Org. Chem.* ***1962***, *27*, 2293.
[694] It has been suggested that a second mechanism, involving a four-center transition state, is also possible: Sander, M.R.; Hedaya, E.; Trecker, D.J. *J. Am. Chem. Soc.* ***1968***, *90*, 7249; Bellus, D. *Adv. Photochem.* ***1971***, *8*, 109.
[695] Meyer, J.W.; Hammond, G.S. *J. Am. Chem. Soc.* ***1972***, *94*, 2219.
[696] See Shine, H.J.; Subotkowski, W. *J. Org. Chem.* ***1987***, *52*, 3815.

of the reaction[697] and that the ArO• radical has been detected by flash photolysis[698] and by nanosecond time-resolved Raman spectroscopy.[699]

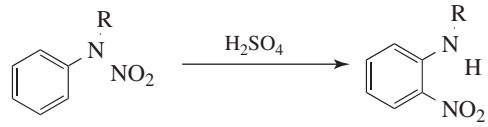
A lithium diisopropylamide (LDA)-mediated anionic Fries rearrangement of aryl carbamates has been reported.[700] So-called *anionic Snieckus-Fries rearrangement* has also been discussed.[701] Treatment of *O*-arylsulfonate esters with $AlCl_3/ZnCl_2$ on silica with microwave irradiation, leads to 2-sulfonyl phenols in a thia-Fries rearrangement.[702] A similar reaction was reported with *O*-arylsulfonamides.[703]

OS **II**, 543; **III**, 280, 282.

B. Groups Cleaving from Nitrogen[704]

It has been shown that $PhNH_2D^+Cl^-$ rearranges to *o*- and *p*-deuterioaniline.[705] The migration of OH, formally similar to reactions **11-28** to **11-32**, is a nucleophilic substitution and is treated in **13-33**.

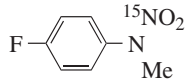
11-28 Migration of the Nitro Group



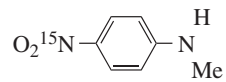
N-Nitro aromatic amines rearrange on treatment with acids to *o*- and *p*-nitroamines, with the *ortho* compounds predominating.[706] Aside from this indication of an intramolecular process, there is also the fact that virtually no *meta* isomer is produced in this reaction,[707] although direct nitration of an aromatic amine generally gives a fair amount of *meta* product. Thus, a mechanism in which NO_2^+ is dissociated from the ring and then is attacked by another molecule must be ruled out. Further results indicating an intramolecular process include the observation that rearrangement of several substrates in the presence of $K^{15}NO_3$ gave products containing no ^{15}N,[708] and that rearrangement of a mixture of $PhNH^{15}NO_2$ and unlabeled $p\text{-}MeC_6H_4NHNO_2$ gave 2-nitro-4-methylaniline containing no ^{15}N.[709] On

[697] Adam, W. *J. Chem. Soc., Chem. Commun.* ***1974***, 289.
[698] Kalmus, C.E.; Hercules D.M. *J. Am. Chem. Soc.* ***1974***, *96*, 449.
[699] Beck, S.M.; Brus, L.E. *J. Am. Chem. Soc.* ***1982***, *104*, 1805.
[700] For a discussion of the role of aggregates and mixed aggregates in this reaction, see Singh, K.J.; Collum, D.B. *J. Am. Chem. Soc.* ***2006***, *128*, 13753.
[701] Riggs, J.C.; Singh, K.J.; Yun, M.; Collum, D.B. *J. Am. Chem. Soc.* ***2008***, *130*, 13709.
[702] Moghaddam, F.M.; Dakamin, M.G. *Tetrahedron Lett.* ***2000***, *41*, 3479.
[703] Benson, G.A.; Maughan, P.J.; Shelly, D.P.; Spillane, W.J. *Tetrahedron Lett.* ***2001***, *42*, 8729.
[704] See Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, NJ, ***1973***, pp. 192–199.
[705] Okazaki, N.; Okumura, A. *Bull. Chem. Soc. Jpn.* ***1961***, *34*, 989.
[706] See Williams, D.L.H. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 127–153; White, W.N. *Mech. Mol. Migr.* ***1971***, *3*, 109–143; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 235–249.
[707] Hughes, E.D.; Jones, G.T. *J. Chem. Soc.* ***1950***, 2678.
[708] Banthorpe, D.V.; Thomas, J.A.; Williams, D.L.H. *J. Chem. Soc.* ***1965***, 6135.
[709] Geller, B.A.; Dubrova, L.N. *J. Gen. Chem. USSR* ***1960***, *30*, 2627.

the other hand, rearrangement of **43** in the presence of unlabeled $PhNMeNO_2$ gave labeled **44**, which did not arise by displacement of F.[710]

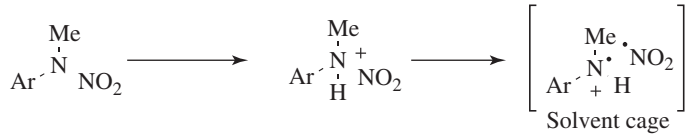


43

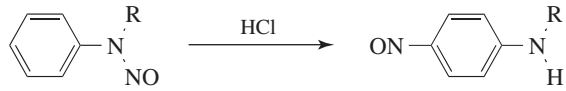


44

The R group may be hydrogen or alkyl. Two principal mechanisms have been suggested, one involving cyclic attack by the oxygen of the nitro group at the *ortho* position before the group cleaves,[711] and the other involving a cleavage into a radical and a radical ion held together in a solvent cage.[712] Among the evidence for the latter view[713] are the effects of substituents on the rate of the reaction,[714] Kinetic isotope effects using ^{15}N and ^{14}C that show nonconcertedness,[715] as do the fact that both *N*-methylaniline and nitrous acid are produced in sizable and comparable amounts in addition to the normal products *o*- and *p*-nitro-*N*-methylaniline.[716] These side products are formed when the radicals escape from the solvent cage.



11-29 Migration of the Nitroso Group: The Fischer-Hepp Rearrangement



The migration of a nitroso group, formally similar to **11-28**, is important because *p*-nitroso secondary aromatic amines cannot generally be prepared by direct *C*-nitrosation of secondary aromatic amines (see **12-49**). The reaction, known as the *Fischer-Hepp rearrangement*,[717] is brought about by treatment of *N*-nitroso secondary aromatic amines with HCl. Other acids give poor or no results. In benzene systems the *para* product is usually formed

[710] White, W.N.; Golden, J.T. *J. Org. Chem.* ***1970***, *35*, 2759.

[711] Banthorpe, D.V.; Thomas, J.A. *J. Chem. Soc.* ***1965***, 7149, 7158. Also see, Banthorpe, D.V.; Thomas, J.A.; Williams, D.L.H. *J. Chem. Soc.* ***1965***, 6135.

[712] White, W.N.; White, H.S.; Fentiman, A. *J. Org. Chem.* ***1976***, *41*, 3166.

[713] See White, W.N.; Klink, J.R. *J. Org. Chem.* ***1977***, *42*, 166; Ridd, J.H.; Sandall, J.P.B. *J. Chem. Soc., Chem. Commun.* ***1982***, 261.

[714] White, W.N.; Klink, J.R. *J. Org. Chem.* ***1970***, *35*, 965.

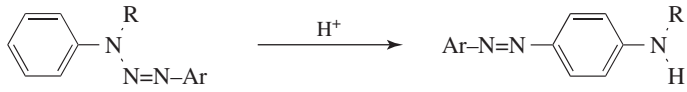
[715] Shine, H.J.; Zygmunt, J.; Brownawell, M.L.; San Filippo Jr., J. *J. Am. Chem. Soc.* ***1984***, *106*, 3610.

[716] White, W.N.; White, H.S. *J. Org. Chem.* ***1970***, *35*, 1803.

[717] See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 113–128; Williams, D.L.H. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 231–235.

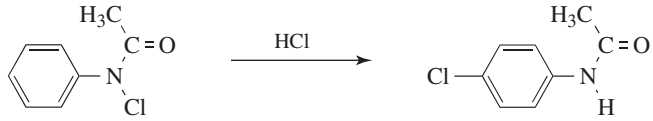
exclusively.[718] The mechanism of the rearrangement is not completely understood. The fact that the reaction takes place in a large excess of urea[719] shows that it is intramolecular[720] since, if NO^+, NOCl, or some similar species were free in the solution, they would be captured by the urea, preventing the rearrangement.

11-30 Migration of an Arylazo Group



Rearrangement of aryl triazenes can be used to prepare azo derivatives of primary and secondary aromatic amines.[721] These are first diazotized at the amino group (see **11-6**) to give triazenes, which are then rearranged by treatment with acid. The rearrangement always gives the *para* isomer, unless that position is occupied.

11-31 Migration of Halogen: The Orton Rearrangement

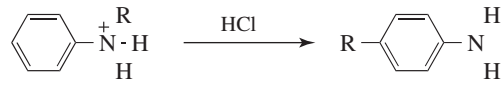


Migration of a halogen from a nitrogen side chain to the ring by treatment with HCl is called the *Orton rearrangement*.[722] The main product is the *para* isomer, though some *ortho* product may also be formed. The reaction has been carried out with *N*-chloroamines and *N*-bromoamines and less often with *N*-iodo compounds. The amine must be acylated, except that $PhNCl_2$ gives 2,4-dichloroaniline. The reaction is usually performed in water or acetic acid. There is considerable evidence (cross-halogenation, labeling, etc.) that this is an intermolecular process.[723] First, the HCl reacts with the starting material to give $ArNHCOCH_3$ and Cl_2; then the chlorine halogenates the ring as in **11-10**. Among the evidence is that chlorine has been isolated from the reaction mixture.

The Orton rearrangement can also be brought about photochemically[724] and by heating in the presence of benzoyl peroxide.[725] These two reactions are free-radical processes.

[718] See Titova, S.P.; Arinich, A.K.; Gorelik, M.V. *J. Org. Chem. USSR* ***1986***, *22*, 1407.
[719] Morgan, T.D.B.; Williams, D.L.H. *J. Chem. Soc., Perkin Trans. 2* ***1972***, 74.
[720] See also, Williams, D.L.H. *J. Chem. Soc., Perkin Trans. 2* ***1982***, 801.
[721] See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 212–221.
[722] See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 221–230, 362–364: Bieron, J.F.; Dinan, F.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 263–269.
[723] Golding, P.D.; Reddy, S.; Scott, J.M.W.; White, V.A.; Winter, J.G. *Can. J. Chem.* ***1981***, *59*, 839.
[724] See Hodges, F.W. *J. Chem. Soc.* ***1933***, 240.
[725] See Coulson, J.; Williams, G.H.; Johnston, K.M. *J. Chem. Soc. B* ***1967***, 174.

11-32 Migration of an Alkyl or Aryl Group[726]



When HCl salts of arylalkylamines are heated at ~200–300 °C, migration occurs in what is called the *Hofmann-Martius reaction*. It is an intermolecular reaction, since crossing is found. For example, methylanilinium bromide gave not only the normal products *o*- and *p*-toluidine but also aniline and di- and trimethylanilines.[727] As expected for an intermolecular process, there is isomerization when R is primary.

With primary R, the reaction probably goes through the alkyl halide formed initially in an S_N2 reaction:

$$RNH_2Ar^+ + Cl^- \rightarrow RCl + ArNH_2$$

Evidence for this view is that alkyl halides have been isolated from the reaction mixture and that Br^-, Cl^-, and I^- gave different *ortho*/*para* ratios, which indicates that the halogen is involved in the reaction.[727] Further evidence is that the alkyl halides isolated are not rearranged (as would be expected if they are formed by an S_N2 mechanism), even though the alkyl groups in the ring are rearranged. Once the alkyl halide is formed, it reacts with the substrate by a normal *Friedel-Crafts alkylation* process (**11-11**), accounting for the rearrangement. When R is secondary or tertiary, carbocations may be directly formed so that the reaction does not go through the alkyl halides.[728]

It is also possible to carry out the reaction by heating the amine (not the salt) at a temperature between 200 and 350 °C with a metal halide, such as $CoCl_2$, $CdCl_2$, or $ZnCl_2$. When this is done, the reaction is called the *Reilly-Hickinbottom rearrangement*. Primary R groups larger than ethyl give both rearranged and unrearranged products.[729] The reaction is not generally useful for secondary and tertiary R groups, which are usually cleaved to alkenes under these conditions.

When acylated arylamines are photolyzed, migration of an acyl group takes place[730] in a process that resembles the photo-Fries reaction (**11-27**). The migration of phenyl groups is known via ipso arenium ions.[731]

11.F.iii. Other Leaving Groups

Three types of reactions are considered in this section.

1. Reactions in which hydrogen replaces another leaving group:

$$ArX + H^+ \rightarrow ArH$$

[726] See Grillot, G.F. *Mech. Mol. Migr.* ***1971***, *3*, 237; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 249–257.
[727] Ogata, Y.; Tabuchi, H.; Yoshida, K. *Tetrahedron* ***1964***, *20*, 2717.
[728] Hart, H.; Kosak, J.R. *J. Org. Chem.* ***1962***, *27*, 116.
[729] See Birchal, J.M.; Clark, M.T.; Goldwhite, H.; Thorpe, D.H. *J. Chem. Soc., Perkin Trans. 1* ***1972***, 2579.
[730] See Nassetta, M.; de Rossi, R.H.; Cosa, J.J. *Can. J. Chem.* ***1988***, *66*, 2794.
[731] Ajaz, A.; McLaughlin, E.C.; Skraba, S.L.; Thamatam, R.; Johnson, R.P. *J. Org. Chem.* ***2012***, *77*, 9487.

2. Reactions in which an electrophile other than hydrogen replaces another leaving group:

$$ArX + Y^+ \rightarrow ArY$$

3. Reactions in which a group (other than hydrogen) migrates from one position in a ring to another. Such migrations can be either inter- or intramolecular, as in the migration of an *ortho* X group to the *para* position.

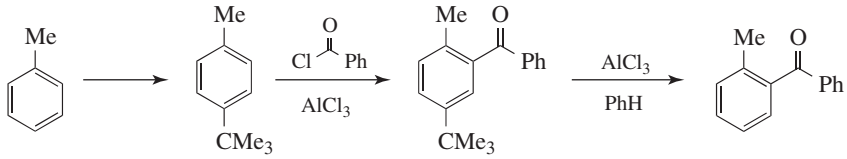
The three types are not treated separately, but reactions are classified by leaving group.

A. Carbon Leaving Groups

11-33 Reversal of Friedel-Crafts Alkylation

$$ArR + H^+ \xrightarrow{AlCl_3} ArH$$

Alkyl groups can be cleaved from aromatic rings by treatment with proton acids and/or Lewis acids. Tertiary R groups are the most easily cleaved; because this is true, the *tert*-butyl group is occasionally introduced into a ring, used to direct another group, and then removed.[732] For example, 4-*tert*-butyltoluene (**45**) reacted with benzoyl chloride and $AlCl_3$ to give the acylated product, and subsequent treatment with $AlCl_3$ led to loss of the *tert*-butyl group to give **46**.[733]



45 **46**

Because of this reaction, care must be taken when using Friedel-Crafts catalysts (Lewis acids or proton acids) on aromatic compounds containing alkyl groups. Secondary R groups are harder to cleave, and primary R harder still. True cleavage, in which the R becomes an alkene, occurs only at high temperatures, >400 °C.[734] At ordinary temperatures, the R group attacks another ring, so that the bulk of the product may be dealkylated, but there is a residue of heavily alkylated material.

The isomerization reaction, in which a group migrates from one position in a ring to another or to a different ring, is more important than true cleavage. In these reactions, the *meta* isomer is generally the most favored product among the dialkylbenzenes; and the 1,3,5 product the most favored among the trialkylbenzenes, because they have the highest thermodynamic stabilities.

Alkyl migrations can be inter- or intramolecular, depending on the conditions and on the R group. The following experiments can be cited:

[732] Tashiro, M. *Synthesis* ***1979***, 921; Tashiro, M.; Fukata, G. *Org. Prep. Proced. Int.* ***1976***, *8*, 51.
[733] Hofman, P.S.; Reiding, D.J.; Nauta, W.T. *Recl. Trav. Chim. Pays-Bas* ***1960***, *79*, 790.
[734] Olah, G.A. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, pp. 36–38.

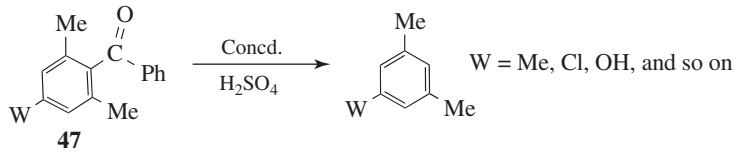
- Ethylbenzene treated with HF and BF_3 gave, almost completely, benzene and diethylbenzenes[735] (entirely intermolecular).
- Propylbenzene labeled in the β position gave benzene, propylbenzene, and di- and tripropylbenzenes, but the propylbenzene recovered was partly labeled in the α position and not at all in the γ position[736] (both intra- and intermolecular).
- *o*-Xylene treated with HBr and $AlBr_3$ gave a mixture of *o*- and *m*- but no *p*-xylene, while *p*-xylene gave *p*- and *m*- but no *o*-xylene, and no trimethyl compounds could be isolated in these experiments[737] (exclusively intramolecular rearrangement).

Apparently, methyl groups migrate only intramolecularly, while other groups may follow either path.[738]

The mechanism[739] of intermolecular rearrangement can involve free alkyl cations, but there is much evidence to show that this is not necessarily the case. For example, many of them occur without rearrangement within the alkyl group.[740] Evidence for this mechanism is that optically active $PhCHDCH_3$ labeled in the ring with ^{14}C and treated with $GaBr_3$ in the presence of benzene gave ethylbenzene containing no deuterium and also ethylbenzene that contained two deuterium atoms. The rate of loss of radioactivity was about equal to the rate of loss of optical activity.[740] The mechanism of intramolecular rearrangement is not very clear. 1,2 shifts of this kind have been proposed.[741] There is evidence from ^{14}C labeling that intramolecular migration occurs only through 1,2 shifts.[742] Any 1,3 or 1,4 migration takes place by a series of two or more 1,2 shifts.

Phenyl groups have also been found to migrate. Thus *o*-terphenyl, heated with $AlCl_3/H_2O$, gave a mixture containing 7% *o*-, 70% *m*-, and 23% *p*-terphenyl.[743] Alkyl groups have also been replaced by groups other than hydrogen (e.g., nitro groups).

Unlike alkylation, *Friedel-Crafts acylation* has been generally considered to be irreversible, but a number of instances of electrofugal acyl groups have been reported,[744] especially where there are two *ortho* substituents, for example the hydro-debenzoylation of **47**.[745]



47

OS **V**, 332. Also see OS **III**, 282, 653; **V**, 598.

[735] McCaulay, D.A.; Lien, A.P. *J. Am. Chem. Soc.* ***1953***, *75*, 2407. For similar results, see Bakoss, H.J.; Roberts, R.M.G.; Sadri, A.R. *J. Org. Chem.* ***1982***, *47*, 4053.
[736] Roberts, R.M.G.; Douglass, J.E. *J. Org. Chem.* ***1963***, *28*, 1225.
[737] Allen, R.H.; Yats, L.D. *J. Am. Chem. Soc.* ***1959***, *81*, 5289.
[738] Allen, R.H. *J. Am. Chem. Soc.* ***1960***, *82*, 4856.
[739] See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 1–55.
[740] Streitwieser Jr., A.; Reif, L. *J. Am. Chem. Soc.* ***1964***, *86*, 1988.
[741] Olah, G.A.; Meyer, M.W.; Overchuk, N.A. *J. Org. Chem.* ***1964***, *29*, 2313.
[742] See Steinberg, H.; Sixma, F.L.J. *Recl. Trav. Chim. Pays-Bas* ***1962***, *81*, 185; Koptyug, V.A.; Isaev, I.S.; Vorozhtsov Jr., N.N. *Doklad. Akad. Nauk SSSR,* ***1963***, *149*, 100.
[743] Olah, G.A.; Meyer, M.W. *J. Org. Chem.* ***1962***, *27*, 3682.
[744] See Giordano, C.; Villa, M.; Annunziata, R. *Synth. Commun.* ***1990***, *20*, 383.
[745] Al-Ka'bi, J.; Farooqi, J.A.; Gore, P.H.; Moonga, B.S.; Waters, D.N. *J. Chem. Res. (S)* ***1989***, 80.

11-34 Decarbonylation of Aromatic Aldehydes

$$\mathrm{ArCHO} \xrightarrow{\mathrm{H_2\ SO_4}} \mathrm{ArH} + \mathrm{CO}$$

The decarbonylation of aromatic aldehydes with sulfuric acid[746] is the reverse of the *Gatterman-Koch reaction* (**11-18**). It has been carried out with trialkyl- and trialkoxybenzaldehydes. The reaction takes place by the ordinary arenium ion mechanism: the attacking species is H^+ and the leaving group is HCO^+, which can lose a proton to give CO or combine with OH^- from the water solvent to give formic acid.[747] Aromatic aldehydes have also been decarbonylated with basic catalysts.[748] When basic catalysts are used, the mechanism is probably similar to the S_E1 process of **11-35**. See also, **14-26**. A Ni-catalyzed decarbonylation reaction has been reported.[749] The extrusion of CO from ketones using a Rh catalyst was used to produce biaryls and alkyl/alkenyl arenes.[750]

11-35 Decarboxylation of Aromatic Acids

$$\mathrm{ArCOOH} \xrightarrow[\text{Quinoline}]{\mathrm{Cu}} \mathrm{ArH} + \mathrm{CO_2}$$

The decarboxylation of aromatic acids is most often carried out by heating with Cu and quinoline. However, two other methods can be used with certain substrates. In one method the salt of the acid ($ArCOO^-$) is heated, and in the other the carboxylic acid is heated with a strong acid, often sulfuric. The latter method is accelerated by the presence of electron-donating groups in *ortho* and *para* positions and by the steric effect of groups in the *ortho* positions; in benzene systems it is generally limited to substrates that contain such groups. In this method, decarboxylation takes place by the arenium ion mechanism,[751] with H^+ as the electrophile and CO_2 as the leaving group.[752] Evidently, the order of electrofugal ability is $CO_2 > H^+ > COOH^+$, so that it is necessary, at least in most cases, for the COOH to lose a proton before it can cleave.

When carboxylate *ions* are decarboxylated, the mechanism is entirely different, being of the S_E1 type. Evidence for this mechanism is that the reaction is first order and that electron-withdrawing groups, which would stabilize a carbanion, facilitate the reaction.[753]

Despite its synthetic importance, the mechanism of the Cu-quinoline method has been studied very little, but it has been shown that the actual catalyst is cuprous ion (Cu^+).[754] In fact, the reaction proceeds much faster if the acid is heated in quinoline with cuprous

[746] See Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 316–323; Schubert, W.M.; Kintner, R.R. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 695–760.

[747] Burkett, H.; Schubert, W.M.; Schultz, F.; Murphy, R.B.; Talbott, R. *J. Am. Chem. Soc.* ***1959***, *81*, 3923.

[748] See Forbes, E.J.; Gregory, M.J. *J. Chem. Soc. B* ***1968***, 205.

[749] Ding, K.; Xu, S.; Alotaibi, R.; Paudel, K.; Reinheimer, E.W.; Weatherly, J. *J. Org. Chem.* ***2017***, *82*, 4924.

[750] Lei, Z.-Q.; Li, H.; Li, Y.; Zhang, X.-S.; Chen, K.; Wang, X.; Sun, J.; Shi, Z.-J. *Angew. Chem. Int. Ed.* ***2012***, *51*, 2690.

[751] See Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 303–316; Willi, A.V. *Isot. Org. Chem.* ***1977***, *3*, 257.

[752] See Willi, A.V.; Cho, M.H.; Won, C.M. *Helv. Chim. Acta* ***1970***, *53*, 663.

[753] See Segura, P.; Bunnett, J.F.; Villanova, L. *J. Org. Chem.* ***1985***, *50*, 1041.

[754] Cohen, T.; Schambach, R.A. *J. Am. Chem. Soc.* ***1970***, *92*, 3189. See also, Aalten, H.L.; van Koten, G.; Tromp, J.; Stam, C.H.; Goubitz, K.; Mak, A.N.S. *Recl. Trav. Chim. Pays-Bas* ***1989***, *108*, 295.

oxide (Cu_2O) instead of Cu, provided that atmospheric oxygen is rigorously excluded. A mechanism has been suggested in which it is the cuprous salt of the acid that actually undergoes the decarboxylation.[754] It has been shown that cuprous salts of aromatic acids are easily decarboxylated by heating in quinoline[755] and that arylcopper compounds are intermediates that can be isolated in some cases.[756] Metallic silver has been used in place of copper, with higher yields.[757] Silver acetate has also been used to promote decarboxylation.[758] A photolytic decarboxylation has also been reported, under a dioxygen atmosphere in the presence of HgF_2.[759] The *ortho* position exerts dual effects in the decarboxylation event: *ortho* substituents destabilize but an *ortho* electron-withdrawing group adds stabilization, with the net effect that the decarboxylation energy barrier is lowered.[760] The photochemical decarboxylation of aryl carboxylic acids has been reported using a silver compound and $K_2S_2O_8$.[761] A decarboxylative coupling reaction of aryl halides and arylcarboxylic acids has been reported, using Pd and Cu catalysts, to give the corresponding biaryl.[762]

Rearrangements are also known to take place. For example, when the phthalate ion is heated with a catalytic amount of cadmium, the terphthalate ion is produced.[763] In a similar process, potassium benzoate heated with Cd salts disproportionates to benzene and the dianion of terephthalic acid. The term *Henkel reaction* (named for the company that patented the process) is used for these rearrangements.[764] An S_E1 mechanism has been suggested.[765] The terphthalate is the main product because it crystallizes from the reaction mixture, driving the equilibrium in that direction.[766]

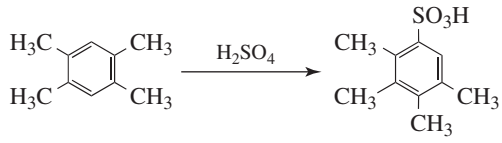
A decarboxylative etherification reaction has been reported in which a potassium arylcarboxylate reacted with $Si(OR)_4$, in the presence of Ag_2CO_3, $Cu(OAc)_2$, and oxygen, and gave the aryl alkyl ether.[767] Arylamines have been prepared by the decarboxylative coupling of aryl carboxylic acids and hydroxylamines, in the presence of DCC and a Pd catalyst.[768] Aryl carboxylic acids reacted with CuX_2 at 110 °C, with Ag_2CO_3 and a Pd catalyst, to give the ipso-substituted halo aromatic compound.[769] A decarboxylative aryl–aryl coupling reaction was reported in which aryl carboxylic acids were coupled with arylboroxins or aryl(trialkxoy)silanes, with a silver compound and a Pd catalyst, in air.[770] The decarboxylative coupling of aryl carboxylic acids and benzene to give the biaryl used a silver(I) compound and 3 equivalents of $K_2S_2O_8$, heated to 120 °C.[771]

For aliphatic decarboxylation, see **12-39**.

[755] Cohen, T.; Berninger, R.W.; Wood, J.T. *J. Org. Chem.* ***1978***, *43*, 37.
[756] See Ibne-Rasa, K.M. *J. Am. Chem. Soc.* ***1962***, *84*, 4962.
[757] Chodowska-Palicka, J.; Nilsson, M. *Acta Chem. Scand.* ***1970***, *24*, 3353.
[758] Gooßen, L.J.; Linder, C.; Rodríguez, N.; Lange, P.P.; Fromm, A. *Chem. Commun.* ***2009***, 7173.
[759] Farhadi, S.; Zaringhadam, P.; Sahamieh, R.Z. *Tetrahedron Lett.* ***2006***, *47*, 1965.
[760] Grainger, R.; Cornella, J.; Blakemore, D.C.; Larrosa, I.; Campanera, J.M. *Chem. Eur. J.* ***2014***, *20*, 16680.
[761] Seo, S.; Taylor, J.B.; Greaney, M.F. *Chem. Commun.* ***2012***, *48*, 8270.
[762] Goossen, L.J.; Rodrguez, N.; Linder, C. *J. Am. Chem. Soc.* ***2008***, *130*, 15248.
[763] Ogata, Y.; Nakajima, K. *Tetrahedron* ***1965***, *21*, 2393; Ratusky, J.; Sorm, F. *Chem. Ind. (London)*, ***1966***, 1798.
[764] Ratusky, J. in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, ***1979***, pp. 915–944.
[765] Ratusky, J. *Collect. Czech. Chem. Commun.* ***1973***, *38*, 74, 87, and references cited therein.
[766] Ratusky, J. *Collect. Czech. Chem. Commun.* ***1968***, *33*, 2346.
[767] Bhadra, S.; Dzik, W.I.; Goossen, L.J. *J. Am. Chem. Soc.* ***2012***, *134*, 9938.
[768] Dai, Q.; Li, P.; Ma, N.; Hu, C. *Org. Lett.* ***2016***, *18*, 5560.
[769] Peng, X.; Shao, X.-F.; Liu, Z.-Q. *Tetrahedron Lett.* ***2013***, *54*, 3079.
[770] Mino, T.; Yoshizawa, E.; Watanabe, K.; Abe, T.; Hirai, K.; Sakamoto, M. *Tetrahedron Lett.* ***2014***, *55*, 3184.
[771] Kan, J.; Huang, S.; Lin, J.; Zhang, M.; Su, W. *Angew. Chem. Int. Ed.* ***2015***, *54*, 2199.

OS **I**, 274, 455, 541; **II**, 100, 214, 217, 341; **III**, 267, 272, 471, 637; **IV**, 590, 628; **V**, 635, 813, 982, 985. Also see OS **I**, 56.

11-36 The Jacobsen Reaction



When polyalkyl- or polyhalobenzenes are treated with sulfuric acid, the ring is sulfonated, but rearrangement also takes place. The reaction, known as the *Jacobsen reaction*, is limited to benzene rings that have at least four substituents, which can be any combination of alkyl and halogen groups, where the alkyl groups can be ethyl or methyl and the halogens can be iodo, chloro, or bromo. When isopropyl or *tert*-butyl groups are on the ring, these groups are cleaved to give alkenes. Since a sulfo group can later be removed (**19-74**), the Jacobsen reaction can be used as a means of rearranging polyalkylbenzenes. The rearrangement always brings the alkyl or halo groups closer together than they were originally. Side products in the case illustrated above are pentamethylbenzenesulfonic acid, 2,4,5-trimethylbenzenesulfonic acid, and so on, indicating an intermolecular process, at least partially.

The mechanism of the Jacobsen reaction is not established,[772] but there is evidence, at least for polymethylbenzenes, that the rearrangement is intermolecular, and that the species to which the methyl group migrates is a polymethylbenzene, not a sulfonic acid. Sulfonation takes place after the migration.[773] It has been shown by labeling that ethyl groups migrate without internal rearrangement.[774] Isomerization of alkyl groups in substituted biphenyls has been observed[775] when the medium is a superacid (Sec. 5.A.ii).

B. Halogen Leaving groups

11-37 Formation of Aryl Organometallic Compounds

$$\mathrm{ArBr + M \longrightarrow ArM}$$
$$\mathrm{ArBr + RM \longrightarrow ArM + RBr}$$

The LiCl-free 2- or 4-lithiation of 1-chloro-3-(trifluoromethyl)benzene was reported using LDA in THF at −78 °C.[776] Arylzinc reagents were prepared from aryl iodides and zinc

[772] See Koeberg-Telder, A.; Cerfontain, H. *J. Chem. Soc., Perkin Trans. 2* ***1977***, 717; Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Wiley, NY, ***1968***, pp. 214–226; Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 22–32, 48–55.

[773] Cerfontain, H.; Koeberg-Telder, A. *Can. J. Chem.* ***1988***, *66*, 162.

[774] Marvell, E.N.; Webb, D. *J. Org. Chem.* ***1962***, *27*, 4408.

[775] Sherman, S.C.; Iretskii, A.V.; White, M.G.; Gumienny, C.; Tolbert, L.M.; Schiraldi, D.A. *J. Org. Chem.* ***2002***, *67*, 2034.

[776] Hoepker, A.C.; Gupta, L.; Ma, Y.; Faggin, M.F.; Collum, D.B. *J. Am. Chem. Soc.* ***2011***, *133*, 7135. See Liang, J.; Hoepker, A.C.; Bruneau, A.M.; Ma, Y.; Gupta, L.; Collum, D.B. *J. Org. Chem.* ***2014***, *79*, 11885.

metal, in THF, with a cobalt–Xantiphos catalyst, mediated by LiCl.[777] Aryl or heteroaryl bromides were converted to the corresponding arylindium reagent by reaction with In metal, mediated by LiCl, with a Co catalyst.[778] A computational study of LDA deaggregation has been reported.[779] Magnesation of 2,3-dichloro-5-(trifluoromethyl)pyridine using TMP-MgCl•LiCl under flow reactor conditions gave an ether organometallic, that was subsequently converted to the aryl iodide.[780]

2-Furyllsodium derivatives have been formed *in situ* from NaHMDS, allowing subsequent reactions with electrophiles.[781] Lithium–(magnesium–)zinc and lithium–cobalt combinations have been used for aromatic deprotometalation and subsequent reaction with aldehydes.[782] Reductive elimination from arylpalladium cyanide complexes have been reported.[783]

Also see reactions **12-37** and **12-38**.

C. Metal Leaving Groups

11-38 Hydrolysis of Organometallic Compounds

$$ArM + H^+ \longrightarrow ArH + M^+$$

Organometallic compounds can be hydrolyzed by acid treatment. For active metals, such as Mg, Li, and so on, water is sufficiently acidic. The most important example of this reaction is hydrolysis of Grignard reagents, but M may be many other metals or metalloids. Examples are SiR_3, HgR, Na, and $B(OH)_2$. Since aryl Grignard and aryllithium compounds are fairly easy to prepare, they are often used to prepare salts of weak acids, such as alkynes.

$$PhMgBr + H{-}C{\equiv}C{-}H \longrightarrow H{-}C{\equiv}C:^- + MgBr + PhH$$

Where the bond between the metal and the ring is covalent, the usual arenium ion mechanism operates.[784] Where the bonding is essentially ionic, this is a simple acid–base reaction.

For the aliphatic counterpart of this reaction, see reaction **12-24**.

Other reactions of aryl organometallic compounds are treated with their aliphatic analogs: see reactions **12-25** to **12-27** and **12-29** to **12-36**.

[777] Jin, M.-Y.; Yoshikai, N. *J. Org. Chem.* ***2011***, *76*, 1972. Also see Becker, M.R.; Knochel, P. *Org. Lett.* ***2016***, *18*, 1462.
[778] Adak, L.; Yoshikai, N. *J. Org. Chem.* ***2011***, *76*, 7563.
[779] Hoepker, A.C.; Collum, D.B. *J. Org. Chem.* ***2011***, *76*, 7985.
[780] Petersen, T.P.; Becker, M.R.; Knochel, P. *Angew. Chem. Int. Ed.* ***2014***, *53*, 7933.
[781] Zhao, H.; Dankwardt, J.W.; Koenig, S.G.; Singh, S.P. *Tetrahedron Lett.* ***2012***, *53*, 166.
[782] Tilly, D.; Snégaroff, K.; Dayaker, G.; Chevallier, F.; Gros, P.C.; Mongin, F. *Tetrahedron* ***2012***, *68*, 8761.
[783] Klinkenberg, J.L.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2012***, *134*, 5758.
[784] See Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 278–303, 324–349.

CHAPTER 12

Aliphatic, Alkenyl, and Alkynyl Substitution: Electrophilic and Organometallic

The reactivity of a proton in a chemical reaction usually depends on the acidity. Protons in saturated alkanes are very unreactive, but electrophilic substitutions are often easily carried out at more acidic positions, for example, α to a carbonyl group, or at an alkynyl position (RC≡CH). Since metallic ions are easily able to bear positive charges, organometallic compounds should be especially susceptible to electrophilic substitution, and this is indeed the case.[1] Another important type of electrophilic substitution, known as *anionic cleavage*, involves the breaking of C—C bonds; in these reactions there are carbon leaving groups (**12-39** to **12-45**). A number of electrophilic substitutions at a nitrogen atom are treated at the end of this chapter.

Since a carbanion is generated when an atom or group is removed as a positive species from a carbon atom, the subject of carbanion structure and stability (Chapter 5) is inevitably related to the material in this chapter. Also related is the subject of very weak acids and very strong bases (Chapter 8), because the weakest acids are those in which the hydrogen is bonded to carbon.

12.A. MECHANISMS

For aliphatic electrophilic substitution, at least four possible major mechanisms can be distinguished,[2] S_E1, S_E2 (front), S_E2 (back), and S_Ei. The S_E1 is unimolecular; the other three

[1] See Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, 5 Vols., Wiley, NY, ***1984–1990***; Haiduc, I.; Zuckerman, J.J. *Basic Organometallic Chemistry*, Walter de Gruyter, NY, ***1985***; Negishi, E. *Organometallics in Organic Synthesis*, Wiley, NY, ***1980***; Maslowsky Jr., E. *Chem. Soc. Rev.* ***1980***, *9*, 25; in Tsutsui, M. *Characterization of Organometallic Compounds*, Wiley, NY, ***1969–1971***, the articles by Cartledge, F.K.; Gilman, H. pt. 1, pp. 1–33, and by Reichle, W.T. pt. 2, pp. 653–826.

[2] See Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H. Eds., Vol. 12, Elsevier, NY, ***1973***; Reutov, O.A.; Beletskaya, I.P. *Reaction Mechanisms of Organometallic Compounds*, North-Holland Publishing Company, Amsterdam, ***1968***; Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, pp. 25–149; Reutov, O.A. *Pure Appl. Chem.* ***1978***, *50*, 717; *Tetrahedron* ***1978***, *34*, 2827.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

are bimolecular. It is noted that the term "S_EAr" has been proposed to represent electrophilic aromatic substitution, so that the term "S_E2" refers exclusively to electrophilic substitutions where a steric course is possible.[3] To describe the steric course of an aliphatic substitution reaction, the suffixes "ret" and "inv" were proposed, referring to retention and inversion of configuration, respectively.

12.A.i. Bimolecular Mechanisms. S_E2 and S_Ei

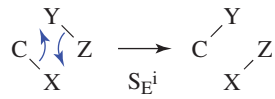
Reactions in which an electrophile (an electron-deficient species) removes a functional group are termed electrophilic aliphatic substitution reactions. The electrophilic substitution *bimolecular* mechanisms are termed S_E2 mechanisms. This mechanism appears to be most prevalent for some organometallic compounds. The most extensive body of work involving substantiated S_E2 processes, based on both kinetic and stereochemical studies, deals with electrophilic cleavages of organomercurials.[4] Retention of configuration is the normal course of electrophilic cleavage of the carbon–mercury bond.[5] These results with mercurials have been generalized, leading to the conclusion that the normal stereochemical course of electrophilic substitution is retention of configuration on carbon. So far, no inversion has been found with an organomercury substrate. It may be that still other examples of backside attack exist,[6] but have escaped detection because of the difficulty in preparing compounds with a configurationally stable carbon–metal bonds.

The bimolecular mechanisms for electrophilic aliphatic substitution are analogous to the S_N2 mechanism in that the new bond forms as the old one breaks. However, in the S_N2 mechanism the incoming group brings with it a pair of electrons (see Chapter 10), and this orbital can overlap with the central carbon only to the extent that the leaving group takes away its electrons; otherwise the carbon would have more than eight electrons at one time in its outer shell. Since electron clouds repel, this means also that the incoming group attacks backside, at a position 180° from the leaving group, resulting in inversion of configuration. When the nucleophilic species attacks (donates electrons to) an electrophile, it brings to the substrate only a vacant orbital. Predicting the direction of the attack is not as straightforward. Two main possibilities can be imagined: delivery of the electrophile to the front, which is S_E2 (front), or delivery of the electrophile to the rear, which is S_E2 (back).

Both the S_E2 (front) and S_E2 (back) mechanisms are designated D_EA_E in the IUPAC system. With substrates in which these possibilities may be distinguished, the former mechanism should result in retention of configuration and the latter in inversion. The reaction of allylsilanes with adamantyl chloride and $TiCl_4$, for example, gives primarily the *anti* product via a S_E2' reaction.[7] When the electrophile reacts from the front, there is a third

[3] Gawley, R.E. *Tetrahedron Lett.* ***1999***, *40*, 4297.
[4] Jensen, F.R.; Rickborn, B. *Electrophilic Substitution of Organomercurials*, McGraw-Hill, New York, ***1968***.
[5] Jensen, F.R.; Gale, L.H. *J. Am. Chem. Soc.* ***1959***, *81*, 1261.
[6] See Bergbreiter, D.E.; Rainville, D.P. *J. Organomet. Chem.* ***1976***, *121*, 19.
[7] Buckle, M.J.C.; Fleming, I.; Gil, S. *Tetrahedron Lett.* ***1992***, *33*, 4479.

possibility. A portion of the electrophile may assist in the removal of the leaving group, forming a bond with it at the same time that the new C—Y bond is formed:



This mechanism, which is called the S_Ei mechanism[8] (IUPAC designation: *cyclo*-$D_EA_ED_nA_n$), also results in retention of configuration.[9] Plainly, where a second-order mechanism involves this kind of internal assistance, backside attack is impossible.

It is evident that these three mechanisms are not easy to distinguish. All three give second-order kinetics, and two result in retention of configuration.[10] In fact, although much work has been done on this question, there are few cases in which one can unequivocally establish that another mechanism is not actually taking place. Clearly, a study of the stereochemistry can distinguish between S_E2 (back) on the one hand and S_E2 (front) or S_Ei on the other. Many such investigations have been made. In the overwhelming majority of second-order electrophilic substitutions, the result has been retention of configuration or some other indication of frontside attack, indicating an S_E2 (front) or S_Ei mechanism.

Another indication of frontside attack is that second-order electrophilic substitutions proceed very easily at *bridgehead* carbons (Sec. 10.A.i).[11] Still another indication is the behavior of neopentyl as a substrate. S_N2 reactions at neopentyl are extremely slow (Sec. 10.G.i), because attack from the rear is blocked and the transition state for the reaction lies very high in energy. The fact that neopentyl systems undergo electrophilic substitution only slightly more slowly than ethyl[12] is further evidence for frontside attack.

Inversion of configuration has been found in certain cases, demonstrating that the S_E2 (back) mechanism can take place. For example, the reaction of optically active *sec*-butyltrineopentyltin with bromine (**12-39**) gives inverted *sec*-butyl bromide.[13] A number of other organometallic compounds have also been shown to give inversion when treated with halogens,[14] although others do not.[15]

Compounds that are chiral because of a stereogenic carbon at which a carbon–metal bond is located[16] are often difficult to resolve and once resolved are often easily racemized.

[8] The names for these mechanisms vary throughout the literature. For example, the S_Ei mechanism has also been called the S_E2, the S_E2 (closed), and the S_E2 (cyclic) mechanism. The original designations, S_E1, S_E2, and so on, were devised by the Hughes-Ingold school.

[9] It has been contended that the S_Ei mechanism violates the principle of conservation of orbital symmetry (see **15-60**, A), and that the S_E2 (back) mechanism partially violates it: Slack, D.A.; Baird, M.C. *J. Am. Chem. Soc.* ***1976***, *98*, 5539.

[10] See Flood, T.C. *Top. Stereochem.* ***1981***, *12*, 37. See also, Jensen, F.R.; Davis, D.D. *J. Am. Chem. Soc.* ***1971***, *93*, 4048.

[11] Schöllkopf, U. *Angew. Chem.* ***1960***, *72*, 147. See Fort Jr., R.C.; Schleyer, P.v.R. *Adv. Alicyclic Chem.* ***1966***, *1*, 283 (pp. 353–370).

[12] Hughes, E.D.; Volger, H.C. *J. Chem. Soc.* ***1961***, 2359.

[13] Jensen, F.R.; Davis, D.D. *J. Am. Chem. Soc.* ***1971***, *93*, 4048; Fukuto, J.M.; Jensen, F.R. *Acc. Chem. Res.* ***1983***, *16*, 177.

[14] See Magnuso, R.H.; Halpern, J.; Levitin, I.Ya.; Vol'pin, M.E. *J. Chem. Soc., Chem. Commun.* ***1978***, 44.

[15] See McGahey, L.F.; Jensen, F.R. *J. Am. Chem. Soc.* ***1979***, *101*, 4397. Also see Rahm, A.; Grimeau, J.; Pereyre, M. *J. Organomet. Chem.* ***1985***, *286*, 305.

[16] See Sokolov, V.I. *Chirality and Optical Activity in Organometallic Compounds*, Gordon and Breach, NY, ***1990***.

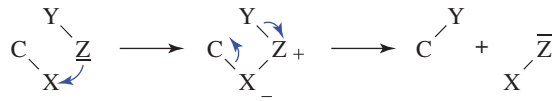
The resolution has been accomplished most often with organomercury compounds,[17] and most stereochemical investigations have therefore been made with these substrates. Only a few optically active *Grignard reagents* (**12-37**) have been prepared[18] (i.e., in which the only stereogenic center is the carbon bonded to the magnesium). Because of this, the steric course of electrophilic substitutions at the C—Mg bond has not often been determined. However, in one such case, the reaction of both the *exo* and *endo* isomers of the 2-norbornyl Grignard reagent with $HgBr_2$ (to give 2-norbornylmercuric bromide) has been shown to proceed with retention of configuration.[19] It is likely that inversion takes place only when steric hindrance prevents reaction on the frontside and when the electrophile does not carry an electron-withdrawing group.

The S_E2 (back) mechanism can be identified in certain cases (if inversion of configuration is found), but it is plain that stereochemical investigations cannot distinguish between the S_E2 (front) and the S_Ei mechanisms and that, in the many cases where configurationally stable substrates cannot be prepared, such investigations are of no help at all in distinguishing among all three of the second-order mechanisms. Unfortunately, there are not many other methods that lead to unequivocal conclusions. One method that has been used in an attempt to distinguish between the S_Ei mechanism on the one hand and the S_E2 pathways on the other involves the study of salt effects on the rate. It may be recalled (Sec. 10.G.iv) that reactions in which neutral starting molecules acquire charges in the transition state are aided by an increasing concentration of added ions. Thus the S_Ei mechanism would be less influenced by salt effects than would either of the S_E2 mechanisms. On this basis Abraham and co-workers[20] concluded that the reactions

$$R_4Sn + HgX_2 \rightarrow RHgX + R_3SnX\,(X = Cl \text{ or } I)$$

take place by S_E2 and not by S_Ei mechanisms. Similar investigations involve changes in solvent polarity[21] (see also, Sec. 12.C.i). In the case of the reactions where R = R′ = *i*-Pr and R = *i*-Pr, R′ = neopentyl, the use of polar solvents gave predominant inversion, while nonpolar solvents gave predominant retention.[22]

On the basis of evidence from reactivity studies, it has been suggested[23] that a variation of the S_Ei mechanism is possible in which the group Z becomes attached to X before the latter becomes detached. This process has been called the S_EC or S_E2 (co-ord) mechanism[22,24] (IUPAC designation A_n + cyclo-$D_EA_ED_n$).



[17] See Jensen, F.R.; Whipple, L.D.; Wedegaertner, D.K.; Landgrebe, J.A. *J. Am. Chem. Soc.* ***1959***, *81*, 1262; Charman, H.B.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1959***, 2523, 2530.

[18] This was done first by Walborsky, H.M.; Young, A.E. *J. Am. Chem. Soc.* ***1964***, *86*, 3288.

[19] Jensen, F.R.; Nakamaye, K.L. *J. Am. Chem. Soc.* ***1966***, *88*, 3437.

[20] Abraham, M.H.; Johnston, G.F. *J. Chem. Soc. A* ***1970***, 188.

[21] See Abraham, M.H.; Dorrell, F.J. *J. Chem. Soc., Perkin Trans. 2* ***1973***, 444.

[22] Fukuto, J.M.; Newman, D.A.; Jensen, F.R. *Organometallics* ***1987***, *6*, 415.

[23] Abraham, M.H.; Hill, J.A. *J. Organomet. Chem.* ***1967***, *7*, 11.

[24] Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H., Eds., Vol. 12, Elsevier, NY, ***1973***, p. 15.

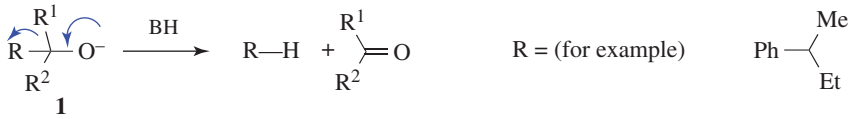
It has been shown that in certain cases (e.g., $Me_4Sn + I_2$) the reactants in an S_E2 reaction, when mixed, give rise to an immediate charge-transfer spectrum (Sec. 3.C.i), showing that an electron donor–acceptor (EDA) complex has been formed.[25] In these cases it is likely that the EDA complex is an intermediate in the reaction.

12.A.ii. The S_E1 Mechanism

The S_E1 mechanism is analogous to the S_N1. It involves two steps: a slow ionization and a fast combination. The IUPAC designation is $D_E + A_E$.

$$\mathrm{R{-}X} \xrightarrow{\text{Slow}} \mathrm{R^- + X^+}$$
$$\mathrm{R^- + Y^+} \longrightarrow \mathrm{R{-}X}$$

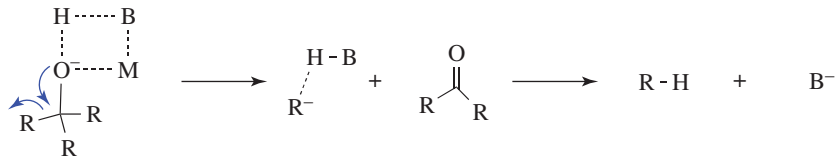
First-order kinetics are predicted and many such examples have been found. Other evidence for the S_E1 mechanism was obtained in a study of base-catalyzed tautomerization. In the reaction the rate of deuterium exchange was the same as the rate of racemization[26] and there was an isotope effect.[27] It is known that S_N1 reactions do not proceed at strained bridgehead carbons (e.g., in [2.2.1] bicyclic systems, Sec. 10.A.ii) because planar carbocations cannot form at these carbons. However, carbanions not stabilized by resonance are probably not planar, and S_E1 reactions readily occur with this type of substrate. Indeed, the question of carbanion structure is intimately tied into the problem of the stereochemistry of the S_E1 reaction. If a carbanion is planar, racemization should occur. If it is pyramidal and *can hold its structure*, the result should be retention of configuration, or at least partial retention. On the other hand, even a pyramidal carbanion will give racemization if it cannot hold its structure (this means that there is pyramidal inversion, as with amines, Sec. 4.C, category 3). Unfortunately, the only carbanions that can be studied easily are those stabilized by resonance, which makes them planar, as expected (Sec. 5.B.i). For simple alkyl carbanions, the main approach to deduce the structure has been to study the stereochemistry of S_E1 reactions rather than the other way around. Racemization is almost always observed, but whether this is caused by planar carbanions or by oscillating pyramidal carbanions is not known. In either case, racemization occurs whenever a carbanion is completely free or is symmetrically solvated.



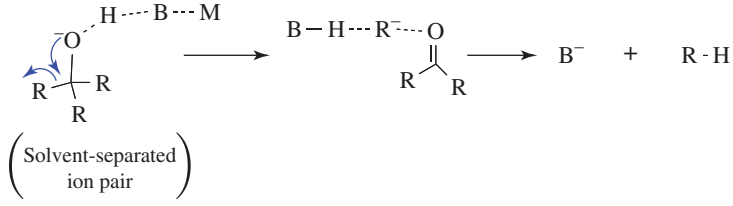
However, even planar carbanions need not give racemization. Cram found that retention and even inversion can occur in an alkoxide (see **1**) cleavage reaction (**12-40**), which is a first-order S_E1 reaction involving resonance-stabilized planar carbanions (here designated R^-).[28] By changing the solvent, Cram was able to produce products ranging from

[25] Fukuzumi, S.; Kochi, J.K. *J. Am. Chem. Soc.* ***1980***, *102*, 2141, 7290.
[26] Hsu, S.K.; Ingold, C.K.; Wilson, C.L. *J. Chem. Soc.* ***1938***, 78.
[27] Wilson, C.L. *J. Chem. Soc.* ***1936***, 1550.
[28] See Hoffman, T.D.; Cram, D.J. *J. Am. Chem. Soc.* ***1969***, *91*, 1009. For a discussion, see Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 138–158.

99% retention to 60% inversion and including complete racemization. These results are explained by a carbanion that is not completely free but is solvated. In nondissociating, nonpolar solvents, such as benzene or dioxane, the alkoxide ion exists as an ion pair, solvated by the solvent BH:



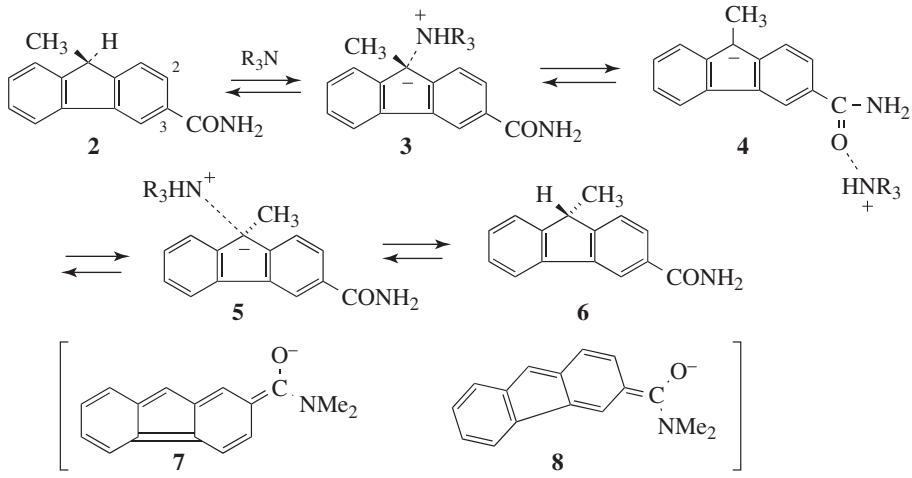
In the course of the cleavage, the proton of the solvent moves in to solvate the newly forming carbanion. This solvation is asymmetrical since the solvent molecule is already on the front side of the carbanion. When the carbanion actually bonds with the proton, the result is retention of the original configuration. In protic solvents, such as diethylene glycol, a good deal of inversion is found. In these solvents, the *leaving group* solvates the carbanion, so the solvent can solve it only from the opposite side:



When C—H bond formation occurs, the result is inversion. Racemization occurs in polar aprotic solvents such as DMSO. In these solvents, the carbanions are relatively long lived (because the solvent has no proton to donate) and symmetrically solvated. Similar behavior was found for carbanions generated by base-catalyzed hydrogen exchange (reaction **12-1**).[29] In this case information was obtained from measurement of the ratio of k_e (rate constant for isotopic exchange) to k_a (rate constant for racemization). A k_e/k_a ratio substantially > 1 means retention of configuration, since many individual isotopic exchanges are not producing a change in configuration. A k_e/k_a ratio of ~ 1 indicates racemization and a ratio of $\frac{1}{2}$ corresponds to inversion (Sec. 10.A.i). All three types of steric behavior were found, depending on R, the base, and the solvent. As with the alkoxide cleavage reaction, retention was generally found in solvents of low dielectric constant, racemization in polar aprotic solvents, and inversion in protic solvents. However, in the proton-exchange reactions, a fourth type of behavior was encountered. In aprotic solvents, with aprotic bases like tertiary amines, the k_e/k_a ratio was found to be *less* than 0.5, indicating that racemization took place *faster* than isotopic exchange (this process is known as *isoracemization*). Under these conditions, the conjugate acid of the amine remains associated with the carbanion as an ion pair. Occasionally, the ion pair dissociates long enough for the carbanion to turn over and recapture the proton. Thus, inversion (and hence racemization, which is

[29] See Roitman, J.N.; Cram, D.J. *J. Am. Chem. Soc.* ***1971***, *93*, 2225, 2231 and references cited therein; Cram, J.M.; Cram, D.J. *Intra-Sci. Chem. Rep.* ***1973***, *7(3)*, 1; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 85–105.

produced by repeated acts of inversion) occurs without exchange. A single act of inversion without exchange is called *isoinversion*.



The isoinversion process can take place by a pathway in which a positive species migrates in a stepwise fashion around a molecule from one nucleophilic position to another. For example, in the exchange reaction of 3-carboxamido-9-methylfluorene (**2**) with Pr_3N in *t*-BuOH, it has been proposed that the amine removes a proton from the 9 position of **2** and via **3** conducts the proton out to the C=O oxygen (**4**), around the molecule, and back to C-9 on the opposite face of the anion. Collapse of **5** gives the inverted product **6**. Of course **4** could also go back to **2** via **3**, but a molecule that undergoes the total process **2** → **3** → **4** → **5** → **6** has experienced an inversion without an exchange. Evidence for this pathway, called the *conducted tour mechanism*,[30] is that the 12-carboxamido isomer of **2** does not give isoracemization. In this case, the negative charge on the oxygen atom in the anion corresponding to **6** is less, because a canonical form in which oxygen acquires a full negative charge (**7**) results in disruption of the aromatic sextet in both benzene rings (cf. **8** where one benzene ring is intact). Whether the isoracemization process takes place by the conducted tour mechanism or a simple nonstructured contact ion-pair mechanism depends on the nature of the substrate (e.g., a proper functional group is necessary for the conducted tour mechanism) and of the base.[31]

It is known that vinylic carbanions *can* maintain configuration, so that S_E1 mechanisms should produce retention, which is the case. For example, *trans*-2-bromobut-2-ene was converted to 64–74% angelic acid (*trans*-2-methylbut-2-enoic acid).[32] Only ~5% of the *cis* isomer, tiglic acid, was produced. In addition, certain carbanions in which the negative charge is stabilized by *d*-orbital overlap can maintain configuration (Sec. 5.B.ii) and S_E1 reactions involving them proceed with retention of configuration.

[30] Cram, D.J.; Ford, W.T.; Gosser, L. *J. Am. Chem. Soc.* ***1968***, *90*, 2598; Ford, W.T.; Cram, D.J. *J. Am. Chem. Soc.* ***1968***, *90*, 2606, 2612. See also, Buchholz, S.; Harms, K.; Massa, W.; Boche, G. *Angew. Chem. Int. Ed.* ***1989***, *28*, 73.

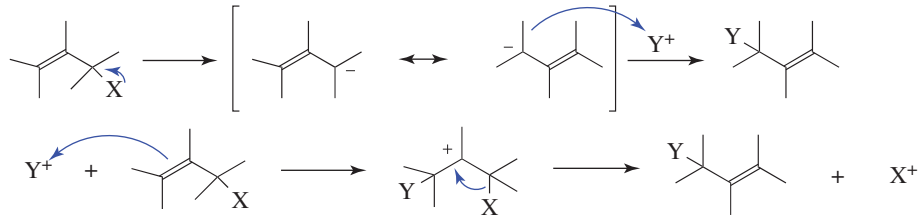
[31] Almy, J.; Hoffman, D.H.; Chu, K.C.; Cram, D.J. *J. Am. Chem. Soc.* ***1973***, *95*, 1185.

[32] Dreiding, A.S.; Pratt, R.J. *J. Am. Chem. Soc.* ***1954***, *76*, 1902. See also, Walborsky, H.M.; Turner, L.M. *J. Am. Chem. Soc.* ***1972***, *94*, 2273.

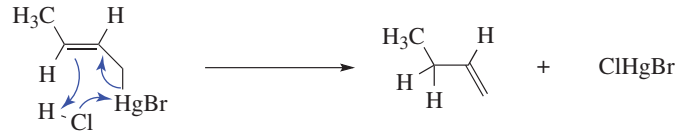
12.A.iii. Electrophilic Substitution Accompanied by Double-Bond Shifts

9 **10**

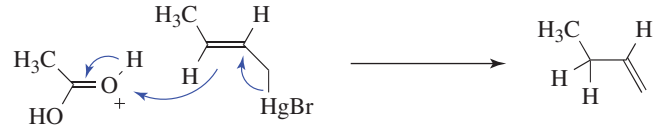
When electrophilic substitution is carried out at an allylic substrate, the product may be rearranged (**9** → **10**). This type of process is analogous to the nucleophilic allylic rearrangements discussed in Sec. 10.D. There are two principal pathways. The first of these is analogous to the S_E1 mechanism in that the leaving group is first removed, giving a resonance-stabilized allylic carbanion, which then attacks the electrophile Y. In the other pathway, the Y group is first attacked by the π bond, giving a carbocation, which then loses X with formation of the alkene unit. These mechanisms are more fully discussed under reaction **12-2**.



Most electrophilic allylic rearrangements involve loss of hydrogen, but they have also been observed with metallic leaving groups.[33] Sleezer, Winstein, and Young found that crotylmercuric bromide reacted with HCl ~10^7 times faster than *n*-butylmercuric bromide and the product was >99% but-1-ene.[34] These facts point to an S_Ei' mechanism (IUPAC designation cyclo-1/3/$D_EA_ED_nA_n$):



The reaction of the same compound with acetic acid/perchloric acid seems to proceed by an S_E2' mechanism (IUPAC designation 1/3/D_EA_E):[34]



The geometry of electrophilic allylic rearrangement has not been studied very much (cf. the nucleophilic case, Sec. 10.E), but in most cases the rearrangement takes place with *anti*

[33] See Courtois, G.; Miginiac, L. *J. Organomet. Chem.* ***1974***, *69*, 1.
[34] Sleezer, P.D.; Winstein, S.; Young, W.G. *J. Am. Chem. Soc.* ***1963***, *85*, 1890. See also, Kashin, A.N.; Bakunin, V.N.; Khutoryanskii, V.A.; Beletskaya, I.P.; Reutov, O.A. *J. Organomet. Chem.* ***1979***, *171*, 309.

stereoselectivity,[35] although *syn* stereoselectivity has also been demonstrated.[36] In one case, use of the electrophile H^+ and the leaving group $SnMe_3$ gave both *syn* and *anti* stereoselectivity, depending on whether the substrate was *cis* or *trans*.[37]

12.A.iv. Other Mechanisms

Addition–elimination (**12-16**) and cyclic mechanisms (**12-39**) are also known. Much less work has been done on electrophilic aliphatic substitution mechanisms than on nucleophilic substitutions, and the exact mechanisms of many of the reactions in this chapter are in doubt. For many of them, not enough work has been done to allow a decision as to which of the mechanisms described in this chapter is operating, if indeed any is. There may be other electrophilic substitution mechanisms, and some of the reactions in this chapter may not even be electrophilic substitutions at all.

12.B. REACTIVITY

Only a small amount of work has been done in this area, compared to the vast amount done for aliphatic nucleophilic substitution and aromatic electrophilic substitution. Therefore, only a few conclusions can be drawn, most of them sketchy or tentative.[38]

1. *Effect of substrate*. For S_E1 reactions, electron-donating groups decrease rates and electron-withdrawing groups increase them. This is expected for a reaction in which the rate-determining step is analogous to the cleavage of a proton from an acid. For the S_E2 (back) mechanism, Jensen and Davis[13] showed that the reactivity of alkyl groups is similar to that for the S_N2 mechanism (i.e., Me > Et > Pr > *i*-Pr > neopentyl), as is expected, since both involve backside attack and both are equally affected by steric hindrance. In fact, this pattern of reactivity can be regarded as evidence for the occurrence of the S_E2 (back) mechanism in cases where stereochemical investigation is not feasible.[39] For S_E2 reactions that proceed with retention, several studies have been made with varying results, depending on the reaction.[40] One such study, which examined the reaction $RHgBr + Br_2 \rightarrow RBr$ catalyzed by Br^-, showed *t*-Bu to have a relative rate of 43370 whereas Me had a relative rate of 1, but neopentyl had a relative rate of 0173.[41] This data shows that branching increased the rates, while β branching decreased them. Sayre and Jensen[41] attributed the decreased rates to steric hindrance, although attack here was definitely frontside, and the increased rates to the electron-donating effect of the alkyl groups, which

[35] Matassa, V.G.; Jenkins, P.R.; Kümin, A.; Damm, L.; Schreiber, J.; Felix, D.; Zass, E.; Eschenmoser, A. *Isr. J. Chem.* ***1989***, *29*, 321.
[36] Young, D.; Kitching, W. *J. Org. Chem.* ***1983***, *48*, 614; *Tetrahedron Lett.* ***1983***, *24*, 5793.
[37] Kashin, A.N.; Bakunin, V.N.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1982***, *18*, 1973. See also, Wickham, G.; Young, D.; Kitching, W. *Organometallics* ***1988***, *7*, 1187.
[38] See Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H., Eds., Vol. 12, Elsevier, NY, ***1973***, pp. 211–241.
[39] Also see Isaacs, N.S.; Laila, A.H. *Tetrahedron Lett.* ***1984***, *25*, 2407.
[40] See Abraham, M.H.; Broadhurst, A.T.; Clark, I.D.; Koenigsberger, R.U.; Dadjour, D.F. *J. Organomet. Chem.* ***1981***, *209*, 37.
[41] Sayre, L.M.; Jensen, F.R. *J. Am. Chem. Soc.* ***1979***, *101*, 6001.

stabilized the electron-deficient transition state.[42] Of course, steric hindrance should also be present with the α-branched groups, so these workers concluded that if it were not, the rates would be even greater. The Br electrophile is a rather large one and it is likely that smaller steric effects are present with smaller electrophiles. The rates of certain second-order substitutions of organotin compounds have been found to increase with increasing electron withdrawal by substituents. This behavior has been ascribed[43] to an S_E2 mechanism involving ion pairs, analogous to Sneen's ion-pair mechanism for nucleophilic substitution (Sec. 10.A.iv). Solvolysis of 2-bromo-1,1,1-trifluoro-2-(*p*-methoxyphenyl)ethane in water proceeds via a free carbocation intermediate, but ion pairing influences the reaction in the presence of bromide ion.[44]

2. *Effect of leaving group.* For both S_E1 and second-order mechanisms, the more polar[45] the C—X bond, the easier it is for the electrofuge to cleave. For metallic leaving groups in which the metal has a valence >1, the nature of the other group or groups attached to the metal thus has an effect on the reaction. For example, consider a series of organomercurials RHgW. Because a more electronegative W decreases the polarity of the C—Hg bond and furthermore results in a less stable HgW^+, the electrofugal ability of HgW decreases with increasing electronegativity of W. Thus, HgR′ (from RHgR′) is a better leaving group than HgCl (from RHgCl). Also in accord with this is the leaving-group order Hg-*t*-Bu > Hg-*i*-Pr > HgEt > HgMe, reported for acetolysis of R_2Hg,[42] since the more highly branched alkyl groups better help to spread the positive charge. It might be expected that, when metals are the leaving groups, S_E1 mechanisms would be favored, while with carbon leaving groups, second-order mechanisms would be found. However, the reported results have been just about the reverse of this. For carbon leaving groups the mechanism is usually S_E1 while for metallic leaving groups the mechanism is almost always S_E2 or S_Ei. A number of reports of S_E1 reactions with metallic leaving groups have appeared,[46] but the mechanism is not easy to prove and many of these reports have been challenged.[47] Reutov and co-workers[46] expressed the view that in such reactions a nucleophile (which may be the solvent) must assist in the removal of the electrofuge and they refer to such processes as $S_E1(N)$ reactions.
3. *Effect of solvent.*[48] In addition to the solvent effects on certain S_E1 reactions, mentioned earlier (Sec. 12.A.ii), solvents can influence the mechanism that is preferred. As with nucleophilic substitution (Sec. 10.G.iv), an increase in solvent polarity increases the possibility of an ionizing mechanism, in this case S_E1, in comparison with the second-order mechanisms, which do not involve ions. As previously mentioned (Sec. 12.A.ii), the solvent can also exert an influence between the S_E2 (front or back) and S_Ei mechanisms, in that the rates of S_E2 mechanisms should be increased by an increase in solvent polarity, while S_Ei mechanisms are much less affected.

[42] Also see Nugent, W.A.; Kochi, J.K. *J. Am. Chem. Soc.* ***1976***, *98*, 5979.
[43] Reutov, O.A. *J. Organomet. Chem.* ***1983***, *250*, 145. See also, Butin, K.P.; Magdesieva, T.V. *J. Organomet. Chem.* ***1985***, *292*, 47.
[44] Richard, J.P. *J. Org. Chem.* ***1992***, *57*, 625.
[45] For a discussion of a method for quantifying polar organic reactivity, see Mayr, H. *Tetrahedron* ***2015***, *71*, 5095.
[46] See Reutov, O.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1980***, *29*, 1461. See also, Dembech, P.; Eaborn, C.; Seconi, G. *J. Chem. Soc., Chem. Commun.* ***1985***, 1289.
[47] See Kitching, W. *Rev. Pure Appl. Chem.* ***1969***, *19*, 1.
[48] See Petrosyan, V.S. *J. Organomet. Chem.* ***1983***, *250*, 157.

12.C. REACTIONS

The reactions in this chapter are arranged in order of leaving group: hydrogen, metals, halogen, and carbon. Electrophilic substitutions at a nitrogen atom are treated last.

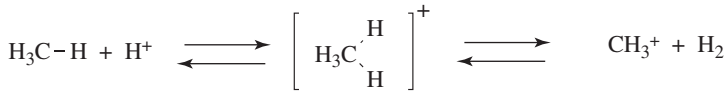
12.C.i. Hydrogen as Leaving Group

A. Hydrogen as the Electrophile

12-1 Hydrogen Exchange

$$R{-}H + D^+ \rightleftharpoons R{-}D + H^+$$

Hydrogen exchange can be accomplished by treatment with acids or bases. As with **11-1**, the exchange reaction is mostly used to study mechanistic questions, such as relative acidities, but it can be used synthetically to prepare deuterated or tritiated molecules. When ordinary strong acids (such as H_2SO_4) are used, only fairly acidic protons on carbon can exchange (for example, acetylenic and allylic). However, primary, secondary, and tertiary hydrogen atoms of alkanes can be exchanged by treatment with superacids (Sec. 5.A.ii).[49] The order of hydrogen reactivity is tertiary > secondary > primary. Where C—C bonds are present, they may be cleaved also (**12-46**). The mechanism of the exchange (illustrated for methane) has been formulated as involving reaction of H^+ with the C—H bond to give the pentavalent methanonium ion, which loses H_2 to give a tervalent carbocation.[50]



Methanonium ion

The methanonium ion CH_5^+ has a three-center, two-electron bond.[51] It is not known whether the methanonium ion is a transition state or a true intermediate, but an ion CH_5^+ has been detected in the mass spectrum.[52] The IR spectrum of the ethanonium ion $C_2H_7^+$ has been measured in the gas phase.[53] Note that the two electrons in the three-center, two-electron bond can move in three directions, in accord with the threefold symmetry of such a structure. The electrons can move to unite the two hydrogen atoms, leaving the CH_3^+ free (the forward reaction), or they can unite the CH_3 with either of the two hydrogen atoms, leaving the other hydrogen as a free H^+ ion (the reverse reaction). Actually, the methyl cation is not stable under these conditions. It can go back to CH_4 by the route shown (leading to H^+ exchange), or it can react with additional CH_4 molecules (**12-20**) to eventually

[49] See Olah, G.A.; Prakash, G.K.S.; Sommer, J. *Superacids*, Wiley, NY, ***1985***, pp. 244–249; Olah, G.A. *Angew. Chem. Int. Ed.* ***1973***, *12*, 173.

[50] See McMurry, J.E.; Lectka, T. *J. Am. Chem. Soc.* ***1990***, *112*, 869; Culmann, J.; Sommer, J. *J. Am. Chem. Soc.* ***1990***, *112*, 4057.

[51] See Olah, G.A.; Prakash, G.K.S.; Williams, R.E.; Field, L.D.; Wade, K. *Hypercarbon Chemistry*, Wiley, NY, ***1987***.

[52] See Sefcik, M.D.; Henis, J.M.S.; Gaspar, P.P. *J. Chem. Phys.* ***1974***, *61*, 4321.

[53] Yeh, L.I.; Pric, J.M.; Lee, Y.T. *J. Am. Chem. Soc.* ***1989***, *111*, 5597.

yield the *tert*-butyl cation, which is stable in these superacid solutions. Hydride ion can also be removed from alkanes (producing tervalent carbocations) by treatment with pure SbF_5 in the absence of any source of H^+.[54] Complete or almost complete perdeuteriation of cyclic alkenes has been achieved by treatment with dilute DCl/D_2O in sealed Pyrex tubes at 165–280 °C.[55]

Exchange with bases involves an S_E1 mechanism. Of course, such exchange is most successful for relatively acidic protons, such as those α to a carbonyl group, but even weakly acidic protons can exchange with bases if the bases are strong enough (Sec. 5.B.i). Alkanes and cycloalkanes, of both low and high molecular weight, can be fully perdeuterated by treatment with D_2 gas and a catalyst, such as Rh, Pt, or Pd.[56]

OS **VI**, 432.

12-2 Migration of Double Bonds

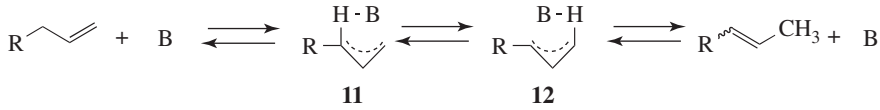
$$C_5H_{11}{-}CH_2{-}CH{=}CH_2 \xrightarrow[Me_2SO]{KNH_2} C_5H_{11}{-}CH{=}CH{-}CH_3$$

The double bonds of many unsaturated compounds may be isomerized[57] upon treatment with strong bases.[58] In many cases equilibrium mixtures are obtained and the thermodynamically most stable isomer predominates.[59] If the new double bond can be in conjugation with one already present or with an aromatic ring, *the conjugated compound is favored*.[60] If the choice is between an exocyclic and an endocyclic double bond (particularly with six-membered rings), *endocyclic is usually preferred*. In the absence of such considerations, *Zaitsev's rule* (Sec. 17.B) applies and the double bond goes to the carbon with the fewest hydrogen atoms (the thermodynamically more stable alkene). All these considerations lead to predictions that terminal alkenes can be isomerized to internal ones, nonconjugated alkenes to conjugated, *exo* six-membered-ring alkenes to *endo*, and so on, and not the other way around.

The term *prototropic rearrangement* is sometimes used as an example of electrophilic substitution with accompanying allylic rearrangement. The mechanism involves abstraction by a base to give a resonance-stabilized allylic carbanion and then reaction with a proton at the position that will give the more stable alkene.[61] This mechanism is exactly analogous to the allylic-rearrangement mechanism for nucleophilic substitution (Sec. 10.D). UV spectra of allylbenzene and 1-propenylbenzene in solutions containing NH_2 are identical, showing

[54] Lukas, J.; Kramer, P.A.; Kouwenhoven, A.P. *Recl. Trav. Chim. Pays-Bas* ***1973***, *92*, 44.
[55] Werstiuk, N.H.; Timmins, G. *Can. J. Chem.* ***1985***, *63*, 530; ***1986***, *64*, 1564.
[56] See Atkinson, J.G.; Luke, M.O.; Stuart, R.S. *Can. J. Chem.* ***1967***, *45*, 1511.
[57] For a list of methods used to shift double and triple bonds, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 220–226, 567–568.
[58] See Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 25–123; DeWolfe, R.H. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 437–449; Hubert, A.J.; Reimlinger, H. ***1970***, 405; Mackenzie, K. in *The Chemistry of Alkenes*, Vol. 1, Patai, S., pp. 416–436, Wiley, NY, ***1964***; Mackenzie, K. in *The Chemistry of Alkenes*, Vol. 2, Zabicky, J., pp. 132–148, Wiley, NY, ***1970***. Broaddus, C.D. *Acc. Chem. Res.* ***1968***, *1*, 231.
[59] See Hine, J.; Skoglund, M.J. *J. Org. Chem.* ***1982***, *47*, 4766. See also, Hine, J.; Linden, S. *J. Org. Chem.* ***1983***, *48*, 584.
[60] For a review of conversions of β,γ-enones to α,β-enones, see Pollack, R.M.; Bounds, P.L.; Bevins, C.L. in Patai, S.; Rappoport, Z. *The Chemistry of Enones,* pt. 1, Wiley, NY, ***1989***, pp. 559–597.
[61] See Pollack, R.M.; Mack, J.P.G.; Eldin, S. *J. Am. Chem. Soc.* ***1987***, *109*, 5048.

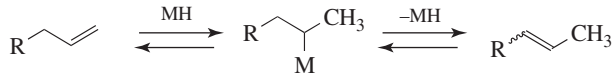
that the same carbanion is present in both cases, as required by this mechanism.[62] A protonic acid BH^+ protonates the carbanion and the more stable product will predominate, although the ratio of the two possible products can vary with the identity of BH^+.[63] It has been shown that base-catalyzed double-bond shifts are partially intramolecular, at least in some cases.[64] The intramolecular nature has been ascribed to a *conducted tour mechanism* (Sec. 12.A.iii) in which the base leads the proton from one carbanionic site to the other (**11** → **12**).[65]



11 **12**

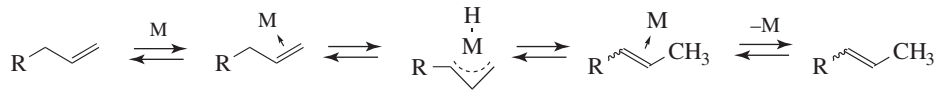
Double bond rearrangements can also take place on treatment with acids. Both proton acids and Lewis acids[66] can be used. The mechanism in the case of proton acids is the reverse of the previous one; first a proton is gained on but-1-ene by reaction with H^+, giving an allylic carbocation, and then another is lost, so the but-1-ene to but-2-ene isomerization is complete. As in the case of the base-catalyzed reaction, the thermodynamically more stable alkene is the one predominantly formed. However, the acid-catalyzed reaction is much less synthetically useful because carbocations give rise to many side products. If the substrate has several possible locations for a double bond, mixtures of all possible isomers are usually obtained. Isomerization of dec-1-ene, for example, gave a mixture that contains not only dec-1-ene and *cis*- and *trans*-dec-2-ene but also the *cis* and *trans* isomers of 3-, 4-, and 5-decene as well as branched alkenes resulting from rearrangement of carbocations. It is true that the most stable alkenes predominate, but many of them have stabilities that are close together.

Double bond isomerization can take place in other ways. Nucleophilic allylic rearrangements were discussed in Sec. 10.E. Electrocyclic and sigmatropic rearrangements are treated at **18-27** to **18-35**. Double bond migrations have also been accomplished photochemically,[67] and by means of metallic ion (most often complex ions containing Pt, Rh, or Ru) or metal carbonyl catalysts.[68] With metal compounds there are at least two possible mechanisms. One of these, which requires external hydrogen, is called the *metal hydride addition–elimination mechanism*:



[62] Rabinovich, E.A.; Astaf'ev, I.V.; Shatenshtein, A.I. *J. Gen. Chem. USSR* ***1962***, *32*, 746.
[63] Hünig, S.; Klaunzer, N.; Schlund, R. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1281.
[64] See Cram, D.J.; Uyeda, R.T. *J. Am. Chem. Soc.* ***1964***, *86*, 5466; Ohlsson, L.; Wold, S.; Bergson, G. *Ark. Kemi.,* ***1968***, *29*, 351.
[65] Hussénius, A.; Matsson, O.; Bergson, G. *J. Chem. Soc., Perkin Trans. 2* ***1989***, 851.
[66] See Cameron G.S.; Stimson, V.R. *Aust. J. Chem.* ***1977***, *30*, 923.
[67] Schönberg, A. *Preparative Organic Photochemistry*, Springer, NY, ***1968***, pp. 22–24.
[68] See Rodriguez, J.; Brun, P.; Waegell, B. *Bull. Soc. Chim. Fr.* ***1989***, 799–823; Otsuka, S.; Tani, K. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, pp. 171–191 (enantioselective); Colquhoun, H.M.; Holton, J.; Thompson, D.J.; Twigg, M.V. *New Pathways for Organic Synthesis*, Plenum, NY, ***1984***, pp. 173–193; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Academic Press, NY, ***1974***, pp. 9–37; Heck, R.F. *Organotransition Metal Chemistry*, Academic Press, NY, ***1974***, pp. 76–82; Jira, R.; Freiesleben, W. *Organomet. React.* ***1972***, *3*, 1 (pp. 133–149).

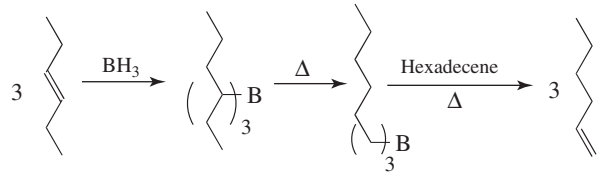
The other mechanism, called the π-*allyl complex mechanism*, does not require external hydrogen and proceeds by hydrogen abstraction to form the η^3-π-allyl complex **13** (Sec. 3.C.i, category 1, and **10-60**).



13

Another difference between the two mechanisms is that the former involves 1,2 shifts and the latter 1,3 shifts. The Rh-catalyzed isomerization of but-1-ene is an example of a reaction that takes place by the metal hydride mechanism,[69] while an example of the π-allyl complex mechanism is found in the $Fe_3(CO)_{12}$-catalyzed isomerization of 3-ethylpent-1-ene.[70] The reaction of an en-yne with $HSiCl_3$ and a Pd catalyst generated an allene with moderate enantioselectivity (Sec. 4.C, category 5 for chiral allenes).[71]

No matter which of the electrophilic methods of double bond shifting is employed, the thermodynamically most stable alkene is usually formed in the largest amount, although a few anomalies are known. Since the migration reaction is always toward the end of a chain (see **14**),



14

terminal alkenes can be produced from internal ones. The rearranged borane can be converted directly to the terminal alkene by heating with an alkene of molecular weight higher than that of the product (**17-13**). Photochemical isomerization can also lead to the thermodynamically less stable isomer.[72]

Triple bonds can also migrate in the presence of bases,[73] but through an allene intermediate:[74]

$$R{-}CH_2{-}C{\equiv}CH \rightleftharpoons R{-}CH{=}C{=}CH_2 \rightleftharpoons R{-}C{\equiv}C{-}CH_3$$

In general, strong bases, for example, $NaNH_2$, convert internal alkynes to terminal alkynes. A particularly good base for this purpose is potassium 3-aminopropylamide $NH_2CH_2CH_2CH_2NHK$[75], because the equilibrium is shifted by formation of the acetylide

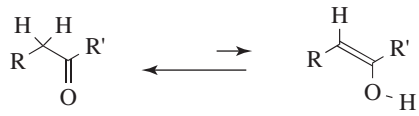
[69] Cramer, R. *J. Am. Chem. Soc.* ***1966***, *88*, 2272.
[70] Casey, C.P.; Cyr, C.R. *J. Am. Chem. Soc.* ***1973***, *95*, 2248.
[71] Han, J.W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* ***2001***, *123*, 12915.
[72] See Duhaime, R.M.; Lombardo, D.A.; Skinner, I.A.; Weedon, A.C. *J. Org. Chem.* ***1985***, *50*, 873.
[73] See Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 124–204; Théron F.; Verny, M.; Vessière, R. in Patai, S. *The Chemistry of Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 381–445; Bushby, R.J. *Q. Rev. Chem. Soc.* ***1970***, *24*, 585; Iwai, I. *Mech. Mol. Migr.* ***1969***, *2*, 73.
[74] See Huntsman, W.D. in Patai, S. *The Chemistry of Ketenes, Allenes, and Related Compounds*, pt. 2, Wiley, NY, ***1980***, pp. 521–667.
[75] Abrams, S.R. *Can. J. Chem.* ***1984***, *62*, 1333.

ion. With weaker bases, such as NaOH (which are not strong enough to remove the acetylenic proton), the internal alkynes are favored because of their greater thermodynamic stability. In some cases the reaction can be stopped at the allene stage.[76] The reaction then becomes a method for the preparation of allenes.[77] Long-chain terminal alkynes that have a distal methyl group, an isobranch, were shown to isomerize to the internal alkyne faster than similar straight-chain terminal alkynes.[78]

The reaction of propargylic alcohols with tosylhydrazine, PPh_3, and DEAD also generates allenes.[79] Acid-catalyzed migration of triple bonds (with allene intermediates) can be accomplished if very strong acids (e.g., HF/PF_5) are used.[80] If the mechanism is the same as that for double bonds, vinyl cations are intermediates.

OS **II**, 140; **III**, 207; **IV**, 189, 192, 195, 234, 398, 683; **VI**, 68, 87, 815, 925; **VII**, 249; **VIII**, 146, 196, 251, 396, 553; **X**, 156, 165; **81**, 147.

12-3 Keto-Enol Tautomerization



The tautomeric equilibrium between enols and ketones or aldehydes (keto-enol tautomerism) is a form of prototropy.[81] For some ketones, both forms can be prepared (Sec. 2.N.i, category 3 for a discussion of this and other types of tautomerism). Keto-enol tautomerism occurs in systems containing one or more carbonyl groups linked to sp^3 carbon atoms bearing one or more hydrogen atoms. *The keto tautomer is generally more stable than the enol tautomer for neutral systems*, and for most ketones and aldehydes only the keto form is detectable under ordinary conditions. The availability of additional intramolecular stabilization through hydrogen bonding or complete electron delocalization (as in phenol), may cause the enol tautomer to be favored.

Keto-enol tautomerism is usually a slow process, but it can be catalyzed by a trace of acid or base.[82] In this equilibrium, the heteroatom is the basic site in the reaction with an acid whereas the proton is the acidic site in the presence of a suitable base. For tautomerism in general (Sec. 2.N.i),[83] the presence of an acid or a base is not necessary to initiate the isomerization since each tautomeric substance possesses amphiprotic properties.[83] Polar protic solvents such as water or alcohol may participate in the proton transfer by forming a cyclic

[76] See Oku, M.; Arai, S.; Katayama, K.; Shioiri, T. *Synlett* ***2000***, 493.

[77] See Cunico, R.F.; Zaporowski, L.F.; Rogers, M. *J. Org. Chem.* ***1999***, *64*, 9307.

[78] Mohammad, I.; Mun, J.-Y.; Onorato, A.; Morton, M.D.; Saleh, A.I.; Smith, M.B. *Tetrahedron. Lett.* ***2017***, *58*, 4162.

[79] Myers, A.G.; Zheng, B. *J. Am. Chem. Soc.* ***1996***, *118*, 4492. See Moghaddam, F.M.; Emami, R. *Synth. Commun.* ***1997***, *27*, 4073 for the formation of alkoxy allenes from propargyl ethers.

[80] Barry, B.J.; Beale, W.J.; Carr, M.D.; Hei, S.; Reid, I. *J. Chem. Soc., Chem. Commun.* ***1973***, 177.

[81] Patai, S. *The Chemistry of the Carbonyl Group*, Wiley, London, ***1966***; Rappoport, Z. *The Chemistry of Enols,* Wiley, NY, ***1990***; Rappoport, Z.; Frey, J.; Sigalov, M.; Rochlin, E. *Pure Appl. Chem.* ***1997***, *69*, 1933; Iglesias, E. *Curr. Org. Chem.* ***2004***, *8*, 1.

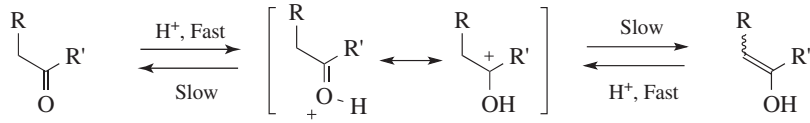
[82] See Kresge, A.J.; Santaballa, J.A.; Wirz, J. *J. Am. Chem. Soc.* ***1988***, *110*, 5506.

[83] See Raczynska, E.D.; Kosinska, W.; Osmialowski, B.; Gawinecki, R. *Chem. Rev.* ***2005***, *105*, 3561 for a general discussion of tautomerism. Also see Rappoport, Z. *The Chemistry of Enols,* Wiley, NY, ***1990***; Patai, S. *The Chemistry of Amino, Nitroso, Nitro and Related Groups, Supplement F2*, Wiley, Chichester, ***1996***; Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1998***.

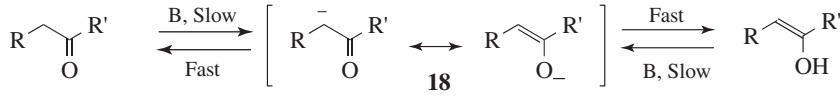
or a linear complex with the tautomers.[84] Whether the complex formed is cyclic or linear depends on the conformation and configuration of the tautomers. In a strongly polar aprotic solvent and in the presence of an acid or a base, the tautomeric molecule may lose or gain a proton and form the corresponding mesomeric anion or cation, which, in turn, may gain or lose a proton, respectively, and yield a new tautomeric form.[85] The structural features of the carbonyl compound influences the equilibrium.[86] Differing conjugative stabilization by CH–π orbital overlap does not directly influence stereoselectivity, and steric effects are generally not large enough to cause the several kcal mol^{-1} energy difference seen between transition structures unless there is exceptional crowding.[87] It is noted that sterically stabilized enols are known,[88] including arylacetaldehydes.[89] Torsional strain involving vicinal bonds does contribute significantly to stereoselectivity in enolate formation.[88]

The acid- and base-catalyzed mechanisms are identical to those in **12-2**.[90]

- Acid catalyzed



- Base catalyzed[91]



For each catalyst, the mechanism for one direction is the exact reverse of the other, by the principle of *microscopic reversibility*.[92] As expected from mechanisms in which the C—H bond is broken in the rate-determining step, substrates of the type RCD_2COR show deuterium isotope effects (of ~5) in both the basic[93] and the acid-catalyzed[94] processes. The keto-enol/enolate anion equilibrium has been studied in terms of the influence

[84] See Guo, J.X.; Ho, J.J. *J. Phys. Chem. A* ***1999***, *103*, 6433.
[85] See Baddar, F.G.; Iskander, Z. *J. Chem. Soc.* ***1954***, 203.
[86] Hegarty, A.F.; Dowling, J.P.; Eustace, S.J.; McGarraghy, M. *J. Am. Chem. Soc.* ***1998***, *120*, 2290.
[87] Behnam, S.M.; Behnam, S.E.; Ando, K.; Green, N.S.; Houk, K.N. *J. Org. Chem.* ***2000***, *65*, 8970.
[88] Miller, A.R. *J. Org. Chem.* ***1976***, *41*, 3599.
[89] Fuson, R.C.; Tan, T.-L. *J. Am. Chem. Soc.* ***1948***, *70*, 602.
[90] See Keeffe, J.R.; Kresge, A.J. in Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***, pp. 399–480. Also see Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell Univ. Press, Ithaca, NY, ***1973***, pp. 171–181; Shelly, K.P.; Venimadhavan, S.; Nagarajan, K.; Stewart, R. *Can. J. Chem.* ***1989***, *67*, 1274. Also see Pollack, R.M. *Tetrahedron* ***1989***, *45*, 4913.
[91] Another mechanism for base-catalyzed enolization has been reported when the base is a tertiary amine: see Bruice, P.Y. *J. Am. Chem. Soc.* ***1990***, *112*, 7361 and references cited therein.
[92] For a proposed concerrted mechanism, see Capon, B.; Siddhanta, A.K.; Zucco, C. *J. Org. Chem.* ***1985***, *50*, 3580. For evidence against it, see Chiang, Y.; Hojatti, M.; Keeffe, J.R.; Kresge, A.J.; Schepp, N.P.; Wirz, J. ***1987***, *109*, 4000 and references cited therein.
[93] Xie, L.; Saunders Jr., W.H. *J. Am. Chem. Soc.* ***1991***, *113*, 3123.
[94] Lienhard, G.E.; Wang, T. *J. Am. Chem. Soc.* ***1969***, *91*, 1146. See also, Toullec, J.; Dubois, J.E. *J. Am. Chem. Soc.* ***1974***, *96*, 3524.

of β-oxygen[95] or β-nitrogen[96] substituents. The stereochemistry of enol protonation can be controlled by varying the proximal group and by changing the acidity of the medium.[97]

The base-induced reaction generates an enolate anion rather than an enol, and the formation of and reactions of enolate anions are discussed further in **10-60**, **10-67**, **16-22**, and **16-34**. It should be noted that ring strain plays no significant role on the rate of base-catalyzed enolization.[98] In certain cases such as benzofuranones, base-induced enolate anion formation may give a transition state in which aromaticity can play a role. One study showed that aromatic stabilization of the transition state is ahead of proton transfer, and aromaticity appears to lower the intrinsic barrier to this reaction.[99] Enolizable hydrogen atoms can be replaced by deuterium (and ^{16}O by ^{18}O) by passage of a sample through a deuterated (or ^{18}O-containing) gas chromatography column.[100]

Although the conversion of an aldehyde or a ketone to its enol tautomer is not generally a preparative procedure for most relatively simple aldehydes or ketones, the reactions do have their preparative aspects. When enol ethers or esters are hydrolyzed, the initially formed enols immediately tautomerize to the aldehydes or ketones. In addition, the overall processes (forward plus reverse reactions) are often used for equilibration purposes. When an optically active compound in which the chirality is due to a stereogenic carbon α to a carbonyl group, as in 2-methylpentan-2-one, is treated with acid or base, racemization results.[101] If there is another stereogenic center in the molecule, the less stable diastereomer can be converted to the more stable one in this manner. For example, *cis*-decalone can be equilibrated to the *trans* isomer. Isotopic exchange can similarly be accomplished at the α position of an aldehyde or ketone. In cyclic compounds such as *cis*- or *trans*-decalone, *cis* to *trans* isomerization can occur via the enol.[102] The role of additives, such as $ZnCl_2$, on the stereogenic enolization reactions using chiral cases has been discussed.[103]

If a full equivalent of base per equivalent of ketone is used, the enolate ion is formed and can be isolated[104] (see, e.g., the alkylation reaction in **10-68**).[105] Enantioselective enolate anion protonation reactions have been studied.[106] Enolate protonation is discussed in reaction **16-34**. For the acid-catalyzed process, exchange or equilibration is accomplished only if the carbonyl compound is completely converted to the enol and then back. However, in the base-catalyzed process exchange or equilibration can take place if only the first step (conversion to the enolate ion) takes place. The difference is usually academic. Aggregation behavior of stereoselective enolizations mediated by Mg and calcium bis(amides) have been studied.[107] It is noted that chiral magnesium amides have been developed.[108]

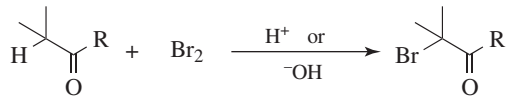
[95] Chiang, Y.; Kresge, A.J.; Meng, Q.; More O'Ferrall, R.A.; Zhu, Y. *J. Am. Chem. Soc.* ***2001***, *123*, 11562.
[96] Chiang, Y.; Griesbeck, A.G.; Heckroth, H.; Hellrung, B.; Kresge, A.J.; Meng, Q.; O'Donoghue, A.C.; Richard, J.P.; Wirz, J. *J. Am. Chem. Soc.* ***2001***, *123*, 8979.
[97] Zimmerman, H.E.; Cheng, J. *J. Org. Chem.* ***2006***, *71*, 873.
[98] Cantlin, R.J.; Drake, J.; Nagorski, R.W. *Org. Lett.* ***2002***, *4*, 2433.
[99] Bernasconi, C.F.; Pérez-Lorenzo, M. *J. Am. Chem. Soc.* ***2007***, *129*, 2704.
[100] See Richter, W.J.; Senn, M.; Burlingame, A.L. *Tetrahedron Lett.* ***1965***, 1235.
[101] For an exception, see Guthrie, R.D.; Nicolas, E.C. *J. Am. Chem. Soc.* ***1981***, *103*, 4637.
[102] Dechoux, L.; Doris, E. *Tetrahedron Lett.* ***1994***, *35*, 2017.
[103] Coggins, P.; Gaur, S.; Simpkins, N.S. *Tetrahedron Lett.* ***1995***, *36*, 1545.
[104] See Wen, J.Q.; Grutzner, J.B. *J. Org. Chem.* ***1986***, *51*, 4220.
[105] See d'Angelo, J. *Tetrahedron* ***1976***, *32*, 2979. Also see Fruchart, J.-S.; Lippens, G.; Kuhn, C.; Gran-Masse, H.; Melnyk, O. *J. Org. Chem.* ***2002***, *67*, 526.
[106] Vedejs, E.; Kruger, A.W.; Suna, E. *J. Org. Chem.* ***1999***, *64*, 7863.
[107] He, X.; Allan, J.F.; Noll, B.C.; Kennedy, A.R.; Henderson, K.W. *J. Am. Chem. Soc.* ***2005***, *127*, 6920.
[108] Kerr, W.J.; Middleditch, M.; Watson, A.J.B. *Synlett* ***2011***, *22*, 177.

In the case of 2,6-dimethylcyclohexanone, a racemic mixture was converted to an optically active mixture (optical yield 46%) by treatment with the chiral lithium dialkylamide.[109] The chiral base reacted with one enantiomer of the racemic ketone faster than with the other (an example of *kinetic resolution*) to give the enolate anion as the conjugate base and the amine as the conjugate acid. It is presumed that the enolate anion remained coordinated with the chiral amine, and it is the amine (rather than an added proton source) that re-protonates the enolate anion to give the optically active 2,6-dimethylcyclohexanone.

B. Halogen Electrophiles

Halogenation of unactivated hydrocarbons is discussed in **14-1**.

12-4 Halogenation of Aldehydes and Ketones



Aldehydes and ketones can be halogenated in the α position with bromine,[110] chlorine, or iodine,[111] although the reaction is less successful with fluorine.[112] Sulfuryl chloride,[113] Me_3SiCl-Me_2SO,[114] and *N*-chlorosuccinimide (NCS)[115] have been used as reagents for chlorination. α-Chloro aldehydes are formed with Cl_2 and a catalytic amount of tetraethylammonium chloride.[116] Bromination methods include reaction with *N*-bromosuccinimide (see **14-3**),[117] or bromine•dioxane on silica with microwave irradiation.[118] α-Chlorination[119] and also bromination[120] have been reported in ionic liquids. Enantioselective chlorination[121] and bromination[122] methods are known, including

[109] Eleveld, M.B.; Hogeveen, H. *Tetrahedron Lett.* ***1986***, *27*, 631. See also, Cain, C.M.; Cousins, R.P.C.; Coumbarides, G.; Simpkins, N.S. *Tetrahedron* ***1990***, *46*, 523.

[110] Vekariya, R.H.; Patel, H.D. *Tetrahedron* ***2014***, *70*, 3949.

[111] See De Kimpe, N.; Verhé, R. *The Chemistry of* α-*Haloketones,* α-*Haloaldehydes, and* α-*Haloimines*, Wiley, NY, ***1988***. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley-VCH, NY, ***1999***, pp.709–719. For the use of hypervalent iodine as an electrophile for the α-functionalization of carbonyl compounds, see Dong, D.-Q.; Hao, S.-H.; Wang, Z.-L.; Chen, C. *Org. Biomol. Chem.* ***2014***, *12*, 4278–4289.

[112] See Rozen, S.; Filler, R. *Tetrahedron* ***1985***, *41*, 1111; German, L.; Zemskov, S. *New Fluorinating Agents in Organic Chemistry*; Springer, NY, ***1989***.

[113] Tabushi, I.; Kitaguchi, H. in Pizey, J.S. *Synthetic Reagents*, Vol. 4; Wiley, NY, ***1981***, pp. 336–396.

[114] Fraser, R.R.; Kong, F. *Synth. Commun.* ***1988***, *18*, 1071.

[115] See Mei, Y.; Bentley, P.A.; Du, J. *Tetrahedron Lett.* ***2008***, *49*, 3802. Also see Pravst, I.; Zupan, M.; Stavber, S. *Tetrahedron* ***2008***, *64*, 5191.

[116] Bellesia, F.; DeBuyck, L.; Ghelfi, F.; Pagnoni, U.M.; Parson, A.F.; Pinetti, A. *Synthesis* ***2003***, 2173.

[117] Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Chem. Commun.* ***2004***, 470. See Arbuj, S.S.; Waghmode, S.B.; Ramaswamy, A.V. *Tetrahedron Lett.* ***2007***, *48*, 1411. See also Sreedhar, B.; Reddy, P.S.; Madhavi, M. *Synth. Commun.* ***2007***, *37*, 4149.

[118] Paul, S.; Gupta, V.; Gupta, R.; Loupy, A. *Tetrahedron Lett.* ***2003***, *44*, 439.

[119] Lee, J.C.; Park, H.J. *Synth. Commun.* ***2006***, *36*, 777.

[120] Pingali, S.R.K.; Madhav, M.; Jursic, B.S. *Tetrahedron Lett.* ***2010***, *51*, 1383.

[121] Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jorgensen, K.A. *J. Am. Chem. Soc.* ***2004***, *126*, 4790. See Wang, L.; Cai, C.; Curran, D.P.; Zhang, W. *Synlett* ***2010***, 433.

[122] See Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K.A. *Chem. Commun.* ***2005***, 4821.

methods that use enolate anions as intermediates.[123] Organocatalyzed asymmetric α-halogenation methods are known that can be applied to the incorporation of virtually any halogen.[124] β-Keto esters and 1,3-diketones are α-brominated using bromodimethylsulfonium bromide.[125] 1,3-Diketones, β-keto esters, and malonates are chlorinated using sodium hypochlorite or brominated using sodium hypobromite.[126]

Iodination has been accomplished by the direct reaction of ketones with molecular iodine,[127] NCS/NaI,[128] or ICl/NaI/$FeCl_3$.[129] Methyl ketones react with *N*-iodosuccinimide (NIS) and tosic acid with microwave irradiation without solvent to give the α-iodo ketone.[130] An asymmetric iodination of aldehydes used NIS, with a catalytic amount of benzoic acid and a chiral biaryl amine.[131]

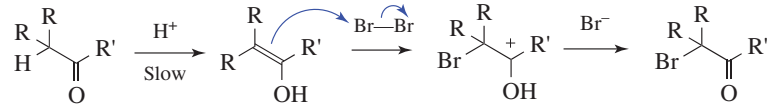
Although less prevalent than those noted above, several methods have been reported for the preparation of α-fluoro aldehydes and ketones,[132] including enantioselective fluorination protocols.[133] Organocatalytic α-fluorination is known for aldehydes and ketones.[134] Selectfluor [1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane *bis*(tetrafluoroborate)] has been used for the monofluorination of ketones.[135] Active compounds, such as β-keto esters and β-diketones, have been fluorinated with an *N*-fluoro-*N*-alkylsulfonamide[136] Note that this reaction can result in enantioselective fluorination, if an optically active *N*-fluorosulfonamide is used.[137] Aldehydes have been α-fluorinated using *N*-fluorobenzenesulfonimide as an electrophilic source of fluorine and an imidazolidinone as an organocatalyst.[138] The enantioselective α-fluorination of oxindoles has been reported using *N*-fluorobenzenesulfonimide, a Pd catalyst, and a chiral ligand,[139] and also with an organocatalyst.[140]

For unsymmetrical ketones, the preferred position of halogenation is usually the more substituted: a CH group, then a CH_2 group, and then CH_3;[141] however, mixtures are frequent. When basic catalysts are used, one α position of a ketone is completely halogenated before the other is attacked, and the reaction cannot be stopped until all the hydrogen atoms of the first carbon have been replaced (see below). If one of the groups is methyl, the

[123] See France, S.; Weatherwax, A.; Lectka, T. *Eur. J. Org. Chem.* ***2005***, 475.
[124] See Ueda, M.; Kano, T.; Maruoka, K. *Org. Biomol. Chem.* ***2009***, *7*, 2005.
[125] Khan, A.T.; Ali, Md.A.; Goswami, P.; Choudhury, L.H. *J. Org. Chem.* ***2006***, *71*, 8961.
[126] Meketa, M.L.; Mahajan, Y.R.; Weinreb, S.M. *Tetrahedron Lett.* ***2005***, *46*, 4749.
[127] Rao, M.L.N.; Jadhav, D.N. *Tetrahedron Lett.* ***2006***, *47*, 6883. Also see Yadav, J.S.; Kondaji, G.; Reddy, M.S.R.; Srihari, P. *Tetrahedron Lett.* ***2008***, *49*, 3810.
[128] Yamamoto, T.; Toyota, K.; Morita, N. *Tetrahedron Lett.* ***2010***, *51*, 1364.
[129] Mohanakrishnan, A.K.; Prakash, C.; Ramesh, N. *Tetrahedron* ***2006***, *62*, 3242.
[130] Lee, J.C.; Bae, Y.H. *Synlett* ***2003***, 507.
[131] Kano, T.; Ueda, M.; Maruoka, K. J. *Am. Chem. Soc.* ***2008***, *130*, 3728.
[132] Davis, F.A.; Kasu, P.V.N. *Org. Prep. Proceed. Int.* ***1999***, *31*, 125.
[133] See Pihko, P.M. *Angew. Chem. Int. Ed.* ***2006***, *45*, 544.
[134] Enders, D.; Hüttl, M.R.M. *Synlett* ***2005***, 991.
[135] See Loghmani-Khouzani, H.; Poorheravi, M.R.; Sadeghi, M.M.M.; Caggiano, L.; Jackson, R.F.W. *Tetrahedron* ***2008***, *64*, 7419.
[136] Barnette, W.E. *J. Am. Chem. Soc.* ***1984***, *106*, 452; For an example with asymmetric induction, see Cahard, D. *Tetrahedron: Asymmetry* ***2004***, *15*, 1007.
[137] Differding, E.; Lang, R.W. *Tetrahedron* ***1988***, *29*, 6087.
[138] Beeson, T.D.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2005***, *127*, 8826.
[139] Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* ***2005***, *127*, 10164.
[140] Steiner, D.D.; Mase, N.; Barbas III, C.F. *Angew. Chem. Int. Ed.* ***2005***, *44*, 3706.
[141] For chlorination, this is reversed if the solvent is methanol: Gallucci, R.R.; Going, R. *J. Org. Chem.* ***1981***, *46*, 2532.

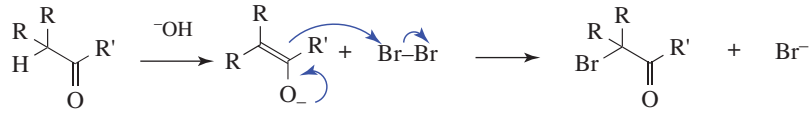
haloform reaction (**12-43**) can take place. With acid catalysts, it is usually possible to stop the reaction after only one halogen has been incorporated, although a second halogen can be introduced by the use of excess reagent. In chlorination the second halogen generally appears on the same side as the first,[142] while in bromination the α,α'-dibromo product is found.[143] Actually, with both halogens it is the α,α-dihalo ketone that is formed first, but in the case of bromination this compound isomerizes under the reaction conditions to the α,α' isomer.[142]

When chlorine, bromine, or iodine is used as the halogenating reagent, it is not the aldehyde or ketone itself that is halogenated, but the corresponding enol or enolate ion. The purpose of the catalyst is to provide a small amount of enol or enolate (**12-3**). The reaction is often done without addition of acid or base, but traces of acid or base are always present, and these are enough to catalyze formation of the enol or enolate. With acid catalysis the mechanism is enol formation, reaction with the halogen, and trapping the halide ion to give the product.



There is a great deal of evidence for this mechanism: (i) the rate is first order in substrate; (ii) bromine does not appear in the rate expression at all,[144] a fact consistent with a rate-determining first step;[145] (iii) the reaction rate is the same for bromination, chlorination, and iodination under the same conditions;[146] (iv) the reaction shows an isotope effect; and (v) the rate of the step 2–step 3 sequence has been independently measured (by starting with the enol) and found to be very fast.[147]

With basic catalysts the mechanism probably involves formation of the enolate ion without formation of the enol, and then reaction with the halogen gives the product.



It was mentioned above that in the base-catalyzed reaction, if the substrate has two or three α halogens on the same side of the C=O group, it is not possible to stop the reaction after just one halogen atom has entered. The reason is that the electron-withdrawing field effect of the first halogen increases the acidity of the remaining hydrogen atoms, that is, a CHX group is more acidic than a CH_2 group, so that the initially formed halo ketone is converted to enolate ion (and hence halogenated) more rapidly than the original substrate.

Regioselectivity in the halogenation of unsymmetrical ketones can be attained by treatment of the appropriate enol borinate of the ketone with *N*-bromo- or

[142] Rappe, C. *Ark. Kemi* ***1965***, *24*, 321. But see also, Teo, K.E.; Warnhoff, E.W. *J. Am. Chem. Soc.* ***1973***, *95*, 2728.
[143] Garbisch Jr., E.W. *J. Org. Chem.* ***1965***, *30*, 2109.
[144] See Tapuhi, E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1982***, *104*, 5758. Also see Pinkus, A.G.; Gopalan, R. *Tetrahedron* ***1986***, *42*, 3411.
[145] See, however, Deno, N.C.; Fishbein, R. *J. Am. Chem. Soc.* ***1973***, *95*, 7445.
[146] Bell, R.P.; Yates, K. *J. Chem. Soc.* ***1962***, 1927.
[147] Hochstrasser, R.; Kresge, A.J.; Schepp, N.P.; Wirz, J. *J. Am. Chem. Soc.* ***1988***, *110*, 7875.

N-chlorosuccinimide.[148] The desired halo ketone is formed in high yield. The appropriate lithium enolate anion can be brominated at a low temperature.[149] α-Halo aldehydes have been prepared in good yield by treatment of silyl enol ethers $R_2C{=}CHOSiMe_3$ with Br_2 or Cl_2,[150] or with sulfuryl chloride (SO_2Cl_2).[151] Enol acetates have been regioselectively iodinated with I_2 and either thallium(I) acetate[152] or copper(II) acetate.[153]

α,α′-Dichloro ketones are formed by reaction of a methyl ketone with an excess of $CuCl_2$ and LiCl in DMF[154] or with HCl and H_2O_2 in methanol.[155] Aryl methyl ketones can be dibrominated in high yields with benzyltrimethylammonium tribromide.[156] Active methylene compounds are chlorinated with NCS and $Mg(ClO_4)_2$.[157] Similar chlorination in the presence of a chiral Cu catalyst led to α-chlorination with modest enantioselectivity.[158]

Cyclohexanone and several other ketones were converted to the α-fluoro ketone by reaction with $(PhO_2S)_2NF$ and a Cinchona alkaloid catalyst, with good enantioselectivity.[159] Using continuous flow techniques (Sec. 7.D), the synthesis of α-halo ketones from *N*-protected amino acids has been described.[160] The formation of α-chloro aldehydes from aldehydes was reported using Cl_3CSO_2Cl, 2,6-luitdine, and a catalytic amount of chiral pyrrolidine derivative.[161] The reaction of a ketone with aqueous HBr/$NaNO_3$/KI in air gave the α-bromo ketone.[162] The α-monochlorination of ketones and 1,3-dicarbonyl compounds was reported using NH_4Cl and Oxone® as an oxidant in methanol.[163] Ketones were converted to α-iodo ketones via treatment with NH_4I and Oxone®,[164] and the identical reaction with NH_4Br gave the α-bromo ketone.[165] Acetophenone derivatives reacted with aqueous HBr in the presence of oxygen, with a Cu catalyst, and gave the α-bromo ketone.[166] The reaction of β-ketophosphates with Selectfluor gave α-mono- and α,α-difluoro-β-ketophosphonates.[167]

The reaction of NCS with β-keto esters and malonates with a Cu catalyst and with a chiral spirooxazoline ligand gave the enantioselective chlorinated product.[168] Reaction of a ketone with 55% aqueous HF and PhIO gave the 2-fluoro derivative.[169] The reaction of

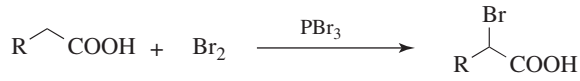
[148] Hooz, J.; Bridson, J.N. *Can. J. Chem.* ***1972***, *50*, 2387.
[149] Stotter, P.L.; Hill, K.A. *J. Org. Chem.* ***1973***, *38*, 2576.
[150] Blanco, L.; Amice, P.; Conia, J.M. *Synthesis* ***1976***, 194.
[151] Olah, G.A.; Ohannesian, L.; Arvanaghi, M.; Prakash, G.K.S. *J. Org. Chem.* ***1984***, *49*, 2032.
[152] Cambie, R.C.; Hayward, R.C.; Jurlina, J.L.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc., Perkin Trans. 1* ***1978***, 126.
[153] Horiuchi, C.A.; Satoh, J.Y. *Synthesis* ***1981***, 312.
[154] Nobrega, J.A.; Goncalves, S.M.C.; Reppe, C. *Synth. Commun.* ***2002***, *32*, 3711.
[155] Terent'ev, A.O.; Khodykin, S.V.; Troitskii, N.A.; Ogibin, Y.N.; Nikishin, G.I. *Synthesis* ***2004***, 2845.
[156] Kajigaeshi, S.; Kakinami, T.; Tokiyama, H.; Hirakawa, T.; Okamoto, T. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 2667.
[157] Yang, D.; Yan, Y.-L.; Lui, B. *J. Org. Chem.* ***2002***, *67*, 7429.
[158] Marigo, M.; Kumaragurubaran, N.; Jørgensen, K.A. *Chem. Eur. J.* ***2004***, *10*, 2133.
[159] Kwiatkowski, P.; Beeson, T.D.; Conrad, J.C.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2011***, *133*, 1738.
[160] Pinho, V.D.; Gutmann, B.; Miranda, L.S.M.; de Souza, R.O.M.A.; Kappe, C.O. *J. Org. Chem.* ***2014***, *79*, 1555.
[161] Jimeno, C.; Cao, L.; Renaud, P. *J. Org. Chem.* ***2016***, *81*, 1251.
[162] Ghorpade, A.K.; Huddar, S.N.; Akamanchi, K.G. *Tetrahedron Lett.* ***2016***, *57*, 4918.
[163] Swamy, P.; Kumar, M.A.; Reddy, M.M.; Narender, N. *Chem. Lett.* ***2012***, *41*, 432.
[164] Marri, M.R.; Macharla, A.K.; Peraka, S.; Nama, N. *Tetrahedron Lett.* ***2011***, *52*, 6554.
[165] Macharla, A.K.; Nappunni, R.C.; Marri, M.R.; Peraka, S.; Nama, N. *Tetrahedron Lett.* ***2012***, *53*, 191.
[166] Wang, J.; Wang, X.; Niu, Z.-Q.; Wang, J.; Zhang, M.; Li, J.-H. *Synth. Commun.* ***2016***, *46*, 165.
[167] Radwan-Olszewska, K.; Palacios, F.; Kafarski, P. *J. Org. Chem.* ***2011***, *76*, 1170.
[168] Shibatomi, K.; Soga, Y.; Narayama, A.; Fujisawa, I.; Iwasa, S. *J. Am. Chem. Soc.* ***2012***, *134*, 9836; Narayama, A.; Shibatomi, K.; Soga, Y.; Muto, T.; Iwasa, S. *Synlett* ***2013***, *24*, 375.
[169] Kitamura, T.; Kuriki, S.; Muta, K.; Morshed, M.H.; Muta, K.; Gondo, K.; Hori, Y.; Miyazaki, M. *Synthesis* ***2013***, *45*, 3125.

a ketone trityl hydrazone with *t*-BuOCl gave a diazene, which readily collapsed to the α-chlorocarbinyl radical and subsequent reduction with EtSH gave the alkyl chloride product, and the use of NBS gave the alkyl bromide.[170]

α,β-Unsaturated ketones can be converted to α-halo-α,β-unsaturated ketones by treatment with phenylselenium bromide or chloride,[171] and can be converted to α-halo-β,γ-unsaturated ketones by two-phase treatment with HOCl.[172] Conjugated ketones were converted to the α-bromo conjugated ketone (a vinyl bromide) using the *Dess-Martin periodinane* (see **19-3**, category 5) and tetraethylammonium bromide.[173]

OS **I**, 127; **II**, 87, 88, 244, 480; **III**, 188, 343, 538; **IV**, 110, 162, 590; **V**, 514; **VI**, 175, 193, 368, 401, 512, 520, 711, 991; **VII**, 271; **VIII**, 286. See also, OS **VI**, 1033; **VIII**, 192.

12-5 Halogenation of Carboxylic Acids and Acyl Halides



The α-hydrogen atoms of carboxylic acids are replaced by bromine or chlorine using a phosphorus halide as catalyst.[174] The reaction, known as the *Hell-Volhard-Zelinskii reaction*, is not applicable to iodine or fluorine. When there are two α-hydrogen atoms, one or both may be replaced, although it is often hard to stop with just one. The reaction actually takes place on the acyl halide formed initially from the carboxylic acid and the halogenating reagent. This means that each molecule of acid is α-halogenated while it is in the acyl halide stage. Carboxylic acids with relatively high enol content, such as malonic acid, are the most reactive. Less than one full molar equivalent of catalyst (per molar equivalent of substrate) is required, because of the exchange reaction between carboxylic acids and acyl halides (see **16-78**). The halogen from the catalyst is *not* transferred to the α position. For example, the use of Cl_2 and PBr_3 results in α-chlorination, not bromination. Acyl halides undergo α halogenation without a catalyst. An enantioselective α-halogenation was reported to give chiral α-halo esters via an alkaloid-catalyzed reaction of acyl halides with perhaloquinone-derived reagents.[175] The mechanism is usually regarded as proceeding through the enol, as in **12-4**.[176] If chlorosulfuric acid $ClSO_2OH$ is used as a catalyst, carboxylic acids can be α-iodinated,[177] as well as chlorinated or brominated.[178] *N*-Bromosuccinimide in a mixture of sulfuric acid/trifluoroacetic acid can mono-brominate simple carboxylic acids.[179]

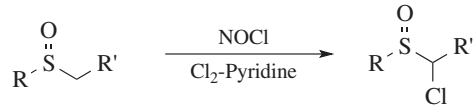
A number of other methods exist for the α-halogenation of carboxylic acids or their derivatives.[180] Under electrolytic conditions with NaCl, malonates are converted to 2-chloro

[170] Reyes, J.R.; Rawal, V.H. *Angew. Chem. Int. Ed.* ***2016***, *55*, 3077.
[171] Ley, S.V.; Whittle, A.J. *Tetrahedron Lett.* ***1981***, *22*, 3301.
[172] Hegde, S.G.; Wolinsky, J. *Tetrahedron Lett.* ***1981***, *22*, 5019.
[173] Fache, F.; Piva, O. *Synlett* ***2002***, 2035.
[174] See Harwood, H.J. *Chem. Rev.* ***1962***, *62*, 99 (pp. 102–103).
[175] Wack, H.; Taggi, A.E.; Hafez, A.M.; Drury III, W.J.; Lectka, T. *J. Am. Chem. Soc.* ***2001***, *123*, 1531. See also, France, S.; Wack, H.; Taggi, A.E.; Hafez, A.M.; Wagerle, Ty.R.; Shah, M.H.; Dusich, C.L.; Lectka, T. *J. Am. Chem. Soc.* ***2004***, *126*, 4245.
[176] See, however, Kwart, H.; Scalzi, F.V. *J. Am. Chem. Soc.* ***1964***, *86*, 5496.
[177] Ogata, Y.; Watanabe, S. *J. Org. Chem.* ***1979***, *44*, 2768; ***1980***, *45*, 2831.
[178] Ogata, Y.; Adachi, K. *J. Org. Chem.* ***1982***, *47*, 1182.
[179] Zhang, L.H.; Duan, J.; Xu, Y.; Dolbier Jr., W.R. *Tetrahedron Lett.* ***1998***, *39*, 9621.
[180] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley-VCH, NY, ***1999***, pp. 730–738.

malonates.[181] Acyl halides can be a brominated or chlorinated by use of *N*-bromo- or *N*-chlorosuccinimide and HBr or HCl.[182] The latter is an ionic, not a free-radical, halogenation (see **14-3**). Direct iodination of carboxylic acids has been achieved with I_2/Cu(II) acetate in HOAc.[183] Carboxylic acids, esters, and amides have been α-fluorinated at −78 °C with F_2 diluted in N_2.[184] Amides have been α-iodinated using iodine and s-collidine.[185] The synthesis of α,α-difluoro esters has been reported, catalyzed by *N*-heterocyclic carbenes.[186]

OS **I**, 115, 245; **II**, 74, 93; **III**, 347, 381, 495, 523, 623, 705, 848; **IV**, 254, 348, 398, 608, 616; **V**, 255; **VI**, 90, 190, 403; **IX**, 526. Also see, OS **IV**, 877; **VI**, 427.

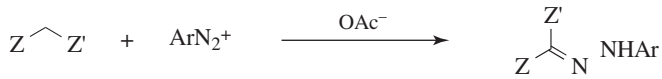
12-6 Halogenation of Sulfoxides and Sulfones



Sulfoxides can be chlorinated in the α position[187] by treatment with Cl_2[188] or *N*-chlorosuccinimide,[189] in the presence of pyridine. These methods involve basic conditions. The reaction can also be accomplished in the absence of base with SO_2Cl_2 in CH_2Cl_2,[190] or with $TsNCl_2$.[191] The bromination reactions of sulfoxides with bromine[192] and with NBS/bromine[193] have also been reported. The α-fluorination of sulfoxides was reported via treatment with diethylaminosulfur trifluoride, Et_2NSF_3 (DAST), to give an α-fluoro thioether, usually in high yield. Oxidation of this compound with *m*-chloroperoxybenzoic acid gave the sulfoxide.[194]

C. Nitrogen Electrophiles

12-7 Aliphatic Diazonium Coupling



If a C—H unit is acidic enough, that carbon couples with diazonium salts in the presence of a base (via the enolate anion), most often aqueous sodium acetate.[195] The reaction is usually

[181] Okimoto, M.; Takahashi, Y. *Synthesis* ***2002***, 2215.
[182] Harpp, D.N.; Bao, L.Q.; Black, C.J.; Gleason, J.G.; Smith, R.A. *J. Org. Chem.* ***1975***, *40*, 3420.
[183] Horiuchi, C.A.; Satoh, J.Y. *Chem. Lett.* ***1984***, 1509.
[184] Purrington, S.T.; Woodard, D.L. *J. Org. Chem.* ***1990***, *55*, 3423.
[185] Kitagawa, O.; Hanano, T.; Hirata, T.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* ***1992***, *33*, 1299.
[186] Dong, X.; Zhao, Y.-M.; Sun, J. *Synlett* ***2013***, *24*, 1221.
[187] For a review, see Venier, C.G.; Barager III, H.J. *Org. Prep. Proced. Int.* ***1974***, *6*, 77 (pp. 81–84).
[188] Tsuchihashi, G.; Iriuchijima, S. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 2271.
[189] Ogura, K.; Imaizumi, J.; Iida, H.; Tsuchihashi, G. *Chem. Lett.* ***1980***, 1587.
[190] Tin, K.; Durst, T. *Tetrahedron Lett.* ***1970***, 4643.
[191] Kim, Y.H.; Lim, S.C.; Kim, H.R.; Yoon, D.C. *Chem. Lett.* ***1990***, 79.
[192] Cinquini, M.; Colonna, S. *J. Chem. Soc., Perkin Trans. 1* ***1972***, 1883. See also, Cinquini, M.; Colonna, S. *Synthesis* ***1972***, 259.
[193] Iriuchijima, S.; Tsuchihashi, G. *Synthesis* ***1970***, 588.
[194] McCarthy, J.R.; Peet, N.P.; LeTourneau, M.E.; Inbasekaran, M. *J. Am. Chem. Soc.* ***1985***, *107*, 735. See also, Umemoto, T.; Tomizawa, G. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 3625.
[195] See Parmerter, S.M. *Org. React.* ***1959***, *10*, 1.

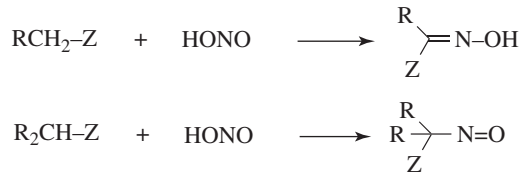
applied to compounds of the form Z—CH_2—Z′, where Z and Z′ are electron-withdrawing groups, as defined in reaction **16-38**; for example, β-keto esters, β-keto amides, malonic ester.

The mechanism is probably of the simple S_E1 type where the enolate anion reacts with the diazo compound to give the R_2CH—N=N—Ar, in which the carbon containing the azo group is attached to a hydrogen. This compound is unstable and tautomerizes to the isomeric hydrazone product, R_2C=N—NH—Ar.

When the reaction is carried out on a compound of the form Z—CHR—Z′, the azo compound does not have a hydrogen that can lead to tautomerism. If at least one Z is acyl or carboxyl, cleavage of the azo group leads to the hydrazone and not the azo compound. The overall process in this case is called the *Japp-Klingemann reaction*[196] and involves conversion of a ketone or a carboxylic acid to a hydrazone. When an acyl and a carboxyl group are both present, the leaving group order has been reported to be MeCO > COOH > PhCO.[197] When there is no acyl or carboxyl group present, the aliphatic azo compound is stable.

OS **III**, 660; **IV**, 633.

12-8 Nitrosation at a Carbon Bearing an Active Hydrogen



Carbons adjacent to a Z group (an electron-withdrawing group) can be nitrosated with nitrous acid or alkyl nitrites.[198] The initial product is the *C*-nitroso compound, but these are stable only when there is no hydrogen that can undergo tautomerism. When there is hydrogen that can undergo tautomerism, the product is the more stable oxime. The situation is analogous to that with azo compounds and hydrazones (**12-7**). The mechanism is similar to that in **12-7**:[199]

$$R{-}H \rightarrow R^- + {}^+N{=}O \rightarrow R{-}N{=}O$$

The reactive species is either NO^+ or a carrier of it. When the substrate is a simple ketone, the mechanism goes through the enol (as in halogenation **12-4**).

Evidence shows that the reaction, in the presence of X^- (Br^-, Cl^-, or SCN^-) is first order in ketone and in H^+, but zero order in HNO_2 and X^-.[200] Furthermore, the rate of the nitrosation was about the same as that for enolization of the same ketones. The species NOX is formed by

$$HONO + X^- + H^+ \rightarrow HOX + H_2O$$

[196] For a review, see Phillips, R.R. *Org. React.* ***1959***, *10*, 143.

[197] Neplyuev, V.M.; Bazarova, I.M.; Lozinskii, M.O. *J. Org. Chem. USSR* ***1989***, *25*, 2011. This paper also includes a sequence of leaving group ability for other Z groups.

[198] See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 1–45.

[199] For a review, see Williams, D.L.H. *Adv. Phys. Org. Chem.* ***1983***, *19*, 381. See also, Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***.

[200] Leis, J.R.; Peña, M.E.; Williams, D.L.H.; Mawson, S.D. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 157.

In the cases of $F_3CCOCH_2COCF_3$ and malononitrile the nitrosation went entirely through the enolate ion rather than the enol.[201]

As in the *Japp-Klingemann reaction*, when Z is an acyl or carboxyl group (in the case of $R_2CH{-}Z$), the azo group can be cleaved. Since oximes and nitroso compounds can be reduced to primary amines, this reaction often provides a route to amino acids. As in the case of **12-4**, the silyl enol ether of a ketone can be used instead of the ketone itself.[202]

Imines can be prepared in a similar manner, by treatment of an active hydrogen compound with a nitroso compound, $R'{-}NO$. Alkanes can be nitrosated photochemically, by treatment with NOCl and UV light.[203] For nitration at an activated carbon, see **12-9**.

OS **II**, 202, 204, 223, 363; **III**, 191, 513; **V**, 32, 373; **VI**, 199, 840. Also see, OS **V**, 650.

12-9 Nitration of Alkanes

$$RH + HNO_3 \xrightarrow{400\,^{\circ}C} RNO_2$$

Nitration of alkanes[204] can be carried out in the gas phase at ~400 °C or in the liquid phase. The reaction is not practical for the production of pure products for any alkane except methane. For other alkanes, not only does the reaction produce mixtures of the mono-, di-, and polynitrated alkanes at every combination of positions, but extensive chain cleavage occurs.[205] A free-radical mechanism is involved.[206]

Activated positions (e.g., ZCH_2Z' compounds) can be nitrated by fuming nitric acid in acetic acid, by acetyl nitrate and an acid catalyst,[207] or by alkyl nitrates ($RONO_2$) under alkaline conditions.[208] In the latter case, it is the carbanionic form of the substrate that is actually nitrated. The conjugate base of the nitro compound is isolated under these alkaline conditions, but yields are not high. Of course, the mechanism in this case is not of the free-radical type, but is electrophilic substitution with respect to the carbon (similar to the mechanisms of **12-7** and **12-8**). Positions activated by only one electron-withdrawing group, for example, α positions of simple ketones, nitriles, sulfones, or *N*,*N*-dialkyl amides, can be nitrated with alkyl nitrates if a very strong base, e.g., *t*-BuOK or $NaNH_2$, is present to convert the substrate to the carbanionic form.[209] The reaction of alkanes with nitric acid and *N*-hydroxysuccinimide (NHS), however, gave moderate to good yields of the corresponding nitroalkane.[210] Similar nitration was accomplished with NO_2, NHS, and air.[211]

OS **I**, 390; **II**, 440, 512.

[201] Iglesias, E.; Williams, D.L.H. *J. Chem. Soc., Perkin Trans. 2* ***1989***, 343; Crookes, M.J.; Roy, P.; Williams, D.L.H. *J. Chem. Soc., Perkin Trans. 2* ***1989***, 1015. See also, Graham, A.; Williams, D.L.H. *J. Chem. Soc., Chem. Commun.* ***1991***, 407.

[202] Rasmussen, J.K.; Hassner, A. *J. Org. Chem.* ***1974***, *39*, 2558.

[203] See Pape, M. *Fortschr. Chem. Forsch.* ***1967***, *7*, 559.

[204] See Olah, G.A.; Malhotra, R.; Narang, S.C. *Nitration: methods and mechanisms*, VCH, NY, ***1989***, pp. 219–295; Ogata, Y. in Trahanovsky, W.S. *Oxidation in Organic Chemisry*, part C, Academic Press, NY, ***1978***, pp. 295–342; Ballod, A.P.; Shtern, V.Ya. *Russ. Chem. Rev.* ***1976***, *45*, 721.

[205] See Matasa, C.; Hass, H.B. *Can. J. Chem.* ***1971***, *49*, 1284.

[206] Titov, A.I. *Tetrahedron* ***1963***, *19*, 557.

[207] Sifniades, S. *J. Org. Chem.* ***1975***, *40*, 3562.

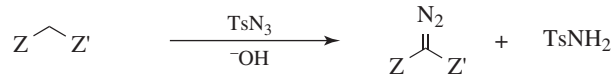
[208] See Larson, H.O. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Vol. 1, Wiley, NY, ***1969***, pp. 310–316.

[209] See Feuer, H.; Van Buren II, W.D.; Grutzner, J.B. *J. Org. Chem.* ***1978***, *43*, 4676.

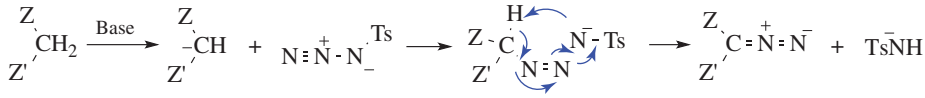
[210] Isozaki, S.; Nishiwaki, Y.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* ***2001***, 1352.

[211] Nishiwaki, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2002***, *67*, 5663.

12-10 Direct Formation of Diazo Compounds From Ketones, Aldehydes, and Active Methylene Compounds

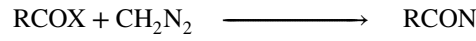


Active methylene compounds (two Z groups) can be converted to diazo compounds[212] upon treatment with tosyl azide in the presence of a base.[213] The use of phase-transfer catalysis increases the convenience of the method.[214] Sulfonyl azides also give the reaction.[215] The *diazo transfer reaction* can also be applied to other reactive positions, e.g., the 5 position of cyclopenta-1,3-diene.[216] The mechanism is probably as follows:



A diazo group can be introduced adjacent to a single carbonyl group indirectly by first converting the ketone to an α-formyl ketone (**16-81**) and then treating it with tosyl azide and the formyl group is cleaved during the reaction.[217] Hydrazones have been oxidized to diazo compounds using *N*-iodo *p*-toluenesulfonamide.[218] A phosphino ester was used to mediate the conversion of azides into diazo compounds in phosphate buffer at neutral pH and room temperature.[219]

OS **V**, 179; **VI**, 389, 414.



The reaction between acyl halides and diazomethane is of wide scope and is the best way to prepare diazo ketones.[220] Diazomethane must be present in excess or the HX produced will react with the diazo ketone (**10-51**). This reaction is the first step of the *Arndt-Eistert synthesis* (**18-8**). Diazo ketones can also be prepared directly from a carboxylic acid and diazomethane or diazoethane in the presence of DCC.[221]

OS **III**, 119; **VI**, 386, 613; **VIII**, 196.

[212] The valence isomerization between diazo compounds and diazrines has been discussed, see Korneev, S.M. *Eur. J. Org. Chem.* ***2011***, 6153.

[213] Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 326–435; Regitz, M. *Synthesis* ***1972***, 351. See also, Koskinen, A.M.P.; Muñoz, L. *J. Chem. Soc., Chem. Commun.* ***1990***, 652.

[214] Ledon, H. *Synthesis* ***1974***, 347, *Org. Synth.* ***VI***, 414; Also see Ghosh, S.; Datta, I. *Synth. Commun.* ***1991***, *21*, 191.

[215] Baum, J.S.; Shook, D.A.; Davies, H.M.L.; Smith, H.D. *Synth. Commun.* ***1987***, *17*, 1709.

[216] Doering, W. von E.; DePuy, C.H. *J. Am. Chem. Soc.* ***1953***, *75*, 5955.

[217] See also Danheiser, R.L.; Miller, R.F.; Brisbois, R.G.; Park, S.Z. *J. Org. Chem.* ***1990***, *55*, 1959.

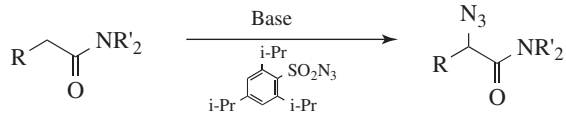
[218] Nicolle, S.M.; Moody, C.J. *Chem. Eur. J.* ***2014***, *20*, 4420.

[219] Chou, H.-H.; Raines, R.T. *J. Am. Chem. Soc.* ***2013***, *135*, 14936.

[220] See Fridman, A.L.; Ismagilova, G.S.; Zalesov, V.S.; Novikov, S.S. *Russ. Chem. Rev.* ***1972***, *41*, 371; Ried, W.; Mengler, H. *Fortschr. Chem. Forsch.* ***1965***, *5*, 1.

[221] Hodson, D.; Holt, G.; Wall, D.K. *J. Chem. Soc. C* ***1970***, 971.

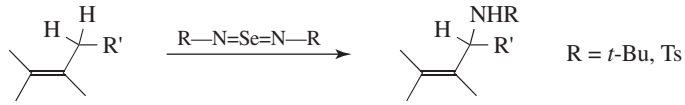
12-11 Conversion of Carboxylic Acid Derivatives to α-Azido Derivatives



In reaction **12-10**, treatment of Z—CH_2—Z′ with tosyl azide gave the α-diazo compound via diazo transfer. When this reaction is performed on a compound with a single Z group (such as an amide), formation of the azide becomes a competing process via the enolate anion.[222] Factors favoring azide formation rather than diazo transfer include K^+ as the enolate counterion rather than Na^+ or Li^+ and the use of 2,4,6-triisopropylbenzenesulfonyl azide rather than TsN_3.

The synthesis of α-diazo ketones was achieved by simply stirring the mixture of 1,3-diketone, TsN_3, and $MeNH_2$ in EtOH.[223] Using microflow reactor technology (Sec. 7.D) and the Bamford-Stevens reaction (**17-11**), *N*-arylsulfonyl hydrazones reacted with triethylamine to give the α-diazo ester, which was converted to an α-amino ester derivative or an α-alkoxy ester derivative.[224]

12-12 Direct Amination at an Activated Position

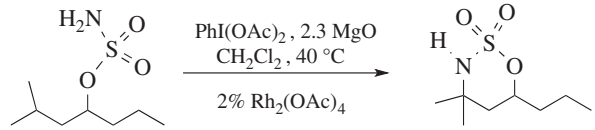


Allylic amination of alkenes[225] has been reported by treatment with solutions of imido selenium compounds, R—N=Se=N—R.[226] The reaction, which is similar to the allylic oxidation of alkenes with SeO_2 (see **19-14**), has been performed with R = *t*-Bu and R = Ts. The imido sulfur compound TsN=S=NTs has also been used.[227] Enantioselective allylic amination has been reported using organocatalysts.[228] A Rh-catalyzed amination of benzylic positions has also been reported.[229]

Tertiary alkyl hydrogen can be replaced in some cases via C—H nitrogen insertion. The reaction of sulfamate ester **15** with $PhI(OAc)_2$, MgO, and a dinuclear Rh carboxylate catalyst, for example, generated oxathiazinane **16**.[230] This transformation

[222] Evans, D.A.; Britton, T.C. *J. Am. Chem. Soc.* ***1987***, *109*, 6881, and references cited therein.
[223] Zhang, J.; Chen, W.; Huang, D.; Zeng, X.; Wang, X.; Hu, Y. *J. Org. Chem.* ***2017***, *82*, 9171.
[224] Bartrum, H.E.; Blakemore, D.C.; Moody, C.J.; Hayes, C.J. *Chem. Eur. J.* ***2011***, *17*, 9586. Also see Deadman, B.J.; Collins, S.G.; Maguire, A.R. *Chem. Eur. J.* ***2015***, *21*, 2298.
[225] See Sheradsky, T. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 395–416.
[226] See Kresze, G.; Münsterer, H. *J. Org. Chem.* ***1983***, *48*, 3561. For a review, see Cheikh, R.B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* ***1983***, 685 (pp. 691–696).
[227] Sharpless, K.B.; Hori, T. *J. Org. Chem.* ***1979***, *41*, 176. See Tsushima, S.; Yamada, Y.; Onami, T.; Oshima, K.; Chaney, M.O.; Jones, N.D.; Swartzendruber, J.K. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 1167.
[228] Poulsen, T.B.; Alemparte, C.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2005***, *127*, 11614.
[229] Fiori, J.W.; Du Bois, J. *J. Am. Chem. Soc.* ***2007***, *129*, 562.
[230] Espino, C.G.; Wehn, P.M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* ***2001***, *123*, 6935.

is a formal oxidation, and primary carbamates have been similarly converted to oxazolidin-2-ones.[231]

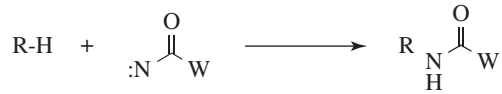


15 **16**

The asymmetric amination of α-substituted cyclic ketones by reaction with di-*tert*-butyl azodicarboxylate was catalyzed by a chiral phosphoric acid to give α-branched ketones, the *N*-containing quaternary stereocenter as a di-*tert*-butyl hydrazine-1,2-dicarboxylate derivative.[232] The enantioselective addition of anilines to azoalkenes using a chiral phosphoric acid catalyst gave α-arylamino hydrazones and subsequent hydrolysis gave enantioenriched α-arylamino ketones.[233] α-Hydroxy ketones reacted with aniline derivatives in the presence of $SnCl_2 \bullet 2H_2O$, solvent free at 80 °C or with microwave irradiation, to give the α-amino ketone.[234] The reaction of amides and simple azides in the presence of Tf_2O gave stereoselective α-amination of amides and formation of the α-amino amide.[235] The reaction of phosphates that have an α carbon with Zn(2,2,6,6-tetramethylpiperidinyl)$_2$ generated an organozinc compound *in situ*, which reacts with *O*-acylhydroxylamines and a Cu catalyst to give the corresponding α-aminophosphonate.[236]

See also **10-39**.

12-13 Insertion by Nitrenes



Nitrenes,[237] R—N, are the nitrogen analogs of carbenes, and most of the comments about carbenes also applies to them. Nitrenes are too reactive for isolation under ordinary conditions.[238] As stated in Sec. 5.E, one of the important reactions of nitrenes is insertion,

[231] Espino, C.G.; Du Bois, J. *Angew. Chem. Int. Ed.* ***2001***, *40*, 598.
[232] Yang, X.; Toste, F.D. *J. Am. Chem. Soc.* ***2015***, *137*, 3205.
[233] Miles, D.H.; Guasch, J.; Toste, F.D. *J. Am. Chem. Soc.* ***2015***, *137*, 7632.
[234] Tamaddon, F.; Dehghani Tafti, A. *Synlett* ***2016***, *27*, 2217.
[235] Tona, V.; de la Torre, A.; Padmanaban, M.; Ruider, S.; González, L.; Maulide, N. *J. Am. Chem. Soc.* ***2016***, *138*, 8348.
[236] McDonald, S.L.; Wang, Q. *Synlett* ***2014***, *25*, 2233.
[237] See Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, ***1984***; Lwowski, W. *React. Intermed. (Wiley)* ***1985***, *3*, 305; Kuznetsov, M.A.; Ioffe, B.V. *Russ. Chem. Rev.* ***1989***, *58*, 732 (*N*- and *O*-nitrenes); Meth-Cohn, O. *Acc. Chem. Res.* ***1987***, *20*, 18 (oxycarbonylnitrenes); Ioffe, B.V.; Kuznetsov, M.A. *Russ. Chem. Rev.* ***1972***, *41*, 131 (*N*-nitrenes). *Nitrenes and Nitrenium Ions. Wiley Series on Reactive Intermediates in Chemistry and Biochemistry, Volume 6.* Falvey, D.E.; Gudmundsdottir, A.D. (Ed.) John Wiley & Sons, Hoboken, ***2013***. For a review of nitrenoids, see Starkov, P.; Jamison, T.F.; Marek, I. *Chem. Eur. J.* ***2015***, *21*, 5278.
[238] McClelland, R.A. *Tetrahedron* ***1996***, *52*, 6823.

especially insertion into C—H bonds as well as some other bonds. A mechanism study of the chemoselectivity of metal-catalyzed N-atom transfer reactions of styryl azide has been reported.[239]

Carbonyl nitrenes, :NCOW (W = R′, Ar, or OR′), are very reactive species (Sec. 5.E) and insert into the C—H bonds of alkanes to give amides (W = R′ or Ar) or carbamates (W = OR′).[240] The nitrenes are generated as discussed in Sec. 5.E. The order of reactivity among alkane C—H bonds is tertiary > secondary > primary.[241] Nitrenes are much more selective (and less reactive) in this reaction than carbenes (**12-17**).[242] It is likely that only singlet and not triplet nitrenes insert.[243] Retention of configuration is found at a stereogenic carbon.[244] The mechanism is presumably similar to the simple one-step mechanism for insertion of carbenes (**12-21**).

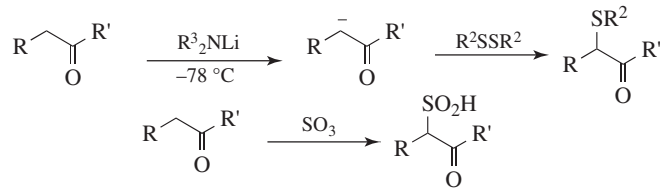
Other nitrenes [e.g., cyanonitrene (NCN)[245] and arylnitrenes (NAr)[246]] can also insert into C—H bonds, but alkylnitrenes usually undergo rearrangement before they can react with the alkane. The Au(III)-catalyzed insertion of nitrenes into aromatic and benzylic C—H groups has been reported.[247] *N*-Carbamoyl nitrenes undergo insertion reactions that often lead to mixtures of products, but exceptions are known,[248] chiefly in cyclizations.[249] Enantioselective nitrene insertion reactions are known.[250]

The reaction of an α-nitro-α-diazo ester with a urea catalyst led to insertion into the N—H bonds of anilines.[251] A myoglobin-catalyzed N—H insertion reaction of α-diazo esters with aryl amines gave the corresponding α-amino ester.[252] Aryl and aliphatic aldehydes were converted to the corresponding amides using an Fe catalyst and reaction with PhI=NTs.[253] Intermolecular N—H insertion of α-diazocarbonyl compounds into dibenzenesulfonimide gave the corresponding protected amino ester.[254] Heating aryl diazoacetates gave the corresponding carbene, and N—H insertion with primary and secondary amines, without a metal catalyst, gave α-amino esters.[255] The reactivity of a triplet vinylnitrene has been discussed.[256] The asymmetric reaction of α-diazo esters led to N—H insertion with anilines, catalyzed by Cu complexes of chiral spiro bisoxazoline ligands.[257]

[239] Kong, C.; Jana, N.; Jones, C.; Driver, T.G. *J. Am. Chem. Soc.* ***2016***, *138*, 13271.
[240] See Lwowski, W. in Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***, pp. 199–207.
[241] See Maslak, P. *J. Am. Chem. Soc.* ***1989***, *111*, 8201.
[242] See Alewood, P.F.; Kazmaier, P.M.; Rauk, A. *J. Am. Chem. Soc.* ***1973***, *95*, 5466.
[243] See Inagaki, M.; Shingaki, T.; Nagai, T. *Chem. Lett.* ***1981***, 1419.
[244] Smolinsky, G.; Feuer, B.I. *J. Am. Chem. Soc.* ***1964***, *86*, 3085.
[245] See Anastassiou, A.G.; Shepelavy, J.N.; Simmons, H.E.; Marsh, F.D. in Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***, pp. 305–344.
[246] See Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, ***1984***, pp. 95–204.
[247] Li, Z.; Capretto, D.A.; Rahaman, R.O.; He, C. *J. Am. Chem. Soc.* ***2007***, *129*, 12058.
[248] See also, Meinwald, J.; Aue, D.H. *Tetrahedron Lett.* ***1967***, 2317.
[249] For a list of examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 1148–1149.
[250] See Müller, P.; Fruit, C. *Chem. Rev.* ***2003***, *103*, 2905.
[251] So, S.S.; Mattson, A.E. *J. Am. Chem. Soc.* ***2012***, *134*, 8798.
[252] Sreenilayam, G.; Fasan, R. *Chem. Commun.* ***2015***, *51*, 1532.
[253] Chen, G.-Q.; Xu, Z.-J.; Liu, Y.; Zhou, C.-Y.; Che, C.-M. *Synlett* ***2011***, *22*, 1174.
[254] Luo, X.; Chen, G.; He, L.; Huang, X. *J. Org. Chem.* ***2016***, *81*, 2943.
[255] Hansen, S.R.; Spangler, J.E.; Hansen, J.H.; Davies, H.M.L. *Org. Lett.* ***2012***, *14*, 4626.
[256] Sarkar, S.S.; Osisioma, O.; Karney, W.L.; Abe, M.; Gudmundsdottir, A.D. *J. Am. Chem. Soc.* ***2016***, *138*, 14905.
[257] Zhu, S.-F.; Xu, B.; Wang, G.-P.; Zhou, Q.-L. *J. Am. Chem. Soc.* ***2012***, *134*, 436.

D. Sulfur Electrophiles

12-14 Sulfenylation, Sulfonation, and Selenylation of Ketones and Carboxylic Esters



Ketones, carboxylic esters (including lactones),[258] and amides (including lactams)[259] can be sulfenylated[260] in the α position by conversion to the enolate anion (Sec. 8.F, part 7) and subsequent treatment with a disulfide.[261] The reaction, shown above for ketones, involves nucleophilic substitution at sulfur. α-Phenylseleno ketones, RCH(SePh)COR′, and α-phenylseleno esters, RCH(SePh)COOR′, can be similarly prepared[262] by treatment of the corresponding enolate anions with PhSeBr,[263] PhSeSePh,[264] or benzeneseleninic anhydride, PhSe(O)OSe(O)Ph.[265] Another method for the introduction of a phenylseleno group into the α position of a ketone involves simple treatment of an ethyl acetate solution of the ketone with PhSeCl (but not PhSeBr) at room temperature.[266] This procedure is also successful for aldehydes but not for carboxylic esters. *N*-Phenylselenophthalimide has been used to convert ketones[267] and aldehydes[268] to the α-PhSe derivative.

The α-seleno and α-sulfenyl carbonyl compounds prepared by this reaction can be converted to α,β-unsaturated carbonyl compounds (**17-10**). The sulfenylation reaction has also been used[269] as a key step in a sequence for moving the position of a carbonyl group to an adjacent carbon.[270]

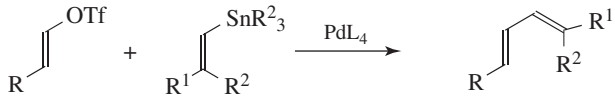
Aldehydes, ketones, and carboxylic acids containing α-hydrogen atoms can be sulfonated with sulfur trioxide.[271] The mechanism is presumably similar to that of **12-4**. Sulfonation has also been accomplished at vinylic hydrogen.

OS **VI**, 23, 109; **VIII**, 550. **IV**, 846, 862.

[258] See Trost, B.M. *Pure Appl. Chem.* ***1975***, *43*, 563, pp. 572–578; Caine, D. in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1, Marcel Dekker, NY, ***1979***, pp. 278–282.
[259] Gassman, P.G.; Balchunis, R.J. *J. Org. Chem.* ***1977***, *42*, 3236.
[260] See Sandrinelli, F.; Fontaine, G.; Perrio, S.; Beslin, P. *J. Org. Chem.* ***2004***, *69*, 6916.
[261] For another reagent, see Scholz, D. *Synthesis* ***1983***, 944.
[262] See Back, T.G. in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 1–125; Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon, Elmsford, NY, ***1986***, pp. 95–98.
[263] Brocksom, T.J.; Petragnani, N.; Rodrigues, R. *J. Org. Chem.* ***1974***, *39*, 2114. See also, Liotta, D. *Acc. Chem. Res.* ***1984***, *17*, 28.
[264] Grieco, P.A.; Miyashita, M. *J. Org. Chem.* ***1974***, *39*, 120. See Miyoshi, N.; Yamamoto, T.; Kambe, N.; Murai, S.; Sonoda, N. *Tetrahedron Lett.* ***1982***, *23*, 4813.
[265] Barton, D.H.R.; Morzycki, J.W.; Motherwell, W.B.; Ley, S.V. *J. Chem. Soc., Chem. Commun.* ***1981***, 1044.
[266] Sharpless, K.B.; Lauer, R.F.; Teranishi, A.Y. *J. Am. Chem. Soc.* ***1973***, *95*, 6137.
[267] Cossy, J.; Furet, N. *Tetrahedron Lett.* ***1993***, *34*, 7755.
[268] Wang, W.; Wang, K.; Li, H. *Org. Lett.* ***2004***, *6*, 2817.
[269] Trost, B.M.; Hiroi, K.; Kurozumi, S. *J. Am. Chem. Soc.* ***1975***, *97*, 438.
[270] See *OS* **VI**, 23, 109; ***68***, 8. See also Morris, D.G. *Chem. Soc. Rev.* ***1982***, *11*, 397; Kane, V.V.; Singh, V.; Martin, A.; Doyle, D.L. *Tetrahedron* ***1983***, *39*, 345.
[271] See Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 33–61.

E. Carbon Reagents

12-15 Coupling of Alkene to Alkene, Alkene to Alkyne (Stille Coupling)



Vinyl triflates (C═C—OSO_2CF_3) react with vinyl tin derivatives in the presence of a Pd catalyst to form dienes, in what is known as *Stille coupling*.[272] Phosphine or bis(phosphine) ligands are most commonly used with the Pd catalyst,[273] but other ligands have been used,[274] including triphenylarsine.[275] Vinyl triflates can be prepared from the enolate anion by reaction with *N*-phenyl triflimide.[276] Vinyltin compounds are generally prepared by the reaction of an alkyne with an trialkyltin halide (see **15-12** and **15-16**).[277] Stille cross-coupling reactions are an important variation of the basic reaction,[278] including cross-coupling reactions of unactivated secondary halides and mono-organotin reagents.[279] Aryl halides,[280] heteroaryl halides,[281] and heteroaryl triflates[282] can be coupled to vinyltin reagents[283] using a Pd catalyst. A Mo-catalyzed variation is known.[284] A Cu-catalyzed cross-coupling variation[285] has been reported in ionic liquids.[286] Vinyl halides can be coupled to alkenes to form dienes.[287] Diazo esters were coupled with aryltrimethylstannanes using a Rh catalyst.[288] Vinyl halides can be used,[289] and allenic tin compounds have been used.[290] Intramolecular reactions are possible.[291] Stille coupling has been done using microwave irradiation,[292]

[272] Heravi, M.M.; Hashemi, E.; Azimian, F. *Tetrahedron* ***2014***, *70*, 7. Scott, W.J.; Crisp, G.T.; Stille, J.K. *J. Am. Chem. Soc.* ***1984***, *106*, 4630. See Echavarren, A.M. *Angew. Chem. Int. Ed.* ***2005***, *44*, 3962; Reiser, O. *Angew. Chem. Int. Ed.* ***2006***, *45*, 2838.

[273] See Ronson, T.O.; Carney, J.R.; Whitwood, A.C.; Taylor, R.J.K.; Fairlamb, I.J.S. *Chem. Commun.* ***2015***, *51*, 3466.

[274] Gajare, A.S.; Jensen, R.S.; Toyota, K.; Yoshifuji, M.; Ozawa, F. *Synlett* ***2005***, 144. For a ligand-free reaction, see Yabe, Y.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Tetrahedron* ***2010***, *66*, 8654.

[275] Lau, K.C.Y.; Chiu, P. *Tetrahedron Lett.* ***2007***, *48*, 1813.

[276] McMurry, J.E.; Scott, W.J. *Tetrahedron Lett.* ***1983***, *24*, 979.

[277] See Maleczka Jr., R.E.; Lavis, J.M.; Clark, D.H.; Gallagher, W.P. *Org. Lett.* ***2000***, *2*, 3655.

[278] Farina, V.; Krishnamurthy, V.; Scott, W.J. *Org. React.* ***1997***, *50*, 1; Li, J.-H.; Liang, Y.; Wang, D.-P.; Liu, W.-J.; Xie, Y.-X.; Yin, D.-L. *J. Org. Chem.* ***2005***, *70*, 2832.

[279] Powell, D.A.; Maki, T.; Fu, G.C. *J. Am. Chem. Soc.* ***2005***, *127*, 510.

[280] Littke, A.F.; Fu, G.C. *Angew. Chem. Int. Ed.* ***1999***, *38*, 2411.

[281] Clapham, B.; Sutherland, A.J. *J. Org. Chem.* ***2001***, *66*, 9033.

[282] Schaus, J.V.; Panek, J.S. *Org. Lett.* ***2000***, *2*, 469.

[283] See Rousset, S.; Abarbri, M.; Thibonnet, J.; Duchêne, A.; Parrain, J.-L. *Org. Lett.* ***1999***, *1*, 701. Also see Minière, S.; Cintrat, J.-C. *J. Org. Chem.* ***2001***, *66*, 7385.

[284] See Sävmarker, J.; Lindh, J.; Nilsson, P. *Tetrahedron Lett.* ***2010***, *51*, 6886.

[285] Mee, S.P.H.; Lee, V.; Baldwin, J.E. *Chem. Eur. J.* ***2005***, *11*, 3294.

[286] Li, J.-H.; Tang, B.-X.; Tao, L.-M.; Xie, Y.-X.; Liang, Y.; Zhang, M.-B. *J. Org. Chem.* ***2006***, *71*, 7488.

[287] Voigt, K.; Schick, U.; Meyer, F.E.; de Meijere, A. *Synlett* ***1994***, 189.

[288] Liu, Z.; Xia, Y.; Feng, S.; Wang, S.; Qiu, D.; Zhang, Y.; Wang, J. *Aust. J. Chem.* ***2015***, *68*, 1379.

[289] Johnson, C.R.; Adams, J.P.; Braun, M.P.; Senanayake, C.B.W. *Tetrahedron Lett.* ***1992***, *33*, 919.

[290] Badone, D.; Cardamone, R.; Guzzi, U. *Tetrahedron Lett.* ***1994***, *35*, 5477.

[291] Segorbe, M.M.; Adrio, J.; Carretero, J.C. *Tetrahedron Lett.* ***2000***, *41*, 1983.

[292] See Hajipour, A.R.; Rafiee, F. *Tetrahedron Lett.* ***2012***, *53*, 4661; Tan, X.; Zhou, Z.J.; Zhang, J.X.; Duan, X.H. *Eur. J. Org. Chem.* ***2014***, 5153.

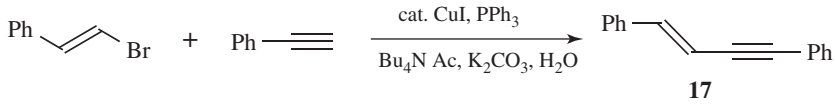
in ionic liquids,[293] in fluorous solvents,[294] and in supercritical CO_2 (Sec. 9.D.ii).[295] Stille coupling using alkynes as a substrate are known.[296]

The accepted mechanism for the Stille reaction involves a catalytic cycle[297] in which the oxidative addition[298] and a reductive elimination steps[299] are fast, relative to the Sn/Pd-transmetalation (the rate-determining step).[300] It appears that the greater coordinating ability of the unsaturated species is important, and a coordinated solvent molecule is likely involved in the electrophilic substitution at tin. Another mechanism has been proposed, in which oxidative addition of the vinyl triflate to the ligated Pd gives a *cis* Pd complex that isomerizes rapidly to *trans* Pd complex, which then reacts with the organotin compound following a S_E2 (cyclic) mechanism, with release of a ligand.[301] This pathway gives a bridged intermediate, and subsequent elimination of $XSnBu_3$ yields a three-coordinate species *cis* Pd complex, which readily gives the coupling product.[301] Most of the major intermediates have been intercepted, isolated, and characterized using electrospray ionization mass spectrometry.[302]

This reaction is highly stereoselective, and proceeds with a retention of geometry of the C═C units, and is usually regiospecific with respect to the newly formed C—C σ bond.[303] Cine substitution is known with this reaction, and its mechanism has been studied.[304] It is noted that the origin of cine substitution has been examined.[305] Carbonylative Stille coupling reactions are known.[306] Stille coupling to enols has been reported.[307] The coupling of vinyl silanes[308] to give the symmetrically conjugated dienes using CuCl and air was reported.[309]

The coupling of alkenes to alkenes or alkenes to alkynes usually requires a transition metal catalyst. The Pd-catalyzed dehydrative coupling of terminal alkynes with allylic alcohols assisted by $Ti(O\textit{i}\text{-}Pr)_4$ gave 1,4-enynes.[310] Conjugated dienes were prepared by the Pd-catalyzed reaction of unactivated alkenes with allylic esters and acrylates.[311] Conjugated enynes such as **17** were prepared via the Cu-catalyzed coupling between vinyl halides and terminal alkynes.[312]

[293] Louaisil, N.; Pham, P.D.; Boeda, F.; Faye, D.; Castanet, A.-S.; Legoupy, S. *Eur. J. Org. Chem.* ***2011***, 143.
[294] Olofsson, K.; Kim, S.-Y.; Larhed, M.; Curran, D.P.; Hallberg, A. *J. Org. Chem.* ***1999***, *64*, 4539.
[295] Jessop, P.G.; Ikariya, T.; Noyori, R. *Chem. Rev.* ***1999***, *99*, 475.
[296] Shi, Y.; Peterson, S.M.; Haberaecker III, W.W.; Blum, S.A. *J. Am. Chem. Soc.* ***2008***, *130*, 2168.
[297] Scott, W.J.; Stille, J.K. *J. Am. Chem. Soc.* ***1986***, *108*, 3033; Stille, J.K. *Angew. Chem. Int. Ed.* ***1986***, *25*, 508; Farina, V. in Abel, E.W.; Stone, F.G.A.; Wilkinson, G. *Comprehensive Organometallic Chemistry II*, Vol. 12, Pergamon, Oxford, UK, ***1995***, Chapter 3.4; Brown, J.M.; Cooley, N.A. *Chem. Rev.* ***1988***, *88*, 1031.
[298] Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* ***1993***, *115*, 9531 and references cited therein.
[299] Ozawa, F.; Fujimori, M.; Yamamoto, T.; Yamamoto, A. *Organometallics* ***1986***, *5*, 2144; Tatsumi, K.; Hoffmann, R.; Moravski, A.; Stille, J.K. *J. Am. Chem. Soc.* ***1981***, *103*, 4182.
[300] Deacon, G.B.; Gatehouse, B.M.; Nelson-Reed, K.T. *J. Organomet. Chem.* ***1989***, *359*, 267.
[301] Casado, A.L.; Espinet, P.; Gallego, A.M. *J. Am. Chem. Soc.* ***2000***, *122*, 11771.
[302] Santos, L.S.; Rosso, G.B.; Pilli, R.A.; Eberlin, M.N. *J. Org. Chem.* ***2007***, *72*, 5809.
[303] See Lu, G.-p.; Voigtritter, K.R.; Cai, C.; Lipshutz, B. *Chem. Commun.* ***2012***, *48*, 8661.
[304] Farina, V.; Hossain, M.A. *Tetrahedron Lett.* ***1996***, *37*, 6997.
[305] Kanoh, N.; Ohno, Y.; Itagaki, T.; Fukuda, H.; Iwabuchi, Y. *Synlett* ***2013***, *24*, 2660.
[306] Sun, J.; Feng, X.; Zhao, Z.; Yamamoto, Y.; Bao, M. *Tetrahedron* ***2014***, *70*, 7166.
[307] Fu, X.; Zhang, S.; Yin, J.; McAllister, T.L.; Jiang, S.A.; Tann, C.-H.; Thiruvengadam, T.K.; Zhang, F. *Tetrahedron Lett.* ***2002***, *43*, 573. See Vallin, K.S.A.; Larhed, M.; Johansson, K.; Hallberg, A. *J. Org. Chem.* ***2000***, *65*, 4537.
[308] Lim, D.S.W.; Anderson, E.A. *Synthesis* ***2012***, *44*, 983.
[309] Nishihara, Y.; Ikegashira, K.; Toriyama, F.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 985.
[310] Li, Y.-X.; Xuan, Q.-Q.; Liu, L.; Wang, D.; Chen, Y.-J.; Li, C.-J. *J. Am. Chem. Soc.* ***2013***, *135*, 12536.
[311] Zhang, Y.; Cui, Z.; Li, Z.; Liu, Z.-Q. *Org. Lett.* ***2012***, *14*, 1838.
[312] Sun, P.; Yan, H.; Lu, L.; Liu, D.; Rong, G.; Mao, J. *Tetrahedron* ***2013***, *69*, 6969.



17

Styrene was dimerized to give 1,4-diphenylbuta-1,3-diene upon treatment with a Pd catalyst and a cupric acetate oxidant and benzyl chloride.[313] 1,3-Enynes were prepared by coupling of vinyl halides and alkynes in the presence of Cu iodide.[314] The Ir-catalyzed dehydrogenative coupling of vinyl arenes gave predominantly (*E*,*E*)-1,4-diarylbuta-1,3-dienes.[315]

Cyclopropylboronic acids (**12-27**) couple with vinylic halides[316] or vinyl triflates[317] to give vinylcyclopropanes, using a Pd catalyst. Vinyl borates (**12-27**) were coupled to vinyl triflates using a Pd catalyst.[318] Vinyltrifluorooborates can be coupled to allylic chlorides using microwave irradiation[319] and vinyl halides react with vinyltrifluoroborates to give dienes with high stereoselectivity.[320]

Alkyl groups can be coupled to a vinyl unit to give substituted alkenes. The reaction of vinyl iodides and EtZnBr, with a Pd catalyst, gave the ethylated alkene (C═C─Et).[321] Aliphatic alkyl bromides reacted with vinyltin compounds to give the alkylated alkene using a Pd catalyst.[322] Allylic tosylates were coupled to conjugated alkenes to give a nonconjugated diene using a Pd catalyst.[323]

Alkynes are added to propargyl acetates using a Pd catalyst to give an alkyne allene.[324] Alkyne-alkenes were formed by coupling terminal alkynes and allenes in the presence of a Pd catalyst.[325] An alkyne was coupled internally to an allene using a Pd catalyst, to give a product that has an exocyclic methylene group and a vinyltin derivative.[326]

12-16 Acylation at Aliphatic or Alkenyl Carbon

Alkenes can be acylated with an acyl halide and a Lewis acid catalyst in what is essentially a *Friedel-Crafts reaction* (**11-17**) at an aliphatic carbon.[327] The product can arise by two

[313] Wen, Y.; Xie, J.; Deng, C.; Wu, Y. *Synlett* ***2015***, *26*, 1755.
[314] Zhu, Y.; Li, T.; Qu, X.; Sun, P.; Yang, H.; Mao, J. *Org. Biomol. Chem.* ***2011***, *9*, 7309.
[315] Emge, T.J.; Goldman, A.S.; Jones, W.D. *J. Am. Chem. Soc.* ***2017***, *139*, 8977.
[316] Zhou, S.-M.; Deng, M.-Z. *Tetrahedron Lett.* ***2000***, *41*, 3951.
[317] Yao, M.-L.; Deng, M.-Z. *J. Org. Chem.* ***2000***, *65*, 5034; Yao, M.-L.; Deng, M.-Z. *Tetrahedron Lett.* ***2000***, *41*, 9083.
[318] Occhiato, E.G.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* ***2001***, *66*, 2459.
[319] Kabalka, G.W.; Dadush, E.; Al-Masum, M. *Tetrahedron Lett.* ***2006***, *47*, 7459.
[320] Molander, G.A.; Felix, L.A. *J. Org. Chem.* ***2005***, *70*, 3950.
[321] Abarbri, M.; Parrain, J.-L.; Kitamura, M.; Noyori, R.; Duchêne, A. *J. Org. Chem.* ***2000***, *65*, 7475.
[322] Menzel, K.; Fu, G.C. *J. Am. Chem. Soc.* ***2003***, *125*, 3718.
[323] Tsukada, N.; Sato, T.; Inoue, Y. *Chem. Commun.* ***2003***, 2404.
[324] Condon-Gueugnot, S.; Linstrumelle, G. *Tetrahedron* ***2000***, *56*, 1851.
[325] Rubin, M.; Markov, J.; Chuprakov, S.; Wink, D.J.; Gevorgyan, V. *J. Org. Chem.* ***2003***, *68*, 6251.
[326] Shin, S.; RajanBabu, T.V. *J. Am. Chem. Soc.* ***2001***, *123*, 8416.
[327] See Groves, E.E. *Chem. Soc. Rev.* ***1972***, *1*, 73; Satchell, D.P.N.; Satchell, R.S. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 259–266, 270–273; Nenitzescu, C.D.; Balaban, A.T. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1033–1152.

paths. The initial attack is by the π bond of the alkene unit on the acyl cation (RCO^+; or on the acyl halide free or complexed; see **11-17**) to give a carbocation, where the positive carbon atom is β relative to the carbonyl. Loss of a proton from the carbocation gives an unsaturated ketone. If the carbocation combines with chloride, the product is a β-halo ketone, which can be isolated, so that the result is addition to the double bond (see **15-43**). On the other hand, the β-halo ketone may, under the conditions of the reaction, lose HCl to give the unsaturated ketone, this time by an addition–elimination mechanism. In the case of unsymmetrical alkenes, the more stable alkene is formed (the more highly substituted and/or conjugated alkene, following *Markovnikov's rule*, Sec. 15.B.ii).

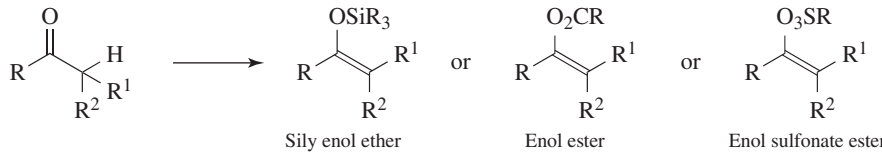
Anhydrides and carboxylic acids (the latter with a protonic acid such as anhydrous HF, H_2SO_4, or polyphosphoric acid as a catalyst) are sometimes used instead of acyl halides. With some substrates and catalysts double-bond migrations are occasionally encountered so that, for example, when 1-methylcyclohexene was acylated with acetic anhydride and zinc chloride, the major product was 6-acetyl-1-methylcyclohexene.[328] Acylation of vinylic ethers has been accomplished with aromatic acyl chlorides, a base, and a Pd catalyst:[329]

$$ROCH{=}CH_2 \rightarrow ROCH{=}CHCOAr$$

Formylation of alkenes can be accomplished with *N*-disubstituted formamides and $POCl_3$.[330] This is an aliphatic *Vilsmeier reaction* (see **11-18**). Vilsmeier formylation can also be performed on the α position of acetals and ketals, so that hydrolysis of the products gives keto aldehydes or dialdehydes.[331] Aromatic compounds were treated with $POCl_3$/DMF to form an aryl-type Vilsmeier reaction, and subsequent treatment with iodine in aqueous ammonia gave the aryl nitrile.[332] Acetylation of acetals or ketals can be accomplished with acetic anhydride and BF_3-etherate.[333] The mechanism with acetals or ketals also involves attack at an alkenyl carbon, since enol ethers are intermediates.[331] Ketones can be formylated in the α position by treatment with CO and a strong base.[334]

OS **IV**, 555, 560; **VI**, 744. Also see, OS **VI**, 28.

12-17 Conversion Of Enolates to Silyl Enol Ethers, Silyl Enol Esters, and Silyl Enol Sulfonate Esters



Sily enol ether Enol ester Enol sulfonate ester

[328] Deno, N.C.; Chafetz, H. *J. Am. Chem. Soc.* ***1952***, *74*, 3940. For other examples, see Grignon-Dubois, M.; Cazaux, M. *Bull. Soc. Chim. Fr.* ***1986***, 332.

[329] Andersson, C.; Hallberg, A. *J. Org. Chem.* ***1988***, *53*, 4257.

[330] See Burn, D. *Chem. Ind. (London)* ***1973***, 870. For a new preparation of the Vilsmeier reagent, see Kimura, Y.; Matsuura, D.; Hanawa, T.; Kobayashi, Y. *Tetrahedron Lett.* ***2012***, *53*, 1116. Also see Venkanna, P.; Rajanna, K.C.; Kumar, M.S.; Ansari, M.B.; Ali, M.M. *Tetrahedron Lett.* ***2015***, *56*, 5164; Gazvoda, M.; Kočevar, M.; Polanc, S. *Eur. J. Org. Chem.* ***2013***, 5381.

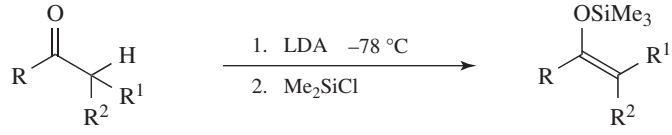
[331] Youssefyeh, R.D. *Tetrahedron Lett.* ***1964***, 2161.

[332] Ushijima, S.; Moriyama, K.; Togo, H. *Tetrahedron* ***2012***, *68*, 4588.

[333] Youssefyeh, R.D. *J. Am. Chem. Soc.* ***1963***, *85*, 3901.

[334] See van der Zeeuw, A.J.; Gersmann, H.R. *Recl. Trav. Chim. Pays-Bas* ***1965***, *84*, 1535.

Silyl enol ethers,[335] important reagents with a number of synthetic uses (see, for example, **10-68**, **12-4**, **15-20**, **15-60**, and **16-36**), can be prepared by base treatment of a ketone (converting it to its enolate anion) followed by addition of a trialkylchlorosilane. Other silylating agents have also been used.[336] Both strong bases (such as lithium diisopropylamide, LDA) and weaker bases (Et_3N) have been used for this purpose.[337] In some cases, the base and the silylating agent can be present at the same time.[338]



Silyl enol ether

The reaction can be applied to aldehydes by the use of the base KH in 1,2-dimethoxyethane.[339] A particularly mild method for conversion of ketones or aldehydes to silyl enol ethers uses Me_3SiI and the base hexamethyldisilazane, $(Me_3Si)_2NH$.[340] *bis*-(Trimethylsilyl)acetamide is an effective reagent for the conversion of ketones to the silyl enol ether, typically giving the thermodynamic product (see below).[341] Silyl enol ethers have also been prepared by the direct reaction of a ketone and a silane (R_3SiH) with a Pt catalyst.[342]

For substituted ketones, (*E*) and (*Z*) isomers are usually formed. A silyl enol ether is (*Z*) when R^1 is the priority group but (*E*) when R^2 is the priority group. In some cases it is possible to control the selectivity to favor more of one isomer than the other. Treatment of 2-methylpentan-3-one with LDA (THF, −78 °C), for example, gave a 60:40 mixture of the (*Z*) and (*E*) enolates.[343] The base used to generate an enolate anion, the solvent and temperature, the conjugate acid of the base used, and the nature of the carbonyl substrate will all play a role in the selectivity. In general, equilibrating (thermodynamic) conditions (protic solvents, e.g., ethanol, water, or ammonia, a base generating a conjugate acid stronger than the starting ketone, more ionic counterions, e.g., K or Na, higher temperatures, and longer reaction times) are expected to give more of the (*E*) isomer. Conversely, kinetic conditions (aprotic solvents, such as ether or THF, a base generating a

[335] See Poirier, J. *Org. Prep. Proced. Int.* ***1988***, *20*, 319; Colvin, E.W. *Silicon Reagents in Organic Synthesis*, Academic Press, NY, ***1988***; Ager, D.J. *Chem. Soc. Rev.* ***1982***, *11*, 493.

[336] See Mizhiritskii, M.D.; Yuzhelevskii, Yu.A. *Russ. Chem. Rev.* ***1987***, *56*, 355. For a list, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1488–1491.

[337] For di-*tert*-butylmagnesium, see Kerr, W.J.; Watson, A.J.B.; Hayes, D. *Synlett* ***2008***, 1386.

[338] Corey, E.J.; Gross, A.W. *Tetrahedron Lett.* ***1984***, *25*, 495. Also see Lipshutz, B.H.; Wood, M.R.; Lindsley, C.W. *Tetrahedron Lett.* ***1995***, *36*, 4385.

[339] Ladjama, D.; Riehl, J.J. *Synthesis* ***1979***, 504. See Orban, J.; Turner, J.V.; Twitchin, B. *Tetrahedron Lett.* ***1984***, *25*, 5099.

[340] Miller, R.D.; McKean, D.R. *Synth. Commun.* ***1982***, *12*, 319. See also, Ahmad, S.; Khan, M.A.; Iqbal, J. *Synth. Commun.* ***1988***, *18*, 1679.

[341] Smietana, M.; Mioskowski, C. *Org. Lett.* ***2001***, *3*, 1037. See also, Tanabe, Y.; Misaki, T.; Kurihara, M.; Iida, A.; Nishii, Y. *Chem. Commun.* ***2002***, 1628.

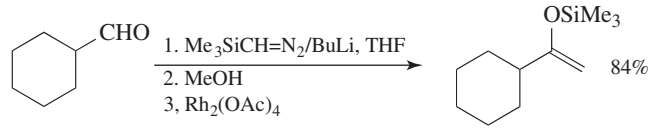
[342] Ozawa, F.; Yamamoto, S.; Kayagishi, S.; Hiraoka, M.; Ideda, S.; Minami, T.; Ito, S.; Yoshifuji, M. *Chem. Lett.* ***2001***, 972. See Blackwell, J.M.; Morrison, D.J.; Piers, W.E. *Tetahedron* ***2002***, *58*, 8247; Mori, A.; Kato, T. *Synlett* ***2002***, 1167.

[343] Heathcock, C.H.; Buse, C.T.; Kleschick, W.A.; Pirrung, M.A.; Sohn, J.E.; Lampe, J. *J. Org. Chem.* ***1980***, *45*, 1066.

conjugate acid weaker than the starting ketone, more covalent counterions, e.g., Li, lower temperatures, and relatively short reaction times) usually give more of the (*Z*) isomer. It is not always easy to predict the ratio, however. Either isomer is possible from aldehydes using the proper Rh catalyst.[344] Magnesium diisopropylamide has been used to prepare kinetic silyl enol ethers in virtual quantitative yield.[345] Reaction with Me_3SiCl/KI in DMF gives primarily the thermodynamic silyl enol ether.[346]

The protonation of silyl enol ethers with a chiral sulfonamide/achiral sulfonic acids as a co-catalyst gave the chiral α-aryl cyclic ketone.[347] The reaction of α,β-unsaturated acylsilanes with BuCu or a Grignard reagent/*t*-BuOCu and then an alkyl halide gave the silyl enol ether with a γ stereocenter.[348]

An interesting synthesis of silyl enol ethers involves chain extension of an aldehyde. Aldehydes are converted to the silyl enol ether of a ketone upon reaction with lithium (trimethylsilyl)diazomethane and then a dirhodium catalyst.[349] For example, initial reaction of lithium (trimethylsilyl)diazomethane [LTMSD, prepared *in situ* by reaction of butyllithium with (trimethylsilyl)diazomethane] with the aldehyde (**18**) gave the alkoxide addition product. Protonation, then capture by a transition metal catalyst, and a 1,2-hydride migration gave the silyl enol ether, **19**.



18 **19**

Enol acetates are generally prepared by the reaction of an enolate anion with a suitable acylating reagent such as acetic anhydride[350] Enolate anions react with acyl halides and with anhydrides to give the acylated product. Both *C*-acylation and *O*-acylation are possible, but in general *O*-acylation predominates.[351] Note that the extent of *O*- versus *C*-acylation is very dependent on the local environment and electronic effects within the enolate anion.[352] *O*-Benzoate enols are formed in good yield from aldehydes or 1,3-diketones in the presence of CuBr and *tert*-butylhydroperoxide.[353] A polymer-supported triflating agent was used to prepare silyl enol triflate from ketones, in the presence of diisopropylethylamine.[354]

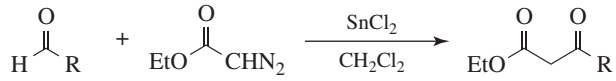
When a silyl enol ether is the trimethylsilyl derivative ($Me_3Si{-}O{-}C{=}C$), treatment with methyllithium will regenerate the lithium enolate anion and the volatile trimethylsilane (Me_3SiH).[355]

[344] Vitale, M.; Lecourt, T.; Sheldon, C.G.; Aggarwal, V.K. *J. Am. Chem. Soc.* ***2006***, *128*, 2524.
[345] Lessène, G.; Tripoli, R.; Cazeau, P.; Biran, C.; Bordeau, M. *Tetrahedron Lett.* ***1999***, *40*, 4037. Also see Patonay, T.; Hajdu, C.; Jeko, J.; Lévai, A.; Micskei, K.; Zucchi, C. *Tetrahedron Lett.* ***1999***, *40*, 1373.
[346] Lin, J.-M.; Liu, B.-S. *Synth. Commun.* ***1997***, *27*, 739.
[347] Beck, E.M.; Hyde, A.M.; Jacobsen, E.N. *Org. Lett.* ***2011***, *13*, 4260.
[348] Tsubouchi, A.; Sasaki, N.; Enatsu, S.; Takeda, T. *Tetrahedron Lett.* ***2013***, *54*, 1264.
[349] Aggarwal, V.K.; Sheldon, C.G.; Macdonald, G.J.; Martin, W.P. *J. Am. Chem. Soc.* ***2002***, *124*, 10300.
[350] For the synthesis of enol acetates, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, 1484–1485.
[351] See Krapcho, A.P.; Diamanti, J.; Cayen, C.; Bingham, R. *Org. Synth. Coll. Vol. V* ***1973***, 198.
[352] See Honda, T.; Namiki, H.; Kudoh, M.; Watanabe, N.; Nagase, H.; Mizutani, H. *Tetrahedron Lett.* ***2000***, *41*, 5927.
[353] Yoo, W.-J.; Li, C.-J. *J. Org. Chem.* ***2006***, *71*, 6266.
[354] Wentworth, A.D.; Wentworth Jr., P.; Mansoor, U.F.; Janda, K.D. *Org. Lett.* ***2000***, *2*, 477.
[355] House, H.O.; Czuba, L.J.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* ***1969***, *34*, 2324.

OS **VI**, 327, 445; **VII**, 282, 312, 424, 512; **VIII**, 1, 286, 460; **IX**, 573. See also, OS **VII**, 66, 266.

For the conversion of ketones to vinylic triflates,[356] see OS **VIII**, 97, 126.

12-18 Conversion of Aldehydes to β-Keto Esters or Ketones



β-Keto esters have been prepared in moderate to high yields by treatment of aldehydes with diethyl diazoacetate in the presence of a catalytic amount of a Lewis acid, such as $SnCl_2$, BF_3, or $GeCl_2$.[357] The reaction was successful for both aliphatic and aromatic aldehydes, but the former react more rapidly than the latter, and the difference is great enough to allow selective reactivity. In a similar process, aldehydes react with certain carbanions stabilized by boron (Ar_2BCH^-R'), in the presence of $(F_3CCO)_2O$ or NCS, to give ketones.[358]

Ketones can be prepared from aryl aldehydes (ArCHO) by treatment with a Rh complex $(Ph_3P)_2Rh(CO)Ar'$, whereby the Ar group is transferred to the aldehyde, producing the ketone, Ar—CO—Ar′.[359] In another Rh-catalyzed reaction, aryl aldehydes (ArCHO) react with Me_3SnAr' to give the diaryl ketone Ar—CO—Ar′.[360] Acylation of aryl halides with aldehydes gives aryl ketones in the presence of a Pd catalyst.[361]

12-19 Cyanation

There are several reactions in which a C—H unit is altered to C—CN. In virtually all cases, the hydrogen being replaced is on a carbon α to a heteroatom or functional group. There are several examples. Introduction of a cyano group α to the carbonyl group of a ketone can be accomplished by prior formation of the enolate anion with LDA in THF and addition of this solution to *p*-TsCN at −78 °C.[362] The products are formed in moderate to high yields but the reaction is not applicable to methyl ketones. Treatment of $TMSCH_2N(Me)C{=}Nt$-Bu with *sec*-butyllithium and $R_2C{=}O$, followed by iodomethane and NaOMe, leads to the nitrile, $R_2CH—CN$.[363]

Cyanation has been shown to occur α to a nitrogen, specifically in *N*,*N*-dimethylaniline derivatives. Treatment with a catalytic amount of $RuCl_3$ in the presence of oxygen and NaCN leads to the corresponding cyanomethylamine.[364] Conversion of tertiary amines to the α-cyanoamine has been reported in the presence of $FeCl_2$ and *t*-BuOOH.[365]

[356] Comins, D.L.; Dehghani, A. *Tetrahedron Lett.* ***1992***, *33*, 6299.
[357] Holmquist, C.R.; Roskamp, E.J. *J. Org. Chem.* ***1989***, *54*, 3258. See Trost, B.M.; Malhotra, S.; Koschker, P.; Ellerbrock, P. *J. Am. Chem. Soc.* ***2012***, *134*, 2075.
[358] Pelter, A.; Smith, K.; Elgendy, S.; Rowlands, M. *Tetrahedron Lett.* ***1989***, *30*, 5643.
[359] Krug, C.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2002***, *124*, 1674.
[360] Pucheault, M.; Darses, S.; Genet, J.-P. *J. Am. Chem. Soc.* ***2004***, *126*, 15356.
[361] Ruan, J.; Saidi, O.; Iggo, J.A.; Xiao, J. *J. Am. Chem. Soc.* ***2008***, *130*, 10510.
[362] Kahne, D.; Collum, D.B. *Tetrahedron Lett.* ***1981***, *22*, 5011.
[363] Santiago, B.; Meyers, A.I. *Tetrahedron Lett.* ***1993***, *34*, 5839.
[364] North, M. *Angew. Chem. Int. Ed.* ***2004***, *43*, 4126.
[365] Han, W.; Ofial, A.R. *Chem. Commun.* ***2009***, 5024.

Allylic tertiary amines reacted with tropylium tetrafluoroborate and KCN to give the α-cyanoamine.[366] Vinyl halides reacted with cyanohydrins with a Pd catalyst to give the vinyl nitrile.[367] Vinylic boronic acids reacted with α-cyanoacetates in the presence of O_2 and a Cu catalyst to give the vinyl nitrile.[368] The Au-catalyzed oxidative α cyanation of tertiary amines has been reported.[369]

In a different kind of reaction, nitro compounds are α cyanated by treatment with ^-CN and $K_3Fe(CN)_6$.[370] The mechanism probably involves ion radicals. In still another reaction, secondary amines are converted to α-cyanoamines by treatment with phenylseleninic anhydride and NaCN or Me_3SiCN.[371,372]

12-20 Alkylation of Alkanes

$$RH + R'^{+} \longrightarrow R{-}R' + H^{+}$$

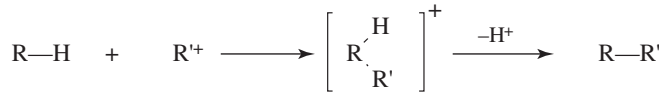
Alkanes can be alkylated by treatment with solutions of stable carbocations[373] (Sec. 5.A.ii), but the availability of such carbocations is limited and mixtures are usually obtained. In a typical experiment, the treatment of propane with isopropyl fluoroantimonate (Me_2HC^+ SbF_6^-) gave 26% 2,3-dimethylbutane, 28% 2-methylpentane, 14% 3-methylpentane, and 32% *n*-hexane, as well as some butanes, pentanes (formed by **12-46**), and higher alkanes. Mixtures arise in part because intermolecular hydrogen exchange

$$RH + R'^{+} \rightarrow R^{+} + R'H$$

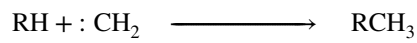
is much faster than alkylation, so that alkylation products are also derived from the new alkanes and carbocations formed in the exchange reaction. Furthermore, the carbocations present are subject to rearrangement (Chapter 18), giving rise to new carbocations. Products result from all the hydrocarbons and carbocations present in the system. As expected from their relative stabilities, secondary alkyl cations alkylate alkanes more readily than tertiary alkyl cations (the *tert*-butyl cation does not alkylate methane or ethane). Stable primary alkyl cations are not available, but alkylation has been achieved with complexes formed between CH_3F or C_2H_5F and SbF_5.[374] The mechanism of alkylation can be formulated (similar to that shown in hydrogen exchange with superacids, **12-1**) as that shown. It is by means of successive reactions of this sort that simple alkanes like methane and ethane give *tert*-butyl cations in superacid solutions (Sec. 5.A.ii).[375]

[366] Allen, J.M.; Lambert, T.H. *J. Am. Chem. Soc.* ***2011***, *133*, 1260.
[367] Powell, K.J.; Han, L.-C.; Sharma, P.; Moses, J.E. *Org. Lett.* ***2014***, *16*, 2158.
[368] Wang, X.-J.; Zhang, S.-L. *New J. Chem.* ***2017***, *41*, 14826.
[369] Yang, W.; Wei, L.; Yi, F.; Cai, M. *Tetrahedron* ***2016***, *72*, 4059.
[370] Kornblum, N.; Singh, N.K.; Kelly, W.J. *J. Org. Chem.* ***1983***, *48*, 332.
[371] Barton, D.H.R.; Billion, A.; Boivin, J. *Tetrahedron Lett.* ***1985***, *26*, 1229.
[372] Lemaire, M.; Doussot, J.; Guy, A. *Chem. Lett.* ***1988***, 1581. See also, Hayashi, Y.; Mukaiyama, T. *Chem. Lett.* ***1987***, 1811.
[373] See Olah, G.A.; Farooq, O.; Prakash, G.K.S. in Hill, C.L. *Activation and Functionalization of Alkanes*, Wiley, NY, ***1989***, pp. 27–78; see Ref. 48; Fabre, P.; Devynck, J.; Trémillon, B. *Chem. Rev.* ***1982***, *82*, 591. See also, Olah, G.A.; Prakash, G.K.S.; Williams, R.E.; Field, L.D.; Wade, K. *Hypercarbon Chemistry*, Wiley, NY, ***1987***.
[374] Olah, G.A.; DeMember, J.R.; Shen, J. *J. Am. Chem. Soc.* ***1973***, *95*, 4952. See also, Sommer, J.; Muller, M.; Laali, K. *Nouv. J. Chem.* ***1982***, *6*, 3.
[375] For example, see Hogeveen, H.; Roobeek, C.F. *Recl. Trav. Chim. Pays-Bas* ***1972***, *91*, 137.

Intramolecular insertion has been reported.[376] The reaction of alkyl halides with the unactivated sp^3 C—H bonds of aliphatic amides used a N catalyst and a bidentate directing group.[377]



12-21 Insertion by Carbenes



The highly reactive species methylene (**:**CH_2) inserts into C—H bonds,[378] both aliphatic and aromatic,[379] although with aromatic compounds subsequent ring expansion is also possible (see **15-60**). This is effectively a homologation reaction.[380] The insertion reactions of dimethylcarbene have been reviewed.[381] The methylene insertion reaction has limited utility because of its nonselectivity (Sec. 5.D.i). The carbenes can be generated in any of the ways mentioned in Sec. 5.D.ii. Alkylcarbenes usually rearrange rather than give insertion (Sec. 5.D.ii, category 4), but, when this is impossible, *intramolecular* insertion[382] is found, rather than intermolecular.[383] Methylene (**:**CH_2) generated by photolysis of diazomethane (CH_2N_2) in the liquid phase is indiscriminate (totally nonselective) in its reactivity (Sec. 5.D.ii, category 2). Methylene (**:**CH_2) generated in other ways and monoalkyl and dialkyl carbenes are less reactive and insert in the order tertiary > secondary > primary.[384] Carbenes have been generated using ultrasound.[385] Carbene insertion with certain allylic systems can proceed with rearrangement of the double bond.[386] Halocarbenes (**:**CCl_2, :CBr_2, etc.) insert much less readily, although a number of instances have been reported.[387] Generation of triplet carbenes has been discussed.[388]

[376] Yamamoto, G.; Oki, M. *Chem. Lett.* ***1987***, 1163.
[377] Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* ***2014***, *136*, 1789.
[378] First reported by Meerwein, H.; Rathjen, H.; Werner, H. *Ber.* ***1942***, *75*, 1610. See Doyle, M.P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* ***2010***, *110*, 704; Bethell, D. in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 92–101; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 209–266.
[379] Terao, T.; Shida, S. *Bull. Chem. Soc. Jpn.* ***1964***, *37*, 687. See also, Moss, R.A.; Fedé, J.-M.; Yan, S. *J. Am. Chem. Soc.* ***2000***, *122*, 9878.
[380] See Marek, I. *Tetrahedron* ***2002***, *58*, 9463.
[381] Cang, H.; Moss, R.A.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* ***2015***, *137*, 2730; Ring, A.; Ford, A.; Maguire, A.R. *Tetrahedron Lett.* ***2016***, *57*, 5399.
[382] Friedman, L.; Berger, J.G. *J. Am. Chem. Soc.* ***1961***, *83*, 492, 500. See Padwa, A.; Krumpe, K.E. *Tetrahedron* ***1992***, *48*, 5385.
[383] See Burke, S.D.; Grieco, P.A. *Org. React.* ***1979***, *26*, 361.
[384] Doering, W. von E.; Knox, L.H. *J. Am. Chem. Soc.* ***1961***, *83*, 1989.
[385] Bertram, A.K.; Liu, M.T.H. *J. Chem. Soc., Chem. Commun.* ***1993***, 467.
[386] Carter, D.S.; van Vranken, D.L. *Org. Lett.* ***2000***, *2*, 1303; Doyle, M.P.; McKervey, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, NY, ***1998***.
[387] See Steinbeck, K. *Tetrahedron Lett.* ***1978***, 1103; Boev, V.I. *J. Org. Chem. USSR* ***1981***, *17*, 1190.
[388] Fuku-en, S.-i.; Yamaguchi, T.; Kojima, S.; Yamamoto, Y. *J. Phys. Org. Chem.* ***2011***, *24*, 1009.

Dirhodium-catalyzed insertion into H—C(sp^2) bonds is known,[389] and also into H—C(*sp*) bonds.[390] It is noted that cyclopropanation may compete with C—H insertion with electron-rich highly substituted alkenes.[391] Insertion of diazoalkane and diazocarbonyl compounds can be catalyzed by Cu compounds[392] and Ag compounds[393] as well. Insertion at an allylic carbon of alkenes has been reported.[394] Insertion into the α-C—H bond of an aldehyde gives an α-substituted aldehyde.[395] Intramolecular insertion at the α carbon of a ketone by a diazo ketone, using $TiCl_4$, gives a bicyclic 1,3-diketone.[396] A Au-catalyzed reaction is known that uses alkynes as an α-diazo ketone equivalent.[397]

The metal carbene insertion reaction, in contrast to the methylene insertion reaction, can be highly selective,[398] and is useful in synthesis.[399] There are numerous examples, usually requiring a transition metal catalyst.[400] The catalyst typically converts a diazoalkane or diazocarbonyl compound to the metal carbene *in situ*, allowing the subsequent insertion reaction. Intermolecular reactions are known, including a diazoalkane insertion reaction with a dirhodium catalyst.[401] Good enantioselectivity is observed in the insertion product when chiral ligands are present.[402]

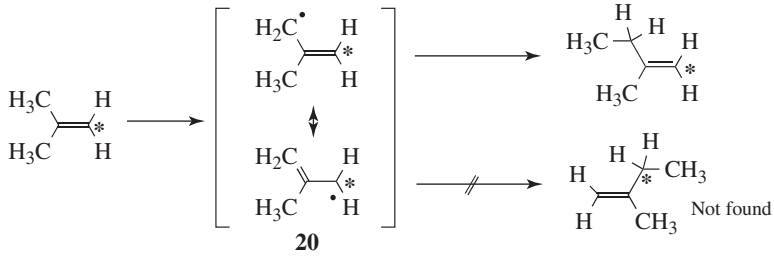
The mechanism[403] of the insertion reaction is not known with certainty, but there seem to be at least two possible pathways.

1. A simple one-step process involving a three-center cyclic transition state:

The most convincing evidence for this mechanism is that in the reaction between isobutene-1-^{14}C and carbene the product 2-methylbut-1-ene was labeled only in the C-1 position.[404] This rules out a free radical or a carbocation or carbanion

[389] Gibe, R.; Kerr, M.A. *J. Org. Chem.* ***2002***, *67*, 6247.
[390] Arduengo III, A.J.; Calabrese, J.C.; Davidson, F.; Dias, H.V.R.; Goerlich, J.R.; Krafczyk, R.; Marshall, W.J.; Tamm, M.; Schmutzler, R. *Helv. Chim. Acta.* ***1999***, *82*, 2348.
[391] Ventura, D.L.; Li, Z.; Coleman, M.G.; Davies, H.M.L. *Tetrahedron* ***2009***, *65*, 3052.
[392] See Caballero, A.; Díaz-Requejo, M.M.; Belderraín, T.R.; Nicasio, M.C.; Trofimenko, S.; Pérez, P.J. *J. Am. Chem. Soc.* ***2003***, *125*, 1446.
[393] Dias, H.V.R.; Browning, R.G.; Polach, S.A.; Diyabalanage, H.V.K.; Lovely, C.J. *J. Am. Chem. Soc.* ***2003***, *125*, 9270.
[394] Davies, H.M.L.; Ren, P.; Jin, Q. *Org. Lett.* ***2001***, *3*, 3587.
[395] Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* ***2008***, *130*, 2434.
[396] Wee, A.G.H.; Duncan, S.C. *J. Org. Chem.* ***2005***, *70*, 8372.
[397] Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* ***2010***, *132*, 3258.
[398] See Sulikowski, G.A.; Cha, K.L.; Sulikowski, M.M. *Tetrahedron: Asymmetry* ***1998***, *9*, 3145.
[399] Ye, T.; McKervey, M.A. *Chem. Rev.* ***1994***, *94*, 1091.
[400] Doyle, M.P. *Pure Appl. Chem.* ***1998***, *70*, 1123. See Taber, D.F.; Malcolm, S.C. *J. Org. Chem.* ***1998***, *63*, 3717 for a discussion of transition state geometry in Rh-mediated C—H insertion.
[401] Davies, H.M.L.; Jin, Q. *Org. Lett.* ***2004***, *6*, 1769; Davies, H.M.L.; Loe, Ø. *Synthesis* ***2004***, 2595. See Li, J.; Qiu, Z. *J. Org. Chem.* ***2015***, *80*, 10686; Lu, W.-j.; Pei, X.; Murai, T.; Sasamori, T.; Tokitoh, N.; Kawabata, T.; Furuta, T. *Synlett* ***2017***, *28*, 679.
[402] See Davies, H.M.L.; Beckwith, R.E.J. *Chem. Rev.* ***2003***, *103*, 2861. See also Suematsu, H.; Katsuki, T. *J. Am. Chem. Soc.* ***2009***, *131*, 14218.
[403] See Bethell, D. *Adv. Phys. Org. Chem.* ***1969***, *7*, 153 (pp. 190–194).
[404] Doering, W. von E.; Prinzbach, H. *Tetrahedron* ***1959***, *6*, 24.

intermediate. If an allylic radical such as **20** (or a corresponding ion) were an intermediate, resonance would ensure that some carbene attacked at the C-1 position:



20

Other evidence is that retention of configuration, which is predicted, has been found in a number of instances.[405] An ylid intermediate was trapped in the reaction of $:CH_2$ with allyl alcohol.[406]

2. A free-radical process in which the carbene directly abstracts a hydrogen atom from the substrate to generate a pair of free radicals:

$$RH + CH_2 \longrightarrow R^{\bullet} + {}^{\bullet}CH_3$$
$$R^{\bullet} + {}^{\bullet}CH_3 \longrightarrow RCH_3$$

One fact supporting this mechanism is that among the products obtained (beside butane and 2-methylpropane) on treatment of propane with CH_2 (generated by photolysis of diazomethane and ketene) were propene and ethane,[407] which could arise, respectively, by disproportionation of the propane radical to prop-1-ene and propane. Note that disproportionation refers to a reaction in which a compound is simultaneously oxidized and reduced to give two different products such as the alkene and the alkane. Alternatively, propane can react with $:CH_2$ to give the propyl radical and the methyl radical, and the methyl radical can couple with a second methyl radical to give ethane.

The disproportionation mechanism can take place under suitable conditions, as has been demonstrated by isotopic labeling[408] and by other means.[409] However, the formation of disproportionation and dimerization products does not always mean that the free-radical abstraction process takes place. In some cases these products arise in a different manner.[410] The product of the reaction between a carbene and a molecule may have excess energy (Sec. 5.D.ii). Therefore, it is possible for the substrate and the carbene to react by mechanism 1 (the direct-insertion process) and for the excess energy to cause the compound thus formed to cleave to free radicals. When this pathway is in operation, the free radicals are formed *after* the actual insertion reaction. The mechanism of

[405] See Seyferth, D.; Cheng, Y.M. *J. Am. Chem. Soc.* ***1971***, *93*, 4072.
[406] Sobery, W.; DeLucca, J.P. *Tetrahedron Lett.* ***1995***, *36*, 3315.
[407] Frey, H.M. *Proc. Chem. Soc.* ***1959***, 318.
[408] McNesby, J.R.; Kelly, R.V. *Int. J. Chem. Kinet.* ***1971***, *3*, 293.
[409] Ring, D.F.; Rabinovitch, B.S. *J. Am. Chem. Soc.* ***1966***, *88*, 4285; *Can. J. Chem.* ***1968***, *46*, 2435.
[410] Bell, J.A. *Prog. Phys. Org. Chem.* ***1964***, *2*, 1 (pp. 30–43).

cyclopropylcarbene reactions has also been discussed.[411] Migratory carbene insertion reactions have been discussed.[412]

It has been suggested[413] that singlet carbenes insert by the one-step direct-insertion process and triplets (which, being free radicals, are more likely to abstract hydrogen) by the free-radical process. In support of this suggestion, CIDNP signals[414] (Sec. 5.C.i) were observed in the ethylbenzene produced from toluene and triplet CH_2, but not from the same reaction with singlet CH_2.[415] Carbenoids (e.g., compounds of the form R_2CMCl, see **12-39**) can insert into a C—H bond by a different mechanism, similar to pathway 2, but involving abstraction of a hydride ion rather than a hydrogen atom.[416]

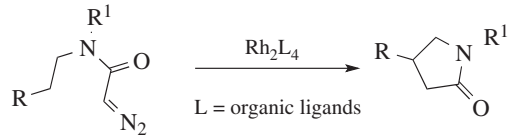
There are many types of insertion reactions, including insertion into C—H bonds, O—H or O—C bonds, or N—H bonds, and there are many variations. The insertion of α-diazo esters into aryl aldehydes gave the α-carbomethoxy aldehyde in the presence of a chiral oxazaborolidinium catalyst.[417] The insertion of α-diazo esters into benzocyclobutenols gave indanol derivatives.[418] *ortho*-Alkylbromobenzene derivatives undergo insertion reactions with diazoalkanes and a Pd catalyst to produce indane derivatives.[419] The carbonylation of carbenes can give ketenes.[420]

α-Diazo esters, in the presence of a Cu catalyst, generated a carbene that reacted via insertion with alkynes with a distal ester unit to give the corresponding alkenyl ester.[421] The Rh-catalyzed insertion of the carbene derived from α-diazocarbonyl compounds into primary alkyl C—H bonds has been reported.[422] The alkylidene carbene reagents,[423] generated from the reaction of ketone with $TMSCHN_2$ and BuLi, gave an intramolecular insertion reaction that generated cyclopentene derivatives.[424] Benzylic diazo compounds reacted with aldehydes to give chiral α-aryl ketones using a chiral oxazaborolidinium catalyst.[425] The Rh-catalyzed insertion reaction of α-diazo esters with functionalized aromatic compounds gave the *ortho*-substituted $CHRCO_2R'$ product.[426] The insertion reaction of α-aryl-α-diazo ketones with a Rh catalyst gave α-aryl cyclohexanone derivatives.[427] Gold vinylidene reagents, formed *in situ* from alkynyl ketones by treatment with *N*-bromoacetamide, a Au catalyst, and 10% $AgSbF_6$, gave 2-bromocyclopentenone derivatives.[428] α-Diazo esters reacted with benzylic aromatic compounds in the presence of an immobilized Cu

[411] Cummins, J.M.; Porter, T.A.; Jones Jr., M. *J. Am. Chem. Soc.* ***1998***, *120*, 6473.
[412] See Wang, C.; Ye, F.; Wu, C.; Zhang, Y.; Wang, J. *J. Org. Chem.* ***2015***, *80*, 8748.
[413] Richardson, D.B.; Simmons, M.C.; Dvoretzky, I. *J. Am. Chem. Soc.* ***1961***, *83*, 1934.
[414] See Roth, H.D. *Acc. Chem. Res.* ***1977***, *10*, 85.
[415] Roth, H.D. *J. Am. Chem. Soc.* ***1972***, *94*, 1761. See also, Bethell, D.; McDonald, K. *J. Chem. Soc., Perkin Trans. 2* ***1977***, 671.
[416] See Oku, A.; Yamaura, Y.; Harada, T. *J. Org. Chem.* ***1986***, *51*, 3730; Ritter, R.H.; Cohen, T. *J. Am. Chem. Soc.* ***1986***, *108*, 3718.
[417] Gao, L.; Kang, B.C.; Ryu, D.-H. *J. Am. Chem. Soc.* ***2013***, *135*, 14556.
[418] Xia, Y.; Liu, Z.; Liu, Z.; Ge, R.; Ye, F.; Hossain, M.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* ***2014***, *136*, 3013.
[419] Gutiérrez-Bonet, Á.; Juliá-Hernández, F.; de Luis, B.; Martin, R. *J. Am. Chem. Soc.* ***2016***, *138*, 6384.
[420] Goedecke, C.; Leibold, M.; Siemeling, U.; Frenking, G. *J. Am. Chem. Soc.* ***2011***, *133*, 3557.
[421] Tang, Y.; Chen, Q.; Liu, X.; Wang, G.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* ***2015***, *54*, 9512.
[422] Hou, W.; Yang, Y.; Wu, Y.; Feng, H.; Li, Y. Zou, B. *Chem. Commun.* ***2016***, *52*, 9672.
[423] For a review of alkylidene carbene chemistry, see Grainger, R.S.; Munro, K.R. *Tetrahedron* ***2015***, *71*, 7795.
[424] Zheng, J.-C.; Yun, S.Y.; Sun, C.; Lee N-K; Lee, D. *J. Org. Chem.* ***2011***, *76*, 1986.
[425] Kang, B.C.; Nam, D.G.; Hwang, G.-S.; Ryu, D.-H. *Org. Lett.* ***2015***, *17*, 4810.
[426] Yu, X.; Yu, S.; Xiao, J.; Wan, B.; Li, X. *J. Org. Chem.* ***2013***, *78*, 5444.
[427] Taber, D.F.; Paquette, C.M.; Gu, P.; Tian, W. *J. Org. Chem.* ***2013***, *78*, 9772.
[428] Wang, Y.; Zarca, M.; Gong, L.Z.; Zhang, L. *J. Am. Chem. Soc.* ***2016***, *138*, 7516.

catalyst to give the α-aryl ester.[429] α-Oxo gold carbenes were trapped by carboxylic acids.[430]

Intramolecular insertion reactions are well known,[431] and tolerate a variety of functional groups.[432] The insertion of the diazocarbonyl unit into the C—H bond of an α-diazo amide gives the lactam shown in the reaction.[433]



Insertion into a 2-pyrrolidinone derivative using $Me_3SiCH_2N_2$ followed by $AgCO_2Ph$ with ultrasound gave the ring-expanded 2-piperidone derivative.[434] An intramolecular insertion reaction was reported for α-diazo keto esters with a distal phenyl substituent, using a Rh catalyst to give a dihydronaphthalene derivative.[435] The intramolecular insertion reaction of α-diazo-β-keto esters or α-diazo-β-keto phosphonates with $CuCl_2$ and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate gave the cyclopentanone derivative.[436]

Insertion into the O—H bond of alcohols, to produce ethers, has been reported using a diazocarbonyl compound and an $In(OTf)_3$ catalyst.[437] The Cu-catalyzed insertion of a diazo ester into an oxetane gives the ring-expanded tetrahydrofuran derivative.[438] Insertion is also possible with other ethers, including silyl ethers.[439] Metal-catalyzed silylene insertion into allylic ethers leads to allylic silanes.[440] Similar insertion at the α carbon of an ether leads to cyclic ethers, with high enantioselectivity when a chiral ligand is used with a Rh catalyst.[441]

Phenyl diazoacetates, when heated, gave the carbene, which reacted via N—H insertion with aniline, in the presence of Cinchona alkaloids, to give chiral α-amino esters.[442] The

[429] Fraile, J.M.; Mayoral, J.A.; Muñoz, A.; Santafé-Valero, J. *Tetrahedron* ***2013***, *69*, 7360.
[430] Ji, K.; Zhao, Y.; Zhang, L. *Angew. Chem. Int. Ed.* ***2013***, *52*, 6508.
[431] See Shi, W.; Zhang, B.; Zhang, J.; Liu, B.; Zhang, S.; Wang, J. *Org. Lett.* ***2005***, *7*, 3103.
[432] See Doyle, M.P.; Kalinin, A.V. *Synlett,* ***1995***, 1075; Watanabe, N.; Ohtake, Y.; Hashimoto, S.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* ***1995***, *36*, 1491; Maruoka, K.; Concepcion, A.B.; Yamamoto, H. *J. Org. Chem.* ***1994***, *59*, 4725.
[433] Doyle, M.P.; Protopopova, M.N.; Winchester, W.R.; Daniel, K.L. *Tetrahedron Lett.* ***1992***, *33*, 7819. See also, Clark, J.S.; Hodgson, P.B.; Goldsmith, M.D.; Street, L.J. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 3312.
[434] Coutts, I.G.C.; Saint, R.E.; Saint, S.L.; Chambers-Asman, D.M. *Synthesis* ***2001***, 247.
[435] Rodriguez-Cárdenas, E.; Sabala, R.; Romero-Ortega, M.; Ortiz, A.; Olivo, H.F. *Org. Lett.* ***2012***, *14*, 238.
[436] Slattery, C.N.; Maguire, A.R. *Tetrahedron Lett.* ***2013***, *54*, 2799.
[437] Lombard, F.J.; Coster, M.J. *Org. Biomol. Chem.* ***2015***, *13*, 6413. For an $InCl_3$-catalyzed reaction, see Krishna, P.R.; Prapurna, Y.L.; Alivelu, M. *Tetrahedron Lett.* ***2011***, *52*, 3460. For an enantioselective reaction, see Xie, X.-L.; Zhu, S.-F.; Guo, J.-X.; Cai, Y.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* ***2014***, *53*, 2978.
[438] Lo, M.M.-C.; Fu, G.C. *Tetrahedron* ***2001***, *57*, 2621.
[439] Davies, H.M.L.; Hedley, S.J.; Brooks R.; Bohall, B.R. *J. Org. Chem.* ***2005***, *70*, 10737.
[440] Bourque, L.E.; Cleary, P.A.; Woerpel, K.A. *J. Am. Chem. Soc.* ***2007***, *129*, 12602.
[441] Davies, H.M.L.; Grazini, M.V.A.; Aouad, E. *Org. Lett.* ***2001***, *3*, 1475.
[442] Saito, H.; Morita, D.; Uchiyama, T.; Miyake, M.; Miyairi, S. *Tetrahedron Lett.* ***2012***, *53*, 6662. For an N—H insertion reaction in an ionic liquid, see Akbari, J.; Ebrahimi, A.; Heydari, A. *Tetrahedron Lett.* ***2014***, *55*, 5417. For enantioselective N—H insertion reactions, see Le Maux, P.; Simonneaux, G. *Tetrahedron* ***2015***, *71*, 9333; Xu, B.; Zhu, S.-F.; Zuo, X.-D.; Zhang, Z.-C.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* ***2014***, *53*, 3913.

intramolecular insertion reaction of α-diazo esters with a distal amino, ether, or methylene unit gave the corresponding cyclic amine, cyclic ether, or cyclic hydrocarbon in the presence of a Pd catalyst.[443]

The carbenoid alkene insertion reactions of oxiranyllithium reagents have been reported.[444] A computational study has been carried out for a carbenoid mechanism for the reaction of geminal dihalocyclopropanes with metals or alkyllithiums to give carbenoids that are converted to allenes.[445] The Pd-catalyzed insertion of carbenoids into aminals has been reported.[446] Lithium chloride carbenoids have been used in bond activation reactions.[447] Carbenoid insertion reactions into Si—H and S—H bonds has been reported using α-diazo ketones and α-diazo esters with a Cu catalyst.[448] Alkylidenecyclobutanes have been prepared by the reaction of cyclobutylmagnesium carbenoids with vinyl sulfones.[449] Allenyl carbenoids reacted via insertion with organozirconium bonds to give homopropargyl alcohols.[450]

OS **VII**, 200.

F. Metal Electrophiles

12-22 Metalation With Organometallic Compounds

$$RH + R'M \longrightarrow RM + R'H$$

Many organic compounds can be metalated by treatment with an organometallic compound.[451] In general, the reaction can be performed only with organometallics of active metals such as Li, Na, and K, but Grignard reagents abstract protons from sufficiently acidic C—H bonds, as in R—C≡C—H → R—C≡C—MgX. This is the best method for the preparation of alkynyl Grignard reagents.[452] Lewis acids have been used to promote α-lithiation of amines.[453] Triethylgallium has been used to generate enolate anions from ketones.[454] Note that organolithium compounds are aggregated species and can form hetero-aggregates containing different organic groups.[455] *N*-Lithio-*N*-(trialkylsilyl)allylamines are deprotonated in ether solvents at the *cis*-vinylic position

[443] Daniel Solé, D.; Mariani, F.; Bennasar, L.; Fernández, I. *Angew. Chem. Int. Ed.* ***2016***, *55*, 6467.
[444] Pratt, L.M.; Mai, B.K.; Ramachandran, B.R. *J. Org. Chem.* ***2012***, *77*, 8605.
[445] Voukides, A.C.; Cahill, K.J.; Johnson, R.P. *J. Org. Chem.* ***2013***, *78*, 11815.
[446] Qin, G.; Li, L.; Li, J.; Huang, H. *J. Am. Chem. Soc.* ***2015***, *137*, 12490.
[447] Molitor, S.; Gessner, V.H. *Synlett* ***2015***, *26*, 861.
[448] Keipour, H.; Jalba, A.; Delage-Laurin, L.; Ollevier, T. *J. Org. Chem.* ***2017***, *82*, 3000. Also see Courant, T.; Kumar, R.; Turcaud, S.; Micouin, L. *Org. Lett.* ***2016***, *18*, 4818.
[449] Ishigaki, M.; Inumaru, M.; Satoh, T. *Tetrahedron Lett.* ***2011***, *52*, 5563. Also see Kimura, T.; Satoh, T. *Tetrahedron* ***2013***, *69*, 6371; Kimura, T.; Satoh, T. *J. Phys. Org. Chem.* ***2015***, *28*, 509.
[450] Stec, J.; Henderson, A.R.; Whitby, R.J. *Tetrahedron Lett.* ***2012***, *53*, 1112.
[451] See Wardell, J.L. in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 44–107; Wardell, J.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, pp. 1–157 (pp. 27–71); Narasimhan, M.S.; Mali, R.S. *Synthesis* ***1983***, 957; Biellmann, J.F.; Ducep, J. *Org. React.* ***1982***, *27*, 1.
[452] See Blagoev, B.; Ivanov, D. *Synthesis* ***1970***, 615.
[453] Kessar, S.V.; Singh, P.; Singh, K.N.; Venugopalan, P.; Kaur, A.; Bharatam, P.V.; Sharma, A.K. *J. Am. Chem. Soc.* ***2007***, *129*, 4506.
[454] Nishimura, Y.; Miyake, Y.; Amemiya, R.; Yamaguchi, M. *Org. Lett.* ***2006***, *8*, 5077.
[455] Gossage, R.A.; Jastrzebski, J.T.B.H.; van Koten, G. *Angew. Chem. Int. Ed.* ***2005***, *44*, 1448.

to give 3,*N*-dilithio-*N*-(trialkylsilyl)allylamines.[456] Since the reaction involves a proton transfer, the equilibrium lies on the side of the weaker acid.[457] The most common reagent is probably butyllithium.[458] Reductive lithiation is an important method for the preparation of organolithium reagents.[459] Normally, only active aromatic rings react with butyllithium. Benzene itself reacts with lithium very slowly and in low yield, although benzene can be metalated by butyllithium in the presence of *tert*-BuOK[460] or by coordination with various diamines.[461] Metalation of aliphatic RH is most successful when the carbanions are stabilized by resonance (allylic, benzylic, propargylic,[462] etc.) or when the negative charge is at an *sp* carbon (at triple bonds). Trimethylsilylmethyl potassium (Me_3SiCH_2K)[463] and also a combination of an organolithium compound with a bulky alkoxide (LICKOR superbase)[464] are very good reagents for allylic metalation. The former is also useful for benzylic positions. A combination of BuLi, *t*-BuOK, and tetramethylethylenediamine has been used to convert ethylene to vinylpotassium.[465] The reaction can be used to determine relative acidities of very weak acids by allowing two R—H compounds to compete for the same R′M and to determine which proton in a molecule is the most acidic.[466]

When a heteroatom, such as N, O, S,[467] or a halogen,[468] is present in a molecule containing an aromatic ring or a double bond, lithiation is usually quite regioselective.[469] The reaction of methoxyethene with *t*-butyllithium generates 1-lithio-1-methoxyethene.[470] It has been shown that fluorine is more effective for stabilization of carbanions when compared to the heavier halogens.[471] In such compounds, the lithium usually bonds with the sp^2 carbon closest to the heteroatom, probably because the attacking species coordinates with the heteroatom.[472] This type of reaction with compounds such as anisole are often called directed metalations.[473] In the case of aromatic rings this means attack at the *ortho*

[456] Jacobson, M.A.; Keresztes, I.; Williard, P.G. *J. Am. Chem. Soc.* ***2005***, *127*, 4965. For a computational study of mixed aggregates of chloromethyllithium and lithium dialkylamides, see Pratt, L.M.; Lê, L.T.; Truong, T.N. *J. Org. Chem.* ***2005***, *70*, 8298. Also see Gupta, L.; Hoepker, A.C.; Singh, K.J.; Collum, D.B. *J. Org. Chem.* ***2009***, *74*, 2231 for a LiCl-catalyzed reaction.

[457] See Saá, J.M.; Martorell, G.; Frontera, A. *J. Org. Chem.* ***1996***, *61*, 5194.

[458] See Durst, T. in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, Vol. 5, pt. B, Elsevier, NY, ***1984***, pp. 239–291 (pp. 265–279). For an article on the safe handling of RLi compounds, see Anderson, R. *Chem. Ind. (London)* ***1984***, 205.

[459] Ivanov, R.; Marek, I.; Cohen, T. *Tetrahedron Lett.* ***2010***, *51*, 174.

[460] See Schlosser, M.; Katsoulos, G.; Takagishi, S. *Synlett,* ***1990***, 747.

[461] Rausch, M.D.; Ciappenelli, D.J. *J. Organomet. Chem.* ***1967***, *10*, 127.

[462] See Klein, J. *Tetrahedron* ***1983***, *39*, 2733; Klein, J. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 343–379.

[463] Hartmann, J.; Schlosser, M. *Helv. Chim. Acta* ***1976***, *59*, 453.

[464] Schlosser, M. *Pure Appl. Chem.* ***1988***, *60*, 1627. For sodium analogs, see Schlosser, M.; Hartmann, J.; Stähle, M.; Kramar, J.; Walde, A.; Mordini, A. *Chimia,* ***1986***, *40*, 306.

[465] Brandsma, L.; Verkruijsse, H.D.; Schade, C.; Schleyer, P.v.R. *J. Chem. Soc., Chem. Commun.* ***1986***, 260.

[466] See Shirley, D.A.; Hendrix, J.P. *J. Organomet. Chem.* ***1968***, *11*, 217.

[467] See Figuly, G.D.; Loop, C.K.; Martin, J.C. *J. Am. Chem. Soc.* ***1989***, *111*, 654; Block, E.; Eswarakrishnan, V.; Gernon, M.; Ofori-Okai, G.; Saha, C.; Tang, K.; Zubieta, J. *J. Am. Chem. Soc.* ***1989***, *111*, 658; Smith, K.; Lindsay, C.M.; Pritchard, G.J. *J. Am. Chem. Soc.* ***1989***, *111*, 665.

[468] See Gilday, J.P.; Negri, J.T.; Widdowson, D.A. *Tetrahedron* ***1989***, *45*, 4605.

[469] See Katritzky, A.R.; Lam, J.N.; Sengupta, S. *Prog. Heterocycl. Chem.* ***1989***, *1*, 1.

[470] Baldwin, J.E.; Höfle, G.A.; Lever Jr., O.W. *J. Am. Chem. Soc.* ***1974***, *96*, 7125.

[471] Bickelhaupt, F.M.; Hermann, H.L.; Boche, G. *Angew. Chem. Int. Ed.* ***2006***, *45*, *823*.

[472] See Beak, P.; Meyers, A.I. *Acc. Chem. Res.* ***1986***, *19*, 356; Narasimhan, N.S.; Mali, R.S. *Top. Curr. Chem.* ***1987***, *138*, 63.

[473] Slocum, D.W.; Coffey, D.S.; Siegel, A.; Grimes, P. *Tetrahedron Lett.* ***1994***, *35*, 389.

position,[474] but this is considered in **13-12**. In the case of γ,δ-unsaturated disubstituted amides, the lithium does not go to the closest position, but in this case too the regiochemistry is controlled by coordination to the oxygen.[475] Cyclopropyllithium reagents are rather stable.[476]

The mechanism involves an attack by R'^- (or a polar R′) on the *hydrogen*[477] (an *acid–base reaction*). Evidence is that resonance effects of substituents in R seem to make little difference. When R is aryl, OMe and CF_3 *both* direct *ortho*, while isopropyl directs *meta* and *para* (mostly *meta*).[478] These results are exactly what would be expected from pure field effects, with no contribution from resonance effects, which implies that attack occurs at the hydrogen and not at R. Other evidence for the involvement of H in the rate-determining step is that there are large isotope effects.[479] The nature of R′ also has an effect on the rate. In the reaction between triphenylmethane and R′Li, the rate decreased in the order R′ = allyl > Bu > Ph > vinyl > Me, although this order changed with changing concentration of R′Li, because of varying degrees of aggregation of the R′Li.[480] With respect to the reagent, this reaction is a special case of **12-24**.

Enantioselective reactions are known. The preparation of chlorodeuteriomethylithium proceeds with inversion from the corresponding enantiopure stannyl derivative.[481] Although highly reactive chemically, it is configurationally stable at temperatures up to −78 °C. Enantioselective catalytic deprotonation with chiral ligands has been used for the deprotonation of *N*-Boc amines to give chiral α-trimethylsilyl derivatives.[482] A barrier to enantiomerization has been observed for unstabilized, chelated, and dipole-stabilized organolithium compounds. Studies of lithiopyrrolidines show free energies for enantiomerization in the range of 19–22 kcal mol^{-1} (79.5–92.1 kJ mol^{-1}) at 0 °C.[483]

OS **II**, 198; **III**, 413, 757; **IV**, 792; **V**, 751; **VI**, 436, 478, 737, 979; **VII**, 172, 334, 456, 524; **VIII**, 19, 391, 396, 606.

12-23 Metalation With Metals and Strong Bases

$$2\,RH + M \longrightarrow 2\,RM + H_2$$

Organic compounds can be metalated at suitably acidic positions by active metals and by strong bases.[484] The reaction has been used to study the acidities of very weak

[474] See Snieckus, V. *Chem. Rev.* ***1990***, *90*, 879; *Pure Appl. Chem.* ***1990***, *62*, 2047. For a discussion of the mechanism, see Bauer, W.; Schleyer, P. v.R. *J. Am. Chem. Soc.* ***1989***, *111*, 7191.

[475] Beak, P.; Hunter, J.E.; Jun, Y.M.; Wallin, A.P. *J. Am. Chem. Soc.* ***1987***, *109*, 5403. See also, Stork, G.; Polt, R.L.; Li, Y.; Houk, K.N. *J. Am. Chem. Soc.* ***1988***, *110*, 8360; Barluenga, J.; Foubelo, F.; Fañanas, F.J.; Yus, M. *J. Chem. Res. (S)* ***1989***, 200.

[476] Peñafiel, I.; Pastor, I.M.; Yus, M. *Tetrahedron* ***2010***, *66*, 2928.

[477] Benkeser, R.A.; Trevillyan, E.A.; Hooz, J. *J. Am. Chem. Soc.* ***1962***, *84*, 4971.

[478] Bryce-Smith, D. *J. Chem. Soc.* ***1963***, 5983; Benkeser, R.A.; Hooz, J.; Liston, T.V.; Trevillyan, E.A. *J. Am. Chem. Soc.* ***1963***, *85*, 3984.

[479] Pocker, Y.; Exner, J.H. *J. Am. Chem. Soc.* ***1968***, *90*, 6764.

[480] West, P.; Waack, R.; Purmort, J.I. *J. Am. Chem. Soc.* ***1970***, *92*, 840.

[481] Kapeller, D.C.; Hammerschmidt, F. *J. Am. Chem. Soc.* ***2008***, *130*, 2329.

[482] McGrath, M.J.; O'Brien, P. *J. Am. Chem. Soc.* ***2005***, *127*, 16378.

[483] Ashweek, J.; Brandt, P.; Coldham, I.; Dufour, S.; Gawley, R.E.; Hæffner, F.; Klein, R.; Sanchez-Jimenezy, G. *J. Am. Chem. Soc.* ***2005***, *127*, 449.

[484] See Durst, T. in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, Vol. 5, pt. B, Elsevier, NY, ***1984***, pp. 239–291; Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, pp. 32–44.

acids (Sec. 5.B.i). The conversion of terminal alkynes to acetylide ions is one important application.[485] A Au-catalyst conversion of trimethylsilyl-substituted esters and carbonates to the corresponding enolate anion has been reported.[486] Synthetically, an important use of the method is to convert aldehydes and ketones,[487] carboxylic esters, and similar compounds to their enolate forms,[488] including β-keto esters and malonate derivatives.

OS **I**, 70, 161, 490; **IV**, 473; **VI**, 468, 542, 611, 683, 709; **VII**, 229, 339.

12.C.ii. Metals as Leaving Groups

A. Hydrogen as the Electrophile

12-24 Replacement of Metals by Hydrogen

$$RM + HA \longrightarrow RH + MA$$

Organometallic compounds, including enolate anions, react with compounds that have an acidic hydrogen in reactions that replace the metal with hydrogen.[489] The R group may be aryl (see **11-38**). The reaction is often used to introduce deuterium or tritium into susceptible positions. For *Grignard reagents*, water is usually a strong enough acid, but stronger acids are also used. An important method for the reduction of alkyl halides consists of the process:

$$RX \rightarrow RMgX \rightarrow RH$$

The organometallic compounds that are hydrolyzed by water are the ones high in the electromotive series: Na, K, Li, Zn, and so on. In other words, this reaction is an acid–base reaction and these organometallics are very basic, and react with the relatively weak acid, water (pK_a, 15.7). Enantioselective protonation of lithium enolates[490] and cyclopropyllithium compounds[491] have been reported. When the metal is less active, the organometallic is less basic and stronger acids are required. For example, R_2Zn compounds react explosively with water, slowly with R_2Cd, and not at all with R_2Hg, although the latter can be cleaved with concentrated HCl. However, this general statement has many exceptions, some hard to explain. For example, BR_3 compounds are completely inert to water, GaR_3 at room temperature cleaves just one R group, but AlR_3 reacts violently with water. However, BR_3 can be converted to RH with carboxylic acids.[492] Organometallic compounds of less active

[485] See Ziegenbein, W. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 170–185. For an improved method, see Fisch, A.; Coisne, J.M.; Figeys, H.P. *Synthesis* ***1982***, 211.

[486] Wang, S.; Zhang, L. *Org. Lett.* ***2006***, *8*, 4585.

[487] Hegarty, A.F.; Dowling, J.P.; Eustace, S.J.; McGarraghy, M. *J. Am. Chem. Soc.* ***1998***, *120*, 2290.

[488] See Caine, D. in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1, Marcel Dekker, NY, ***1979***, pp. 95–145, 284–291.

[489] See Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond,* Vol. 2, Wiley, NY, pp. 25–149, pp. 105–136; Abraham, M.H. in *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H. Eds., Vol. 12, Elsevier, NY, ***1973***, pp. 107–134; Schlosser, M. *Angew. Chem. Int. Ed.* ***1964***, *3*, 287, 362; *Newer Methods Prep. Org. Chem.* ***1968***, *5*, 238.

[490] Mitsuhashi, K.; Ito, R.; Arai, T.; Yanagisawa, A. *Org. Lett.* ***2006***, *8*, 1721.

[491] Walborsky, H.M.; Ollman, J.; Hamdouchi, C.; Topolski, M. *Tetrahedron Lett.* ***1992***, *33*, 761.

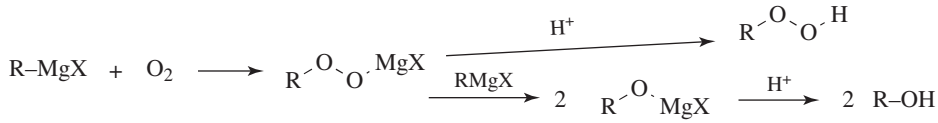
[492] Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, see pp. 242–244.

metals and metalloids (e.g., Si,[493] Sb, and Bi) are quite inert to water. Alkyl–Si bonds are cleaved by H_2SO_4, for example:[494]

$$HOOCCH_2CH_2SiMe_3 \rightarrow 2CH_2 + \left(HOOCCH_2CH_2SiMe_3\right)_2O$$

B. Oxygen Electrophiles

12-25 The Reaction between Organometallic Reagents and Oxygen[495]



Oxygen reacts with *Grignard reagents* to give either hydroperoxides[496] or alcohols. The reaction can be used to convert alkyl halides to alcohols without side reactions. With aryl Grignard reagents, yields are lower and only phenols are obtained, not hydroperoxides. Because of this reaction, oxygen should be excluded when Grignard reagents are prepared and used in various reactions.

Most other organometallic compounds also react with oxygen. In addition, trialkylboranes and alkyldichloroboranes ($RBCl_2$) can be conveniently converted to hydroperoxides by treatment with oxygen followed by hydrolysis.[497] Dilithiated carboxylic acids (see **10-70**) react with oxygen to give α-hydroxy carboxylic acids (after hydrolysis).[498] There is evidence that the reaction between Grignard reagents and oxygen involves a free-radical mechanism.[499]

OS **V**, 918. See also, OS **VIII**, 315.

12-26 Reaction between Organometallic Reagents and Peroxides

A convenient method of preparation of *tert*-butyl ethers consists of treating *Grignard reagents* with *tert*-butyl acyl peroxides.[500] Both alkyl and aryl Grignard reagents can

[493] See Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* ***1989***, *37*, 57, pp. 89–97, 194–243.

[494] Sommer, L.H.; Marans, N.S.; Goldberg, G.M.; Rockett, J.; Pioch, R.P. *J. Am. Chem. Soc.* ***1951***, *73*, 882. See also, Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond,* Vol. 2, Wiley, NY, p. 117.

[495] See Brilkina, T.G.; Shushunov, V.A. *Reactions of Organometallic Compounds with Oxygen and Peroxides*, CRC Press, Boca Raton, FL, ***1969***; Wardell, J.L.; Paterson, E.S. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, see pp. 219–338, pp. 311–316.

[496] See Harada, T.; Kutsuwa, E. *J. Org. Chem.* ***2003***, *68*, 6716.

[497] Brown, H.C.; Midland, M.M. *Tetrahedron* ***1987***, *43*, 4059.

[498] Adam, W.; Cueto, O. *J. Org. Chem.* ***1977***, *42*, 38.

[499] Garst, J.F.; Smith, C.D.; Farrar, A.C. *J. Am. Chem. Soc.* ***1972***, *94*, 7707. See Davies, A.G. *J. Organomet. Chem.* ***1980***, *200*, 87.

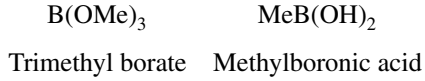
[500] Lawesson, S.; Frisell, C.; Denney, D.B.; Denney, D.Z. *Tetrahedron* ***1963***, *19*, 1229. See Brilkina, T.G.; Shushunov, V.A. *Reactions of Organometallic Compounds with Oxygen and Peroxides*, CRC Press, Boca Raton,

be used. The application of this reaction to Grignard reagents prepared from cyclopropyl halides permits cyclopropyl halides to be converted to *tert*-butyl ethers of cyclopropanols,[501] which can then be easily hydrolyzed to the cyclopropanols. The direct conversion of cyclopropyl halides to cyclopropanols by **10-1** is not generally feasible, because cyclopropyl halides do not generally undergo nucleophilic substitutions without ring opening.

Vinyllithium reagents react with silyl peroxides to give high yields of silyl enol ethers with retention of configuration.[502] Dialky ethers have been prepared from organotrifluoroborates and acetals.[503]

OS **V**, 642, 924.

12-27 Preparation of Boranes, Boronic Acids, and Borates



Trimethyl borate Methylboronic acid

Work continues on the preparation of organoborane and derivatives. Alkyl bromides reacted with B_2Pin_2 in the presence of a Pd catalyst to give RBPin.[504] Aniline derivatives *t*-BuONO and B_2Pin_2 give the arylboronate.[505] Aryl halides reacted with bis(pinacolato)diboron and then irradiation with visible light with tributylamine and an Ir catalyst and then exposure to air is give the phenol.[506]

Organoboron compounds, including alkylboronic acids and arylboronic acids[507] [$RB(OH)_2$ and $ArB(OH)_2$, respectively], are increasingly important in organic chemistry.[508] The Pd-catalyzed coupling reaction of aryl halides and aryl triflates with arylboronic acids (the *Suzuki-Miyaura reaction*, **13-11**) is probably the most notable example. A simple synthesis involves the reaction of a *Grignard reagent*, such as phenylmagnesium bromide, with an alkyl borate to give phenylboronic acid.[509] Alkylboronic acids are similarly prepared.[510] Note that boronic acids are subject to cyclic trimerization with loss of water to form boroxines. Tetrahydroxydiboron has been used to prepare allylboronic acids, as well as potassium trifluoro(allyl)borates.[511] Alkylboronic acids are oxidized to the corresponding alcohol by treatment with hydrogen peroxide and dimethyl carbonate.[512] Borinic acids and borinates were prepared using amine–borane complexes as a water- and air-insensitive

FL, ***1969***; Razuvaev, G.A.; Shushunov, V.A.; Dodonov, V.A.; Brilkina, T.G. in Swern, D. *Organic Peroxides*, Vol. 3, Wiley, NY, ***1972***, pp. 141–270.

[501] Longone, D.T.; Miller, A.H. *Tetrahedron Lett.* ***1967***, 4941.

[502] Davis, F.A.; Lal, G.S.; Wei, J. *Tetrahedron Lett.* ***1988***, *29*, 4269.

[503] Mitchell, T.A.; Bode, J.W. *J. Am. Chem. Soc.* ***2009***, *131*, 18057.

[504] Joshi-Pangu, A.; Ma, X.; Diane, M.; Iqbal, S.; Kribs, R.J.; Huang, R.; Wang, C.-Y.; Biscoe, M.R. *J. Org. Chem.* ***2012***, *77*, 6629.

[505] Qiu, D.; Jin, L.; Zheng, Z.; Meng, H.; Mo, F.; Xi, X.; Zhang, Y.; Wang, J. *J. Org. Chem.* ***2013***, *78*, 1923.

[506] Jiang, M.; Yang, H.; Fu, H. *Org. Lett.* ***2016***, *18*, 5248.

[507] Xu, L.; Wang, G.; Zhang, S.; Wang, H.; Wang, L.; Liu, L.; Jiao, J.; Li, P. *Tetrahedron* ***2017***, *73*, 7123.

[508] See Cazorla, C.; Métay, E.; Lemaire, M. *Tetrahedron* ***2011***, *67*, 8615. Also see Cid, J.; Carbó, J.J.; Fernández, E. *Chem. Eur. J.* ***2012***, *18*, 12794. See Smith, K.; Balakit, A.A.; El-Hiti, G.A. *Tetrahedron* ***2012***, *68*, 7834. Fernández, E.; Whiting, A. (Eds.) *Synthesis and Application of Organoboron Compounds*, Springer, New York, ***2015***.

[509] Bean, F.R.; Johnson, J.R. *J. Am. Chem Soc.* ***1932***, *54*, 4415; Lappert, M.F. *Chem. Rev.* ***1956***, *56*, 959.

[510] Khotinsky, E.; Melamed, M. *Chem. Ber.* ***1909***, *42*, 3090.

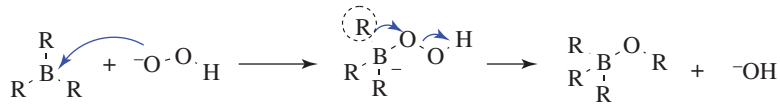
[511] Sebelius, S.; Olsson, V.J.; Szabó, K.J. *J. Am. Chem. Soc.* ***2005***, *127*, 10478.

[512] Wagh, R.B.; Nagarkar, J.M. *Tetrahedron. Lett.* ***2017***, *58*, 4572.

borylating agent.[513] Boronic acids have been prepared using continuous flow techniques (Sec. 7.D).[514]

Alkeneboronic esters and acids are also readily available, for example, by the addition of vinylmagnesium chloride[515] to trimethyl borate below −50 °C, followed by hydrolysis.[516] A nonaqueous workup procedure has been reported for the preparation of arylboronic esters [ArB(OR′$_2$)].[517] Uncontrollable polymerization or oxidation of much of the boronic acid occurred during the final stages of the isolation procedure, but could be avoided by *in situ* conversion to the dibutyl ester by adding the crude product to butan-1-ol. The Sm-catalyzed hydroboration of olefins with catecholborane is a good synthesis of boronate esters.[518]

The reaction of alkenes with borane, monoalkylboranes, and dialkylboranes leads to a new organoborane (see **15-11**). Treatment of organoboranes with alkaline H_2O_2 oxidizes trialkylboranes to esters of boric acid.[519] This reaction does not affect double or triple bonds, aldehydes, ketones, halides, or nitriles that may be present elsewhere in the molecule. While the R group migrates from boron to oxygen,[465] as shown, which led to the B—O—R unit, there is no rearrangement of the R group itself. This reaction is a step in the hydroboration method of converting alkenes to alcohols (**15-11**). The mechanism has been formulated as involving initial formation of an "ate" complex when the hydroperoxide anion attacks the electrophilic boron atom. Rearrangement follows:



Similar migration of the other two R groups and hydrolysis of the B—O bonds leads to the alcohol and boric acid. Retention of configuration is observed in R. Boranes can also be oxidized to borates in good yields with oxygen,[520] with sodium perborate ($NaBO_3$),[521] and with trimethylamine oxide, either anhydrous[522] or in the form of the dihydrate.[523] The reaction with oxygen is free radical in nature.[524]

OS **V**, 918; **VI**, 719, 852, 919.

Trimethylborate, $B(OMe)_3$, can be used in place of tri-*n*-butylborate.[525] Newer methods involve the Pd-mediated borylation of alcohols with bis(pinacolato)diboron[526] or pinacolborane,[527] but deprotection of the boronate esters can be a problem. Diolboranes, such

[513] Richard, J.; Birepinte, M.; Charbonnier, J.B.; Liautard, V.; Pinet, S.; Pucheault, M. *Synthesis* ***2017***, *49*, 736.
[514] Hafner, A.; Meisenbach, M.; Sedelmeier, J. *Org. Lett.* ***2016***, *18*, 3630.
[515] Ramsden, H.E.; Leebrick, J.R.; Rosenberg, S.D.; Miller, E.H.; Walburn, J.J.; Balint, A.E.; Cserr, R. *J. Org. Chem.* ***1957***, *22*, 1602.
[516] Matteson, D.S. *Acc. Chem. Res.* ***1970***, *3*, 186; Matteson, D.S. *Progr. Boron Chem.* ***1970***, *3*, 117.
[517] Wong, K.-T.; Chien, Y.-Y.; Liao, Y.-L.; Lin, C.-C.; Chou, M.-Y.; Leung, M.-K. *J. Org. Chem.* ***2002***, *67*, 1041.
[518] Evans, D.A.; Muci, A.R.; Stuermer, R. *J. Org. Chem.* ***1993***, *58*, 5307.
[519] See Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 244–249; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 321–325. See also, Brown, H.C.; Snyder, C.; Subba Rao, B.C.; Zweifel, G. *Tetrahedron* ***1986***, *42*, 5505.
[520] Brown, H.C.; Midland, M.M.; Kabalka, G.W. *Tetrahedron* ***1986***, *42*, 5523.
[521] Kabalka, G.W.; Shoup, T.M.; Goudgaon, N.M. *J. Org. Chem.* ***1989***, *54*, 5930.
[522] Köster, R.; Arora, S.; Binger, P. *Angew. Chem. Int. Ed.* ***1969***, *8*, 205.
[523] Kabalka, G.W.; Slayden, S.W. *J. Organomet. Chem.* ***1977***, *125*, 273.
[524] Midland, M.M.; Brown, H.C. *J. Am. Chem. Soc.* ***1971***, *93*, 1506.
[525] Soloway, A.H. *J. Am. Chem. Soc.* ***1959***, *81*, 3017.
[526] Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* ***1995***, *60*, 7508.
[527] Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* ***2000***, *65*, 164; Song, Y.L. *Synlett* ***2000***, 1210.

as catecholborane **21**,[528] are prepared by the reaction of a diol with borane. Boronate esters are often prepared as a means to purify the organoboron species, but some of these esters are hydrolytically unstable and difficult to deal with upon completion of the reaction.[529]

21

Trialkyl borates (sometimes called orthoborates) can be prepared by heating the appropriate alcohol with boron trichloride in a sealed tube, but the procedure works well only for relatively simple alkyl groups.[530] Heating alcohols with boron trioxide (B_2O_3) in an autoclave at 110–170 °C gives the trialkyl borate.[531]

Alkenyl boronic esters have been prepared from alkenes using a modified Heck reaction (**13-13**).[532] 3-Nitrophenyl allylic ethers reacted with a Cu/N-heterocyclic carbene catalyst and B_2Pin_2, 30% NaO*t*-Bu, and 2 equivalents of methanol to give the allyl boronate.[533] Cyclopropenes reacted with B_2Pin_2 and a Cu catalyst and in the presence of the ligand (*R*)-di(3,5-di-*t*-butyl-4-methoxyphenyl)-Segphos in methanol to give the cyclopropylboronate.[534] Benzylic ammonium triflates reacted with B_2Pin_2 using a Ni catalyst to give the benzylic boronate.[535] 3,3-Disubstituted allyl boronates have been prepared for the construction of quaternary centers.[536] Stereospecific functionalization and transformation of boronic esters has been discussed.[537] Chiral organoboronates have been prepared using a Suzuki reaction (**13-11**).[538] Allylic chlorides have been converted to allylic boronates with a Pd catalyst and B_2Pin_2, whereas the use of a Ni catalyst allowed allylic acetates to be converted to allylic boronates.[539] Hydroboration of 1,3-enyne compounds with B_2Pin_2 and a Cu catalyst gave 1,2-additon of the alkyne unit and formation of the vinylboronate diene when triphenylphosphine was used as the ligand, whereas the use of diphosphine led to addition of the C=C unit and formation of the homopropargyl boronate.[540,541]

Potassium organotrifluoroborates (RBF_3K) are readily prepared by the addition of inexpensive KHF_2 to a variety of organoboron intermediates.[542] They are monomeric crystalline solids that are readily isolated and indefinitely stable in the air. These reagents can be used

[528] Kanth, J.V.B.; Periasamy, M.; Brown, H.C. *Org. Process Res. Dev.* ***2000***, *4*, 550.
[529] Lightfoot, A.P.; Maw, G.; Thirsk, C.; Twiddle, S.J.R.; Whiting, A. *Tetrahedron Lett.* ***2003***, *44*, 7645.
[530] Councler, C. *Ber.* ***1876***, *9*, 485; ***1877***, *10*, 1655; ***1878***, *11*, 1106.
[531] Schiff, H. *Ann. Suppl.* ***1867***, *6*, 158; Councler, C. *J. Prakt. Chem.* ***1871***, *16*, 371.
[532] Reid, W.B.; Spillane, J.J.; Krause, S.B.; Watson, D.A. *J. Am. Chem. Soc.* ***2016***, *138*, 5539.
[533] Park, J.K.; Lackey, H.H.; Ondrusek, B.A.; McQuade, D.T. *J. Am. Chem. Soc.* ***2011***, *133*, 2410.
[534] Parra, A.; Amenós, L.; Guisán-Ceinos, M.; López, A.; García-Ruano, J.L.; Tortosa, M. *J. Am. Chem. Soc.* ***2014***, *136*, 15833.
[535] Basch, C.H.; Cobb, K.M.; Watson, M.P. *Org. Lett.* ***2016***, *18*, 136.
[536] Biggs, R.A.; Lambadaris, M.; Ogilvie, W.W. *Tetrahedron Lett.* ***2014***, *55*, 6085.
[537] Sandford, C.; Aggarwal, V.K. *Chem. Commun.* ***2017***, *53*, 5481.
[538] Sun, C.; Potter, B.; Morken, J.P. *J. Am. Chem. Soc.* ***2014***, *136*, 6534. For the use of boronic esters in asymmetric synthesis, see Matteson, D.S. *J. Org. Chem.* ***2013***, *78*, 10009.
[539] Zhang, P.; Roundtree, I.A.; Morken, J.P. *Org. Lett.* ***2012***, *14*, 1416.
[540] Sasaki, Y.; Horita, Y.; Zhong, C.; Sawamura, M.; Ito, H. *Angew. Chem. Int. Ed.* ***2011***, *50*, 2778.
[541] Cho, S.H.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2013***, *135*, 8157.
[542] Vedejs, E.; Fields, S.C.; Hayashi, R.; Hitchcock, S.R.; Powell, D.R.; Schrimpf, M.R. *J. Am. Chem. Soc.* ***1999***, *121*, 2460.

in several of the applications where boronic acids or esters are used.[543] Note that vinylboronic acid and even vinylboronate esters are unstable to polymerization,[544] whereas the analogous vinyltrifluoroborate is readily synthesized and completely stable.[545] Aryl chlorides reacted with diboronic acid [$B_2(OH)_4$] and a Pd catalyst to give the arylboronic acid, and subsequent reaction with KHF_2 gave the potassium aryltrifluoroborate.[546] Acyltrifluoroborates have been prepared.[547]

OS **13**, 16; ***81***, 134.

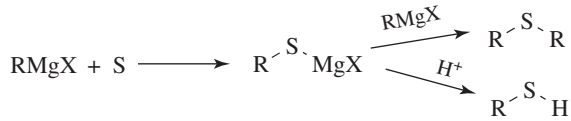
12-28 Oxygenation of Organometallic Reagents and Other Substrates to *O*-Esters and Related Compounds

$$\text{R—M} \longrightarrow \text{R—OOCR}' \qquad \text{R—Y} \longrightarrow \text{R—OOCR}'$$

In some cases, it is possible to oxygenate a nonaromatic carbon atom using various reagents, where the product is an *O*-ester rather than an alcohol. In one example, a vinyl iodonium salt was heated with DMF to product the corresponding formate ester.[548]

C. Sulfur Electrophiles

12-29 Conversion of Organometallic Reagents to Sulfur Compounds



Thiols and sulfides are occasionally prepared by treatment of *Grignard reagents* with sulfur.[549] Analogous reactions are known for selenium and tellurium compounds. Grignard reagents and other organometallic compounds[550] react with sulfuryl chloride to give sulfonyl chlorides,[551] with esters of sulfinic acids to give (stereospecifically) sulfoxides,[552] with disulfides to give sulfides,[553] and with SO_2 to give sulfinic acid salts[554] that can be hydrolyzed to sulfinic acids or treated with halogens to give sulfonyl halides.[555]

OS **III**, 771; **IV**, 667; **VI**, 533, 979.

[543] Molander, G.A.; Biolatto, B. *J. Org. Chem.* ***2003***, *68*, 4302; Molander, G.A.; Yun, C.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* ***2003***, *68*, 5534; Molander, G.A.; Ribagorda, M. *J. Am. Chem. Soc.* ***2003***, *125*, 11148.
[544] Matteson, D. S. *J. Am. Chem. Soc.* ***1960***, *82*, 4228.
[545] Molander, G.A.; Felix, L.A. *J. Org. Chem.* ***2005***, *70*, 3950.
[546] Pilarski, L.T.; Szabó, K.J. *Angew. Chem. Int. Ed.* ***2011***, *50*, 8230.
[547] See Liu, S.M.; Mazunin, D.; Pattabiraman, V.R.; Bode, J.W. *Org. Lett.* ***2016***, *18*, 5336.
[548] Ochiai, M.; Yamamoto, S.; Sato, K. *Chem. Commun.* ***1999***, 1363.
[549] See Wardell, J.L.; Paterson, E.S. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 316–323; Wardell, J.L. in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, ***1974***, pp. 211–215; Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, pp. 135–142.
[550] Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 210–216.
[551] Bhattacharya, S.N.; Eaborn, C.; Walton, D.R.M. *J. Chem. Soc. C* ***1968***, 1265. For similar reactions with organolithium reagents, see Hamada, T.; Yonemitsu, O. *Synthesis* ***1986***, 852.
[552] Harpp, D.N.; Vines, S.M.; Montillier, J.P.; Chan, T.H. *J. Org. Chem.* ***1976***, *41*, 3987.
[553] See Negishi, E. *Organometallics in Organic Synthesis*, Wiley, NY, ***1980***, pp. 243–247.
[554] See Kitching, W.; Fong, C.W. *Organomet. Chem. Rev. Sect. A* ***1970***, *5*, 281.
[555] Asinger, F.; Laue, P.; Fell, B.; Gubelt, C. *Chem. Ber.* ***1967***, *100*, 1696.

D. Halogen Electrophiles

12-30 Halo-de-metalation

$$RMgX + I_2 \longrightarrow RI + MgIX$$

Grignard reagents react with halogens to give alkyl halides. The reaction is useful for the preparation of iodo compounds from the corresponding chloro or bromo compounds. The reaction is not useful for preparing chlorides, since the reagents RMgBr and RMgI react with Cl_2 to give mostly RBr and RI, respectively.[556]

Most organometallic compounds, both alkyl and aryl, also react with halogens to give alkyl or aryl halides.[557] The reaction can be used to convert acetylide ions to 1-haloalkynes.[558] Vinyliodonium tetrafluoroborates were converted to vinyl fluorides by heating.[559] Similarly, vinyl trifluoroborates were converted to the vinyl iodide with NaI and chloramine-T in aqueous THF.[560] The reaction of an alkene with $CuO{\bullet}BF_4$, iodine, and triethylsilane gave the 2-iodoalkane.[561] Vinylzirconate reagents react with I_2 to give the corresponding vinyl iodide.[562]

Trialkylboranes react rapidly with I_2[563] or Br_2[564] in the presence of NaOMe in methanol, or with $FeCl_3$ or other reagents,[565] to give alkyl iodides, bromides, or chlorides, respectively. Combined with the hydroboration reaction (**15-11**), this is an indirect way of adding HBr, HI, or HCl to a double bond to give products with an anti-Markovnikov orientation (see **15-1**). Trialkylboranes can also be converted to alkyl iodides by treatment with allyl iodide and air in a free-radical process.[566] *trans*-1-Alkenylboronic acids were prepared by hydroboration of terminal alkynes with catecholborane (**15-11**) followed by hydrolysis,[567] and subsequent reaction with I_2 in the presence of NaOH at 0 °C in ethereal solvents to give *trans*-vinylic iodides.[568] Treatment with ICl also gives the vinyl iodide.[569] This is an indirect way of accomplishing the anti-Markovnikov addition of HI to a terminal triple bond. The reaction cannot be applied to alkenylboronic acids prepared from internal alkynes.

[556] Zakharkin, L.I.; Gavrilenko, V.V.; Paley, B.A. *J. Organomet. Chem.* ***1970***, *21*, 269.
[557] See Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, pp. 72–105; Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 158–178; Makarova, L.G. *Organomet. React.* ***1970***, *1*, 119 (pp. 325–348).
[558] See Delavarenne, S.Y.; Viehe, H.G. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 665–688. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley-VCH, NY, ***1999***, pp. 655–656. For an improved procedure, see Brandsma, L.; Verkruijsse, H.D. *Synthesis* ***1990***, 984.
[559] Okuyama, T.; Fujita, M.; Gronheid, R.; Lodder, G. *Tetrahedron Lett.* ***2000***, *41*, 5125.
[560] Kabalka, G.W.; Mereddy, A.R. *Tetrahedron Lett.* ***2004***, *45*, 1417.
[561] Campos, P.J.; García, B.; Rodríguez, M.A. *Tetrahedron Lett.* ***2002***, *43*, 6111.
[562] Zhang, D.; Ready, J.M. *J. Am. Chem. Soc.* ***2007***, *129*, 12088.
[563] Brown, H.C.; Rathke, M.W.; Rogic, M.M.; De Lue, N.R. *Tetrahedron* ***1988***, *44*, 2751.
[564] Brown, H.C.; Lane, C.F.; De Lue, N.R. *Tetrahedron* ***1988***, *44*, 2273. Also see Nelson, D.J.; Soundararajan, R. *J. Org. Chem.* ***1989***, *54*, 340.
[565] Nelson, D.J.; Soundararajan, R. *J. Org. Chem.* ***1988***, *53*, 5664. For other reagents, see Jigajinni, V.B.; Brown, H.C.; De Lue, N.R. *Tetrahedron* ***1988***, *44*, 2785.
[566] Brown, H.C.; Midland, M.M. *Angew. Chem. Int. Ed.* ***1972***, *11*, 692 (pp. 699–700); Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithica, NY, ***1972***, pp. 442–446.
[567] See Kabalka, G.W. *Org. Prep. Proced. Int.* ***1977***, *9*, 131.
[568] Brown, H.C.; Hamaoka, T.; Ravindran, N.; Subrahmanyam, C.; Somayaji, V.; Bhat, N.G. *J. Org. Chem.* ***1989***, *54*, 6075.
[569] Stewart, S.K.; Whiting, A. *Tetrahedron Lett.* ***1995***, *36*, 3929.

However, alkenylboronic acids prepared from both internal and terminal alkynes react with Br_2 (2 molar equivalents of Br_2 must be used), followed by base, to give the corresponding vinylic bromide, but in this case with *inversion* of configuration; so the product is the *cis* vinylic bromide.[570] Alkenylboronic acids also give vinylic bromides and iodides when treated with a mild oxidizing agent and NaBr or NaI, respectively.[571] Vinylic boranes can be converted to the corresponding vinylic halide by treatment with NCS or NBS.[572] Vinylic halides can also be prepared from vinylic silanes[573] and from vinylic copper reagents. The latter react with I_2 to give iodides,[574] and with NCS or NBS at −45 °C to give chlorides or bromides.[575] Boronic acids can be fluorinated in a reaction mediated by silver(I) triflate.[576]

The conversion of terminal alkynes to 1-iodo-1-alkynes was reported using NaI under electrochemical conditions.[577] 1-Bromo-1-alkynes were converted to the 1-iodo-1-alkyne with CuI.[578] 1-Trialkyldisilylalkynes were converted to the corresponding 1-bromoalkyne via reaction with NBS and AgF.[579] Terminal alkynes react with (diacetoxyiodo)benzene, KI, and CuI to give 1-iodoalkynes.[580] Trichloroisocyanuric acid has been used to convert terminal alkynes to 1-chloroalkynes.[581]

It is unlikely that a single mechanism suffices to cover all conversions of organometallic compounds to alkyl halides.[582] In a number of cases, the reaction has been shown to involve inversion of configuration (Sec. 12.A.i), indicating an S_E2 (back) mechanism, while in other cases retention of configuration has been shown,[583] implicating an S_E2 (front) or S_Ei mechanism. In still other cases, complete loss of configuration as well as other evidence demonstrated the presence of a free-radical mechanism.[583,584]

OS **I**, 125, 325, 326; **III**, 774, 813; **V**, 921; **VI**, 709; **VII**, 290; **VIII**, 586; **IX**, 573. Also see, OS **II**, 150.

E. Nitrogen Electrophiles

12-31 The Conversion of Organometallic Compounds to Amines

$$\mathrm{RLi} \xrightarrow[\mathrm{MeLi}]{\mathrm{CH_3ONH_2}} \mathrm{RNH_2}$$

[570] Brown, H.C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* ***1973***, *95*, 6456. See also, Brown, H.C.; Bhat, N.G. *Tetrahedron Lett.* ***1988***, *29*, 21.
[571] See Kabalka, G.W.; Sastry, K.A.R.; Knapp, F.F.; Srivastava, P.C. *Synth. Commun.* ***1983***, *13*, 1027.
[572] Hoshi, M.; Shirakawa, K. *Tetrahedron Lett.* ***2000***, *41*, 2595.
[573] See Chou, S.P.; Kuo, H.; Wang, C.; Tsai, C.; Sun, C. *J. Org. Chem.* ***1989***, *54*, 868.
[574] Normant, J.F.; Chaiez, G.; Chuit, C.; Villieras, J. *J. Organomet. Chem.* ***1974***, *77*, 269; *Synthesis* ***1974***, 803.
[575] Westmijze, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* ***1977***, *96*, 168; Levy, A.B.; Talley, P.; Dunford, J.A. *Tetrahedron Lett.* ***1977***, 3545.
[576] Furuya, T.; Ritter, T. *Org. Lett.* ***2009***, *11*, 2860.
[577] Nishiguchi, I.; Kanbe, O.; Itoh, K.; Maekawa, H. *Synlett* ***2000***, 89.
[578] Abe, H.; Suzuki, H. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 787.
[579] Lee, T.; Kang, H.R.; Kim, S.; Kim, S. *Tetrahedron* ***2006***, *62*, 4081.
[580] Yan, J.; Li, J.; Cheng, D. *Synlett* ***2007***, 2442.
[581] Vilhelmsen, M.H.; Andersson, A.S.; Nielsen, M.B. *Synthesis* ***2009***, 1469.
[582] See Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond,* Vol. 2, Wiley, NY, p. 72; Abraham, M.H. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 12, Elsevier, NY, ***1973***, pp. 135–177; Jensen, F.R.; Rickborn, B. *Electrophilic Substitution of Organomercurials*, McGraw-Hil, NY, ***1968***, pp. 75–97.
[583] See Jensen, F.R.; Gale, L.H. *J. Am. Chem. Soc.* ***1960***, *82*, 148.
[584] See de Ryck, P.H.; Verdonck, L.; van der Kelen, G.P. *Bull. Soc. Chim. Belg.* ***1985***, *94*, 621.

There are several methods for the conversion of alkyl- or aryllithium compounds to primary amines.[585] The two most important are treatment with hydroxylamine derivatives and with certain azides.[586] First, treatment of RLi with methoxyamine and MeLi in ether at −78 °C gives RNH_2.[587] *Grignard reagents* from aliphatic halides give lower yields. The reaction can be extended to give secondary amines by the use of *N*-substituted methoxyamines CH_3ONHR'.[588] There is evidence[589] that the mechanism involves the direct displacement of OCH_3 by R on an intermediate $CH_2ONR'^-$:

$$CH_2ONR'^-Li^+ + RLi \rightarrow CH_3OLi + RNR'^-Li^+$$

Tosyl azide (TsN_3) is a highly useful azide.[590] The initial product is usually RN_3, but this is easily reduced to the amine (**19-55**). With some azides, such as azidomethyl phenyl sulfide ($PhSCH_2N_3$), the group attached to the N_3 is a poor leaving group, so the initial product is a triazene (in this case $ArNHN{=}NCH_2SPh$ from ArMgX), which can be hydrolyzed to the amine.[591]

Organoboranes react with a mixture of aqueous NH_3 and NaOCl to produce primary amines.[592] It is likely that the actual reagent is chloramine (NH_2Cl). Chloramine itself,[593] hydroxylamine-*O*-sulfonic acid in diglyme,[594] and trimethylsilyl azide[595] also give the reaction. Since the boranes can be prepared by the hydroboration of alkenes (**15-11**), this is an indirect method for the addition of NH_3 to a double bond with *anti-Markovnikov* orientation. Secondary amines can be prepared[596] by the treatment of alkyl- or aryldichloroboranes or dialkylchloroboranes with alkyl or aryl azides. The use of an optically active R^*BCl_2 gave secondary amines of essentially 100% optical purity.[597] Aryllead triacetates, $ArPb(OAc)_3$, give secondary amines (ArNHAr′) when treated with primary aromatic amines $Ar'NH_2$ and $Cu(OAc)_2$.[598]

Metal-catalyzed amination reactions are increasingly important in organic methodology. In a typical reaction, an amine is coupled to an alkyl, vinyl, or aryl halide (or with a different leaving group) in the presence of a transition metal, usually Pd. Presumably, the amination occurs via reaction with a transient organometallic species. In one example, a vinyl triflate is converted to an enamine via reaction with pyrrole in the presence of a Pd catalyst.[599]

[585] See Erdik, E.; Ay, M. *Chem. Rev.* ***1989***, *89*, 1947.
[586] See Genet, J.P.; Mallart, S.; Greck, C.; Piveteau, E. *Tetrahedron Lett.* ***1991***, *32*, 2359.
[587] Beak, P.; Kokko, B.J. *J. Org. Chem.* ***1982***, *47*, 2822; Colvin, E.W.; Kirby, G.W.; Wilson, A.C. *Tetrahedron Lett.* ***1982***, *23*, 3835; See Boche, G.; Schrott, W. *Tetrahedron Lett.* ***1982***, *23*, 5403.
[588] Kokko, B.J.; Beak, P. *Tetrahedron Lett.* ***1983***, *24*, 561.
[589] Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* ***1986***, *108*, 6016.
[590] Reed, J.N.; Snieckus, V. *Tetrahedron Lett.* ***1983***, *24*, 3795; Mori, S.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* ***1984***, *25*, 429.
[591] Trost, B.M.; Pearson, W.H. *J. Am. Chem. Soc.* ***1981***, *103*, 2483; ***1983***, *105*, 1054.
[592] Kabalka, G.W.; Wang, Z.; Goudgaon, N.M. *Synth. Commun.* ***1989***, *19*, 2409. See Kabalka, G.W.; Wang, Z. *Synth. Commun.* ***1990***, *20*, 231.
[593] Brown, H.C.; Heydkamp, W.R.; Breuer, E.; Murphy, W.S. *J. Am. Chem. Soc.* ***1964***, *86*, 3565.
[594] Brown, H.C.; Kim, K.; Srebnik, M.; Singaram, B. *Tetrahedron* ***1987***, *43*, 4071.
[595] Kabalka, G.W.; Goudgaon, N.M.; Liang, Y. *Synth. Commun.* ***1988***, *18*, 1363.
[596] Carboni, B.; Vaultier, M.; Courgeon, T.; Carrié, R. *Bull. Soc. Chim. Fr.* ***1989***, 844.
[597] Brown, H.C.; Salunkhe, A.M.; Singaram, B. *J. Org. Chem.* ***1991***, *56*, 1170.
[598] Barton, D.H.R.; Donnelly, D.M.X.; Finet, J.; Guiry, P.J. *Tetrahedron Lett.* ***1989***, *30*, 1377.
[599] Movassaghi, M.; Ondrus, A.E. *J. Org. Chem.* ***2005***, *70*, 8638.

Aryl and heteroaryl aluminum compounds reacted with *N*,*N*-dialkyl-*O*-benzoylhydroxylamines, in the presence of a CuI catalyst, to give the arylamine.[600] The reaction of secondary amines with NCS and then arylmagnesium halides with Ti(O*i*-Pr)$_4$ gave the arylamine.[601] Secondary amines have been converted to tertiary amines by treatment with lithium dialkylcuprate reagents:[602]

$$R_2CuLi + NHR \rightarrow RNR'_2$$

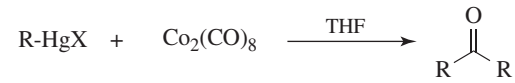
The reaction was also used to convert primary amines to secondary ones, but yields were lower.[603]

Terminal alkynes reacted with chlorodiphenylphosphine (Ph_2PCl) and a Ni catalyst to give the 1-diphenylphosphino alkyne (R—C≡C—PPh_2).[604] Alkynyl halides can be used for a similar reaction. Treatment of methyl carbamates with KHMDS and CuI, followed by 2 equivalents of 1-bromo phenylacetylene gave the *N*-substituted alkyne, Ph—C≡C—N(CO_2Me)R.[605]

OS **VI**, 943.

F. Carbon Electrophiles

12-32 The Conversion of Organometallic Compounds to Ketones, Aldehydes, Carboxylic Esters, or Amides



Symmetrical ketones[606] can be prepared in good yields by the reaction of organomercuric halides[607] with dicobalt octacarbonyl in THF,[608] or with nickel carbonyl in DMF or certain other solvents.[609] The R group may be aryl or alkyl. However, when R is alkyl, rearrangements may intervene in the $Co_2(CO)_8$ reaction, although the $Ni(CO)_4$ reaction seems to be free from such rearrangements.[610] Divinylic ketones (useful in the *Nazarov cyclization*, **15-15**) have been prepared in high yields by treatment of vinylic mercuric halides with CO and a Rh catalyst.[610]

[600] Zhou, S.; Yang, Z.; Chen, X.; Li, Y.; Zhang, L.; Fang, H.; Wang, W.; Zhu, X.; Wang, S. *J. Org. Chem.* ***2015***, *80*, 6323.
[601] Barker, T.J.; Jarvo, E.R. *Angew. Chem. Int. Ed.* ***2011***, *50*, 8325.
[602] Yamamoto, H.; Maruoka, K. *J. Org. Chem.* ***1980***, *45*, 2739.
[603] Merkushev, E.B. *Synthesis* ***1988***, 923.
[604] Beletskaya, I.P.; Affanasiev, V.V.; Kazankova, M.A.; Efimova, I.V. *Org. Lett.* ***2003***, *5*, 4309.
[605] Dunetz, J.R.; Danheiser, R.L. *Org. Lett.* ***2003***, *5*, 4011.
[606] See Narayana, C.; Periasamy, M. *Synthesis* ***1985***, 253; Gulevich, Yu.V.; Bumagin, N.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1988***, *57*, 299.
[607] See Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***; Larock, R.C. *Tetrahedron* ***1982***, *38*, 1713; *Angew. Chem. Int. Ed.* ***1978***, *17*, 27.
[608] Seyferth, D.; Spohn, R.J. *J. Am. Chem. Soc.* ***1969***, *91*, 3037.
[609] Ryu, I.; Ryang, M.; Rhee, I.; Omura, H.; Murai, S.; Sonoda, N. *Synth. Commun.* ***1984***, *14*, 1175 and references cited therein. For another method, see Hatanaka, Y.; Hiyama, T. *Chem. Lett.* ***1989***, 2049.
[610] Larock, R.C.; Hershberger, S.S. *J. Org. Chem.* ***1980***, *45*, 3840.

In a more general synthesis of unsymmetrical ketones, tetraalkyltin compounds (R_4Sn) are treated with a halide R′X (R′ = aryl, vinylic, benzylic), CO, and a Pd-complex catalyst.[611] Similar reactions use *Grignard reagents*, $Fe(CO)_5$, and an alkyl halide.[612]

Grignard reagents react with formic acid to give good yields of aldehydes. Two molar equivalents of RMgX are used; the first converts HCO_2H to $HCOO^-$, which reacts with the second equivalent to give RCHO.[613] Alkyllithium reagents and Grignard reagents react with CO to give symmetrical ketones.[614] An interesting variation reacts CO_2 with an organolithium, which is then treated with a different organolithium reagent to give the unsymmetrical ketone.[615] α,β-Unsaturated aldehydes can be prepared by treatment of vinylic silanes with dichloromethyl methyl ether and $TiCl_4$ at −90 °C.[616] Continuous flow techniques (Sec. 7.D) were used to prepare ketones with CO_2 and organolithium reagents or Grignard reagents.[617] Alkyl and aryl Grignard reagents can be converted to carboxylic esters with $Fe(CO)_5$ instead of CO.[618]

α,β-Unsaturated esters can be prepared by treating boronic esters with CO, $PdCl_2$, and NaOAc in MeOH.[619] The synthesis of α,β-unsaturated esters has also been accomplished by treatment of vinylic mercuric chlorides with CO at atmospheric pressure and a Pd catalyst in an alcohol as solvent, for example.[620]

Amides have been prepared by the treatment of trialkyl or triarylboranes with CO and an imine, in the presence of catalytic amounts of cobalt carbonyl.[621] In another method for the conversion RM → RCONR, *Grignard reagents* and organolithium compounds are treated with a formamide ($HCONR'_2$) to give the intermediate $RCH(OM)NR'_2$, which is not isolated but instead is treated with PhCHO or Ph_2CO to give the product $RCONR'_2$.[622]

Direct conversion of a hydrocarbon to an aldehyde

$$R{-}H \rightarrow R{-}CHO$$

was reported by treatment of the hydrocarbon with $GaCl_3$ and CO.[623]

OS **VIII**, 97.

12-33 Cyano-de-metalation

$$R\text{-}M + CuCN \longrightarrow R\text{-}CN$$

[611] Tanaka, M. *Tetrahedron Lett.* ***1979***, 2601.
[612] Yamashita, M.; Suemitsu, R. *Tetrahedron Lett.* ***1978***, 761. See also, Vitale, A.A.; Doctorovich, F.; Nudelman, N.S. *J. Organomet. Chem.* ***1987***, *332*, 9.
[613] Sato, F.; Oguro, K.; Watanabe, H.; Sato, M. *Tetrahedron Lett.* ***1980***, *21*, 2869. See Amaratunga, W.; Fréchet, J.M.J. *Tetrahedron Lett.* ***1983***, *24*, 1143.
[614] Trzupek, L.S.; Newirth, T.L.; Kelly, E.G.; Sbarbati, N.E.; Whitesides, G.M. *J. Am. Chem. Soc.* ***1973***, *95*, 8118.
[615] Zadel, G.; Breitmaier, E. *Angew. Chem. Int. Ed.* ***1992***, *31*, 1035.
[616] Yamamoto, K.; Yohitake, J.; Qui, N.T.; Tsuji, J. *Chem. Lett.* ***1978***, 859.
[617] Wu, J.; Yang, X.; He, Z.; Mao, X.; Hatton, T.A.; Jamison, T.F. *Angew. Chem. Int. Ed.* ***2014***, *53*, 8416.
[618] Yamashita, M.; Suemitsu, R. *Tetrahedron Lett.* ***1978***, 1477.
[619] Miyaura, N.; Suzuki, A. *Chem. Lett.* ***1981***, 879. See also, Yamashina, N.; Hyuga, S.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* ***1989***, *30*, 6555.
[620] Larock, R.C. *J. Org. Chem.* ***1975***, *40*, 3237.
[621] Alper, H.; Amaratunga, S. *J. Org. Chem.* ***1982***, *47*, 3593.
[622] Screttas, C.G.; Steele, B.R. *J. Org. Chem.* ***1988***, *53*, 5151.
[623] Oshita, M.; Chatani, N. *Org. Lett.* ***2004***, *6*, 4323.

Vinylic copper reagents react with ClCN to give vinyl cyanides, although BrCN and ICN give the vinylic halide instead.[624] Vinylic cyanides have also been prepared by the reaction between vinylic lithium compounds and phenyl cyanate (PhOCN).[625] Alkyl nitriles (RCN) have been prepared, in varying yields, by treatment of sodium trialkylcyanoborates with NaCN and lead tetraacetate.[626] Vinyl bromides reacted with KCN, in the presence of a Ni complex and Zn metal, to give the vinyl nitrile.[627] Vinyl triflates react with LiCN, in the presence of a Pd catalyst, to give the vinyl nitrile.[628]

For other electrophilic substitutions of the type RM → RC, which are discussed under nucleophilic substitutions in Chapter 10, see also, **16-28**, **16-79** to **16-81**, and **16-93**.

OS **IX**, 548.

G. Metal Electrophiles

12-34 Transmetalation With a Metal

$$RM + M' \rightleftharpoons RM' + M$$

Many organometallic compounds are best prepared by this reaction, which involves replacement of one metal in an organometallic compound by another metal. The RM′ compound can be successfully prepared only when M′ is above M in the electromotive series, unless some other way is found to shift the equilibrium. That is, RM is usually an unreactive compound and M′ is a metal more active than M. Most often, RM is R_2Hg, since mercury alkyls[607] are easy to prepare and mercury is far down in the electromotive series.[629] Alkyls of Li, Na, K, Be, Mg, Al, Ga, Zn, Cd, Te, Sn, and so on, have been prepared this way. An important advantage of this method over **12-37** is that it ensures that the organometallic compound will be prepared free of any possible halide. This method can be used for the isolation of solid sodium and potassium alkyls.[630] If the metals lie too close together in the series, it may not be possible to shift the equilibrium. For example, alkylbismuth compounds cannot be prepared in this way from alkylmercury compounds.

OS **V**, 1116.

12-35 Transmetalation with a Metal Halide

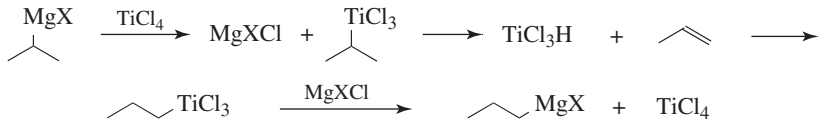
$$RM + M'X \rightleftharpoons RM' + MX$$

In contrast to **12-34**, the reaction between an organometallic compound and a metal *halide* is successful only when M′ is *below* M in the electromotive series.[631] The two

[624] Westmijze, H.; Vermeer, P. *Synthesis* ***1977***, 784.
[625] Murray, R.E.; Zweifel, G. *Synthesis* ***1980***, 150.
[626] Masuda, Y.; Hoshi, M.; Yamada, T.; Arase, A. *J. Chem. Soc., Chem. Commun.* ***1984***, 398.
[627] Sakakibara, Y.; Enami, H.; Ogawa, H.; Fujimoto, S.; Kato, H.; Kunitake, K.; Sasaki, K.; Sakai, M. *Bull. Chem. Soc. Jpn.* ***1995***, *68*, 3137.
[628] Piers, E.; Fleming, F.F. *Can. J. Chem.* ***1993***, *71*, 1867.
[629] See Makarova, L.G. *Organomet. React.* ***1970***, *1*, 119 (pp. 190–226); Wardell, J.L. in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 31–44.
[630] Pi, R.; Bauer, W.; Brix, B.; Schade, C.; Schleyer, P.v.R. *J. Organomet. Chem.* ***1986***, *306*, C1.
[631] See Abraham, M.H. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 12; Elsevier, NY, ***1973***, pp. 39–106; Jensen, F.R.; Rickborn, B. *Electrophilic Substituton of Organomercurials,* McGraw-Hill,

reactions considered together therefore constitute a powerful tool for preparing all kinds of organometallic compounds. In this reaction, the most common substrates are Grignard reagents and organolithium compounds.[632]

The MgX of *Grignard reagents*[633] can migrate to terminal positions in the presence of small amounts of $TiCl_4$.[634] The proposed mechanism consists of metal exchange (**12-34**), elimination–addition, and metal exchange:



The addition step is similar to **15-11** or **15-12** and follows Markovnikov's rule, so the positive titanium goes to the terminal carbon.

Among others, alkyls of Be, Zn,[635] Cd, Hg, Al, Sn, Pb, Co, Pt, and Au have been prepared by treatment of *Grignard reagents* with the appropriate halide.[636] The reaction has been used to prepare alkyls of almost all nontransition metals and even of some transition metals. Alkyls of metalloids and of nonmetals, including Si, B,[637] Ge, P, As, Sb, and Bi, can also be prepared in this manner.[638] Except for alkali metal alkyls and Grignard reagents, the reaction between RM and M′X is the most common method for the preparation of organometallic compounds.[639] Boranes can also be prepared. In the presence of Ir catalysts,[640] or Pd catalysts,[641] aromatic compounds react with boranes to give the corresponding arylborane.

Lithium dialkylcopper reagents are prepared from 2 molar equivalents of RLi with 1 molar equivalent of a cuprous halide in ether at low temperatures.[642] The formation of organocuprates of this type are discussed in more detail in reaction **10-58**, in connection with the coupling reaction of organocuprates with alkyl halides. Another way is to dissolve

NY, ***1968***, pp. 100–192. Also see, Schlosser, M. *Angew. Chem. Int. Ed.* ***1964***, *3*, 287, 362; *Newer Methods Prep. Org. Chem.* ***1968***, *5*, 238.

[632] See Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***; Wakefield, B.J. *The Chemistry of Organolithium Compounds*, Pergamon, Elmsford, NY, ***1974***.

[633] See Hill, E.A. *Adv. Organomet. Chem.* ***1977***, *16*, 131; *J. Organomet. Chem.* ***1975***, *91*, 123.

[634] Fell, B.; Asinger, F.; Sulzbach, R.A. *Chem. Ber.* ***1970***, *103*, 3830. See also, Ashby, E.C.; Ainslie, R.D. *J. Organomet. Chem.* ***1983***, *250*, 1.

[635] See Erdik, E. *Tetrahedron* ***1987***, *43*, 2203.

[636] See Noltes, J.G. *Bull. Soc. Chim. Fr.* ***1972***, 2151.

[637] See Brown, H.C.; Racherla, U.S. *Tetrahedron Lett.* ***1985***, *26*, 4311.

[638] See Wakefield, B.J. *Organolithium Methods,* Academic Press, NY, ***1988***, pp. 149–158; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 1306–1345.

[639] See Mole, T. *Organomet. React.* ***1970***, *1*, 1 (pp. 31–43); Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 9–26; van Koten, G. in Zuckerman, J.J. *Inorganic Reactions and Method*s, Vol. 11, VCH, NY, ***1988***, pp. 219–232; Wardell, J.L. in Zuckerman, J.J. *Inorganic Reactions and Methods,* Vol. 11, VCH, NY, ***1988***, pp. 248–270.

[640] Harrisson, P.; Morris, J.; Marder, T.B.; Steel, P.G. *Org. Lett.* ***2009***, *11*, 3586.

[641] Billingsley, K.L.; Buchwald, S.L. *J. Org. Chem.* ***2008***, *73*, 5589.

[642] House, H.O.; Chu, C.; Wilkins, J.M.; Umen, M.J. *J. Org. Chem.* ***1975***, *40*, 1460. But see also, Lipshutz, B.H.; Whitney, S.; Kozlowski, J.A.; Breneman, C.M. *Tetrahedron Lett.* ***1986***, *27*, 4273; Bertz, S.H.; Dabbagh, G. *Tetrahedron* ***1989***, *45*, 425.

an alkylcopper compound in an alkyllithium solution. Higher order cuprates can also be prepared, as well as "non-ate" copper reagents.[643]

Metallocenes (Sec. 2.I.ii) are usually made by this method. Among others, metallocenes of Sc, Ti, V, Cr, Mn, Fe, Co, and Ni have been prepared in this manner.[644] In a related reaction, sulfurated boranes ($R_2B{-}SSiR'_2$) react with *Grignard reagents*, such as methylmagnesium bromide, to give the *B*-alkyl borane (e.g., $R_2B{-}Me$) upon heating *in vacuo*.[645]

OS **I**, 231, 550; **III**, 601; **IV**, 258, 473, 881; **V**, 211, 496, 727, 918, 1001; **VI**, 776, 875, 1033; **VII**, 236, 290, 524; **VIII**, 23, 57, 268, 474, 586, 606, 609. Also see, OS **IV**, 476.

12-36 Transmetalation With an Organometallic Compound

$$RM + R'M' \rightleftharpoons RM' + R'M$$

This type of metallic exchange is used much less often than **12-34** and **12-35**. It is an equilibrium reaction and is useful only if the equilibrium lies in the desired direction. Usually the goal is to prepare a lithium compound that is not prepared easily in other ways.[646] For example, it can be used to prepare a vinylic or an allylic lithium, most commonly from an organotin substrate. Examples are the preparation of vinyllithium from phenyllithium and tetravinyltin and the formation of α-dialkylamino organolithium compounds from the corresponding organotin compounds.[647]

The reaction has also been used to prepare 1,3-dilithiopropanes[648] and 1,1-dilithiomethylenecyclohexane[649] from the corresponding mercury compounds. In general, the equilibrium lies in the direction in which the more electropositive metal is bonded to that alkyl or aryl group that is the more stable carbanion (Sec. 5.B.i). The reaction proceeds with retention of configuration;[650] an S_Ei mechanism is likely.[651]

OS **V**, 452; **VI**, 815; **VIII**, 97.

12.C.iii. Halogen as Leaving Group

The reduction of alkyl halides is considered in **19-57**.

12-37 Metalo-de-halogenation

$$RX + M \longrightarrow RM$$

Alkyl halides react directly with certain metals to give organometallic compounds.[652] The most common metal is Mg, and of course this is by far the most common method for

[643] Stack, D.E.; Klein, W.R.; Rieke, R.D. *Tetrahedron Lett.* ***1993***, *34*, 3063.

[644] See Bublitz, D.E.; Rinehart Jr., K.L. *Org. React.* ***1969***, *17*, 1; Birmingham, J.M. *Adv. Organomet. Chem.* ***1965***, *2*, 365 (pp. 375).

[645] Soderquist, J.A.; DePomar, J.C.J. *Tetrahedron Lett.* ***2000***, *41*, 3537.

[646] See Wardell, J.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond*, Vol. 4, Wiley, NY, pp. 1–157 (see pp. 81–89); Kauffmann, T. *Top. Curr. Chem.* ***1980***, *92*, 109 (pp. 130).

[647] Pearson, W.H.; Lindbeck, A.C. *J. Org. Chem.* ***1989***, *54*, 5651.

[648] Seetz, J.W.F.L.; Schat, G.; Akkerman, O.S.; Bickelhaupt, F. *J. Am. Chem. Soc.* ***1982***, *104*, 6848.

[649] Maercker, A.; Dujardin, R. *Angew. Chem. Int. Ed.* ***1984***, *23*, 224.

[650] Sawyer, J.S.; Kucerovy, A.; Macdonald, T.L.; McGarvey, G.J. *J. Am. Chem. Soc.* ***1988***, *110*, 842.

[651] Dessy, R.E.; Kaplan, F.; Coe, G.R.; Salinger, R.M. *J. Am. Chem. Soc.* ***1963***, *85*, 1191.

[652] See Massey, A.G.; Humphries, R.E. *Aldrichimica Acta* ***1989***, *22*, 31; Negishi, E. *Organometallics in Organic Synthesis*, Wiley, NY, ***1980***, pp. 30–37.

the preparation of *Grignard reagents*.[653] The Grignard reaction with aldehydes or ketones is discussed in **16-22**. The order of halide activity is I > Br > Cl. The reaction can be applied to many alkyl halides (primary, secondary, and tertiary) and to aryl halides, although aryl *chlorides* require the use of THF or another higher-boiling solvent instead of the usual ether, or special entrainment methods.[654] Aryl iodides and bromides can be treated in the usual manner. Allylic Grignard reagents can also be prepared in the usual manner (or in THF),[655] although in the presence of excess halide these may give *Wurtz-type coupling* products (see **10-56**).[656] Like aryl chlorides, vinylic halides require higher-boiling solvents (see OS **IV**, 258). For benzylic and allylic halides, activated magnesium turnings have also been used.[657] Alkynyl Grignard reagents are generally prepared by the method in **12-22**.

Dihalides[658] can be converted to Grignard reagents if the halogens are different and are at least three carbons apart. If the halogens are the same, it is possible to obtain dimagnesium compounds (e.g., $BrMg(CH_2)_4MgBr$).[659] 1,2-Dihalides give elimination[660] rather than Grignard reagent formation (**17-20**), and the reaction is seldom successful with 1,1-dihalides, although the preparation of *gem*-disubstituted compounds, such as $CH_2(MgBr)_2$, has been accomplished.[661] Alkylmagnesium fluorides can be prepared by refluxing alkyl fluorides with Mg in the presence of appropriate catalysts (e.g., I_2 or EtBr) in THF for several days.[662] Nitrogen-containing Grignard reagents have been prepared.[663]

The presence of other functional groups in the halide usually affects the preparation of the Grignard reagent. Groups that contain active hydrogen (defined as any hydrogen that will react with a Grignard reagent), such as OH, NH_2, and CO_2H, can be present in the molecule, but only if they are converted to the salt form (O^-, NH^-, COO^-, respectively). Groups that react with Grignard reagents, such as C=O, C≡N, NO_2, CO_2R, cannot be in the molecule. It is known that β-halo ethers generally give β elimination when treated with Mg (see **17-22**), and Grignard reagents from α-halo ethers[664] can only be formed in THF or dimethoxymethane at a low temperature,[665] because such reagents immediately undergo α elimination (see **12-38**) at room temperature in ether solution.

Grignard reagents are strong bases so they react with water (**12-24**), and they also react with oxygen (**12-25**), it is generally best to prepare them in an anhydrous nitrogen atmosphere. Grignard reagents are generally neither isolated nor stored and solutions of Grignard reagents are used directly for the required synthesis. However, it is possible to obtain Grignard reagents in powdered form, by complexing them with tris(3,6-dioxaheptyl)amine

[653] See Raston, C.L.; Salem, G. in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond*, Vol. 4, Wiley, NY, pp. 159–306 (pp. 162–175); Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 5–91.
[654] Pearson, D.E.; Cowan, D.; Beckler, J.D. *J. Org. Chem.* ***1959***, *24*, 504.
[655] See Benkeser, R.A. *Synthesis* ***1971***, 347.
[656] See Oppolzer, W.; Schneider, P. *Tetrahedron Lett.* ***1984***, *25*, 3305.
[657] Baker, K.V.; Brown, J.M.; Hughes, N.; Skarnulis, A.J.; Sexton, A. *J. Org. Chem.* ***1991***, *56*, 698.
[658] See Raston, C.L.; Salem, G. in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond*, Vol. 4, Wiley, NY, pp. 187–193; Heaney, H. *Organomet. Chem. Rev.* ***1966***, *1*, 27. For a review of di-Grignard reagents, see Bickelhaupt, F. *Angew. Chem. Int. Ed.* ***1987***, *26*, 990.
[659] See Seetz, J.W.F.L.; Hartog, F.A.; Böhm, H.P.; Blomberg, C.; Akkerman, O.S.; Bickelhaupt, F. *Tetrahedron Lett.* ***1982***, *23*, 1497.
[660] See van Eikkema Hommes, N.J.R.; Bickelhaupt, F.; Klumpp, G.W. *Angew. Chem. Int. Ed.* ***1988***, *27*, 1083.
[661] Bruin, J.W.; Schat, G.; Akkerman, O.S.; Bickelhaupt, F. *J. Organomet. Chem.* ***1985***, *288*, 13.
[662] Yu, S.H.; Ashby, E.C. *J. Org. Chem.* ***1971***, *36*, 2123.
[663] Sugimoto, O.; Yamada, S.; Tanji, K. *J. Org. Chem.* ***2003***, *68*, 2054.
[664] See Peterson, D.J. *Organomet. Chem. Rev. Sect. A* ***1972***, *7*, 295.
[665] See Castro, B. *Bull. Soc. Chim. Fr.* ***1967***, 1533, 1540, 1547.

$N(CH_2CH_2OCH_2CH_2OCH_3)_3$, a chelating agent (see OS **VI**, 845).[666] Grignard reagents can also be prepared in benzene or toluene, if a tertiary amine is added to complex with the RMgX.[667] This method eliminates the need for an ether solvent. With certain primary alkyl halides it is even possible to prepare alkylmagnesium compounds in hydrocarbon solvents in the absence of an organic base.[668]

The efficiency of the organometallic formation can often be improved by use of the metal in its powdered[669] or vapor[670] form. This approach has permitted the preparation of some organometallic compounds that cannot be prepared by the standard procedures. Among the metals produced in an activated form are Mg,[671] Ca,[672] Zn,[673] Al, Sn, Cd,[674] Ni, Fe, Ti, Cu,[675] Pd, and Pt.[676]

The mechanism of Grignard reagent formation involves free radicals.[677] There is much evidence for this, from CIDNP[678] (Sec. 5.C.i) and from stereochemical, rate, and product studies.[679] Further evidence is that free radicals have been trapped,[680] and that experiments that studied the intrinsic reactivity of MeBr on a magnesium single-crystal surface showed that Grignard reagent formation does not take place by a single-step insertion mechanism.[681] The following SET mechanism has been proposed:[678]

$$\mathrm{R{-}X + Mg \longrightarrow R{-}X^{\bullet -} + Mg_s{}^{+\bullet}}$$

$$\mathrm{R{-}X^{\bullet -} \longrightarrow R^{\bullet} + X^{-}}$$

$$\mathrm{X^{-} + Mg_s{}^{+\bullet} \longrightarrow XMg_s{}^{\bullet}}$$

$$\mathrm{R^{\bullet} + XMg^{\bullet}}g_s \longrightarrow \mathrm{RMgX}$$

Other evidence has been offered to support a SET-initiated radical process for the second step of this mechanism.[682] The species $-X^{\bullet -}$ and $Mg^{\bullet +}$ are radical ions.[683] The subscript "s" in the mechanism is meant to indicate that the species so marked are bound to the surface of

[666] Boudin, A.; Cerveau, G.; Chuit, C.; Corriu, R.J.P.; Reye, C. *Tetrahedron* ***1989***, *45*, 171.
[667] Gitlitz, M.H.; Considine, W.J. *J. Organomet. Chem.* ***1970***, *23*, 291.
[668] Smith Jr., W.N. *J. Organomet. Chem.* ***1974***, *64*, 25.
[669] See Rieke, R.D. *Science* ***1989***, *246*, 1260.
[670] See Klabunde, K.J. *React. Intermed. (Plenum)* ***1980***, *1*, 37; *Acc. Chem. Res.* ***1975***, *8*, 393; Skell, P.S.; Havel, J.J.; McGlinchey, M.J. *Acc. Chem. Res.* ***1973***, *6*, 97.
[671] Ebert, G.W.; Rieke, R.D. *J. Org. Chem.* ***1988***, *53*, 4482. See also, Baker, K.V.; Brown, J.M.; Hughes, N.; Skarnulis, A.J.; Sexton, A. *J. Org. Chem.* ***1991***, *56*, 698.
[672] Wu, T.; Xiong, H.; Rieke, R.D. *J. Org. Chem.* ***1990***, *55*, 5045.
[673] Rieke, R.D.; Li, P.T.; Burns, T.P.; Uhm, S.T. *J. Org. Chem.* ***1981***, *46*, 4323. See also, Zhu, L.; Wehmeyer, R.M.; Rieke, R.D. *J. Org. Chem.* ***1991***, *56*, 1445.
[674] Burkhardt, E.R.; Rieke, R.D. *J. Org. Chem.* ***1985***, *50*, 416.
[675] Stack, D.E.; Dawson, B.T.; Rieke, R.D. *J. Am. Chem. Soc.* ***1991***, *113*, 4672, and references cited therein.
[676] See Lai, Y. *Synthesis* ***1981***, 585; Rieke, R.D. *Acc. Chem. Res.* ***1977***, *10*, 301.
[677] See Blomberg, C. *Bull. Soc. Chim. Fr.* ***1972***, 2143.
[678] Bodewitz, H.W.H.J.; Blomberg, C.; Bickelhaupt, F. *Tetrahedron* ***1975***, *31*, 1053. See also, Schaart, B.J.; Blomberg, C.; Akkerman, O.S.; Bickelhaupt, F. *Can. J. Chem.* ***1980***, *58*, 932.
[679] See Rogers, H.R.; Hill, C.L.; Fujiwara, Y.; Rogers, R.J.; Mitchell, H.L.; Whitesides, G.M. *J. Am. Chem. Soc.* ***1980***, *102*, 217; Barber, J.J.; Whitesides, G.M. *J. Am. Chem. Soc.* ***1980***, *102*, 239.
[680] Root, K.S.; Hill, C.L.; Lawrence, L.M.; Whitesides, G.M. *J. Am. Chem. Soc.* ***1989***, *111*, 5405.
[681] Nuzzo, R.G.; Dubois, L.H. *J. Am. Chem. Soc.* ***1986***, *108*, 2881.
[682] Hoffmann, R.W.; Brönstrup, M.; Müller, M. *Org. Lett.* ***2003***, *5*, 313.
[683] See Sergeev, G.B.; Zagorsky, V.V.; Badaev, F.Z. *J. Organomet. Chem.* ***1983***, *243*, 123. See, however, de Souza-Barboza, J.C.; Luche, J.; Pétrier, C. *Tetrahedron Lett.* ***1987***, *28*, 2013.

the magnesium. It is known that this is a surface reaction.[684] It has been suggested that some of the R• radicals diffuse from the magnesium surface into the solution and then return to the surface to react with the XMg•. There is evidence both for[685] and against[686] this suggestion. Another proposal is that the fourth step is not the one shown here, but that the R• is reduced by Mg^+ to the carbanion R^-, which combines with MgX^+ to give RMgX.[687]

There are too many preparations of Grignard reagents in *Organic Syntheses* to list here. Chiral Grignard reagents are rare, since they are configurationally unstable in most cases, but a few chiral Grignard reagents are known.[688] Use of the reaction to prepare other organometallic compounds can be found in OS **I**, 228; **II**, 184, 517, 607; **III**, 413, 757; **VI**, 240; **VII**, 346; **VIII**, 505. The preparation of unsolvated butylmagnesium bromide is described at OS **V**, 1141.

Next to the formation of Grignard reagents, the most important application of this reaction is the conversion of alkyl and aryl halides to organolithium reagents (RLi),[689] but it has also been carried out with many other metals (e.g., Na, Be, Zn, Hg, As, Sb, and Sn). With Na, the *Wurtz reaction* (**10-56**) is an important side reaction. In some cases where the reaction between a halide and a metal is too slow, an alloy of the metal with K or Na can be used instead. The most important example is the preparation of tetraethyl lead from ethyl bromide and a Pb/Na alloy.

Organolithium reagents are usually written as R—Li, but this simple representation does not describe their actual structure.[690] The extent of association of the organolithium is important since it can affect the rate of metal–halogen or metal–hydrogen exchange, as well as the product distribution. The degree of association of several common organolithium reagents in various solvents has been reported,[690,691,692] and it was shown that the degree of association decreases as the coordinating ability of the solvent increases. This observation can loosely be compared with increasing solvent polarity. Some physical data[690] suggest that the C—Li bond in an organolithium reagent is highly covalent, and it is known that organolithium reagents exist as associated aggregates, due in part to this covalent character. Both methyllithium (CH_3Li)[693] and ethyllithium (CH_3CH_2Li)[694] have been obtained in crystalline form and their crystal structure determined by X-ray crystallography. The crystal structure of isopropyllithium was reported by Siemeling and co-workers,[695] and it was shown to exist as a hexamer, $(i\text{-PrLi})_6$.

[684] See Walborsky, H.M. *Accts. Chem. Res.* ***1990***, *23*, 286.
[685] Garst, J.F. *Acc. Chem. Res.* ***1991***, *24*, 95; Garst, J.F.; Ungváry, F.; Batlaw, R.; Lawrence, K.E. *J. Am. Chem. Soc.* ***1991***, *113*, 5392.
[686] Walborsky, H.M. *Acc. Chem. Res.* ***1990***, *23*, 286.
[687] de Boer, H.J.R.; Akkerman, O.S.; Bickelhaupt, F. *Angew. Chem. Int. Ed.* ***1988***, *27*, 687.
[688] See Hölzer, B.; Hoffmann, R.W. *Chem. Commun.* ***2003***, 732; Dakternieks, D.; Dunn, K.; Henry, D.J.; Schiesser, C.H.; Tiekink, E.R. *Organometallics* ***1999***, *18*, 3342.
[689] See Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, pp. 21–32; Wardell, J.L. in Hartley, F.R.; Patai, S. Vol. 4, pp. 1–157 (pp. 5–27); Newcomb, M.E. in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 3–14. For a study of halogen–lithium exhange in hydrocarbon solvents, see Slocum, D.W.; Kusmic, D.; Raber, J.C.; Reinscheld, T.K.; Whitley, P.E. *Tetrahedron Lett.* ***2010***, *51*, 4793.
[690] Mallan, J.M.; Bebb, R.L. *Chem. Rev.* ***1969***, *69*, 693; Deberitz, J. *Janssen Chimica Acta* ***1984***, *2*, 3; Brown, J.M. *Chem. Ind. (London)* ***1972***, 454.
[691] Brown, T.L. *Acc. Chem. Res.* ***1968***, *1*, 23; West, P.; Waack, R. *J. Am. Chem. Soc.* ***1967***, *89*, 4395.
[692] Brown, T.L. *Advan. Organomet. Chem.* ***1965***, *3*, 365.
[693] Weiss, E.; Lucken, E.A.C. *J. Organomet. Chem.* ***1964***, *2*, 197.
[694] Dietrich, H. *Acta Crystallogr.* ***1963***, *16*, 681.
[695] Siemeling, U.; Redecker, T.; Neumann, B.; Stammler, H.-G. *J. Am. Chem. Soc.* ***1994***, *116*, 5507.

Methyllithium and ethyllithium are tetrameric in the solid state,[694,696] and most organolithium reagents are highly associated in solution.[690,697] The structure of an unsymmetrical heptalithum cage complex has been reported.[698] The degree of association is related to the solvent and structure of the organolithium, but tends to be higher for straight chain reagents when compared with branched (secondary and tertiary) organolithium reagents.

12-38 Replacement of a Halogen by a Metal from an Organometallic Compound

$$RX + R'M \longrightarrow RM + R'X$$

The exchange reaction between halides and organometallic compounds occurs most readily when M is lithium and X is bromide or iodide,[699] although it has been shown to occur with magnesium.[700] The R′ group is usually, although not always, alkyl, and often butyl; R is usually aromatic.[701] Alkyl halides are generally not reactive enough, while allylic and benzylic halides usually give Wurtz coupling. Of course, the R that becomes bonded to the halogen is the one for which RH is the weaker acid. Despite the preponderance of reactions with bromides and iodides, 1-octyllithium has been prepared.[702] Vinylic halides react with retention of configuration.[703] The reaction can be used to prepare α-halo organolithium[704] and α-halo organomagnesium compounds.[705] Such compounds can also be prepared by hydrogen–metal exchange, for example.[706] These α-halo organometallic compounds are stable (and configurationally stable as well[707]) only at low temperatures (ca. −100 °C) and only in THF or mixtures of THF and other solvents (e.g., HMPA). At ordinary temperatures they lose MX (α-elimination) to give carbenes (which then react further) or carbenoid reactions. The α-chloro-α-magnesio sulfones $ArSO_2CH(Cl)MgBr$ are exceptions, being stable in solution at room temperature and even under reflux.[708] Compounds in which a halogen and a transition metal are on the same carbon can be more stable than the ones with lithium.[709]

[696] Dietrich, H. *Z. Naturforsch.* ***1959***, *14B*, 739.
[697] Wakefield, B.J. *The Chemistry of Organolithium Compounds*, Pergamon Press, Oxford, ***1974.***
[698] Henderson, K.W.; Dorigo, A.E.; MacEwan, G.J.; Williard, P.G. *Tetrahedron* ***2011***, *67*, 10291.
[699] See Wardell, J.L. in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 107–129; Parham, W.E.; Bradsher, C.K. *Acc. Chem. Res.* ***1982***, *15*, 300.
[700] See Tamborski, C.; Moore, G.J. *J. Organomet. Chem.* ***1971***, *26*, 153.
[701] See Bailey, W.F.; Punzalan, E.R. *J. Org. Chem.* ***1990***, *55*, 5404; Negishi, E.; Swanson, D.R.; Rousset, C.J. *J. Org. Chem.* ***1990***, *55*, 5406.
[702] Yus, M.; Herrera, R.P.; Guijarro, A. *Tetrahedron Lett.* ***2003***, *44*, 5025.
[703] For examples of exchange, R = vinylic, see Miller, R.B.; McGarvey, G. *Synth. Commun.* ***1979***, *9*, 831; Sugita, T.; Sakabe, Y.; Sasahara, T.; Tsukuda, M.; Ichikawa, K. *Bull. Chem. Soc. Jpn.* ***1984***, *57*, 2319.
[704] Hoeg, D.F.; Lusk, D.I.; Crumbliss, A.L. *J. Am. Chem. Soc.* ***1965***, *87*, 4147. See also, Villieras, J.; Tarhouni, R.; Kirschleger, B.; Rambaud, M. *Bull. Soc. Chim. Fr.* ***1985***, 825.
[705] See Siegel, H. *Top. Curr. Chem.* ***1982***, *106*, 55; Negishi, E. *Organometallics in Organic Synthesis*, Wiley, NY, ***1980***, pp. 136–151; Köbrich, G. *Angew. Chem. Int. Ed.* ***1972***, *11*, 473. Also see Krief, A. *Tetrahedron* ***1980***, *36*, 2531; Normant, H. *J. Organomet. Chem.* ***1975***, *100*, 189.
[706] Villieras, J. *Bull. Soc. Chim. Fr.* ***1967***, 1520.
[707] Schmidt, A.; Köbrich, G.; Hoffmann, R.W. *Chem. Ber.* ***1991***, *124*, 1253; Hoffmann, R.W.; Bewersdorf, M. *Chem. Ber.* ***1991***, *124*, 1259.
[708] Stetter, H.; Steinbeck, K. *Liebigs Ann. Chem.* ***1972***, *766*, 89.
[709] Kauffmann, T.; Fobker, R.; Wensing, M. *Angew. Chem. Int. Ed.* ***1988***, *27*, 943.

There is evidence that the mechanism[710] of the reaction of alkyllithium compounds with alkyl and aryl iodides involves free radicals.[711]

$$RX + R'M \rightleftharpoons \underset{\text{Solvent cage}}{[R\bullet,\ X,\ M,\ R'\bullet]} \rightleftharpoons RM + R'X$$

Among the evidence is the fact that coupling and disproportionation products are obtained from R• and R′• and the observation of CIDNP.[711,712] However, in the degenerate exchange between PhI and PhLi the ate complex $Ph_2I^-\ Li^+$ has been shown to be an intermediate,[713] and there is other evidence that radicals are not involved in all instances of this reaction.[714]

OS **VI**, 82; **VII**, 271, 326, 495; **VIII**, 430. See also, OS **VII**, 512; **VIII**, 479.

12.C.iv. Carbon Leaving Groups

In these reactions (**12-39** to **12-47**), a carbon–carbon bond cleaves. The substrate is the side that retains the electron pair; hence the reactions are considered electrophilic substitutions. The incoming group is hydrogen in all but one (**12-41**) of the cases. The reactions in groups A and B are sometimes called *anionic cleavages*,[715] although they do not always occur by mechanisms involving free carbanions (S_E1). When they do, the reactions are facilitated by increasing stability of the carbanion.

A. Carbonyl-Forming Cleavages

Any carbon leaving group must be stabilized because C—C, C—O, and C—N bonds are relatively strong. With respect to the leaving group, the reaction is elimination to form a C=O bond. Retrograde aldol reactions (**16-34**) and cleavage of cyanohydrins (**16-51**) belong to this classification but are treated in Chapter 16 under their more important reverse reactions. Other eliminations to form C=O bonds are discussed in **17-30**.

12-39 Decarboxylation of Aliphatic Acids

$$RCOOH \longrightarrow RH + CO_2$$

Many carboxylic acids that have a suitable group at the β position can be successfully decarboxylated, either as the free acid or in the salt form, but not simple aliphatic acids.[716] An exception is acetic acid, which as the acetate, heated with base, gives good yields of methane. Malonic acid derivatives are the most common substrates for decarboxylation, giving the corresponding monocarboxylic acid. Decarboxylation of 2-substituted malonic

[710] For reviews of the mechanism, see Bailey, W.F.; Patricia, J.J. *J. Organomet. Chem.* ***1988***, *352*, 1; Beletskaya, I.P.; Artamkina, G.A.; Reutov, O.A. *Russ. Chem. Rev.* ***1976***, *45*, 330.

[711] Ashby, E.C.; Pham, T.N. *J. Org. Chem.* ***1987***, *52*, 1291. See also, Bailey, W.F.; Patricia, J.J.; Nurmi, T.T.; Wang, W. *Tetrahedron Lett.* ***1986***, *27*, 1861.

[712] Ward, H.R.; Lawler, R.G.; Loken, H.Y. *J. Am. Chem. Soc.* ***1968***, *90*, 7359.

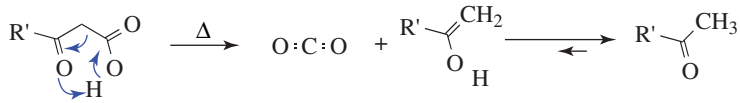
[713] See Reich, H.J.; Green, D.P.; Phillips, N.H. *J. Am. Chem. Soc.* ***1989***, *111*, 3444.

[714] Beak, P.; Allen, D.J.; Lee, W.K. *J. Am. Chem. Soc.* ***1990***, *112*, 1629.

[715] See Artamkina, G.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1987***, *56*, 983.

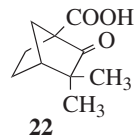
[716] March, J. *J. Chem. Educ.* ***1963***, *40*, 212.

acids has been reported using microwave irradiation.[717] Aliphatic acids that do undergo successful decarboxylation have certain functional groups or double or triple bonds in the α or β position.[718] Some acids can also be decarboxylated directly and, in most of these cases, there is a cyclic, six-center mechanism:



Here too there is an enol that tautomerizes to the product. The mechanism is illustrated for the case of β-keto acids,[719] but it is likely that malonic acids, α-cyano acids, α-nitro acids, and β,γ-unsaturated acids[720] behave similarly, since similar six-membered transition states can be written for them.

When the carboxylate *ion* is decarboxylated, the mechanism can be either S_E1 or S_E2. In the case of the S_E1 mechanism, the reaction is of course aided by the presence of electron-withdrawing groups, which stabilize the carbanion.[721] Decarboxylation of carboxylate ions can be accelerated by the addition of a suitable crown ether, which in effect removes the metallic ion.[722] The reaction without the metallic ion has also been performed in the gas phase.[723] Some α,β-unsaturated acids are also decarboxylated by this mechanism by isomerizing to the β,γ isomers before they actually decarboxylate.[724] Evidence is bicyclic β-keto acids where the COOH moiety is attached to a bridgehead carbon atom, as in **22**, resist decarboxylation.[725]



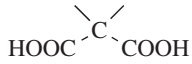
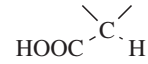
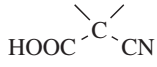
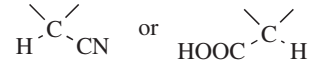
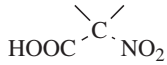
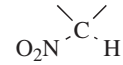
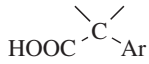
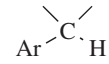
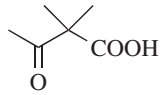
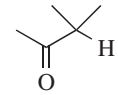
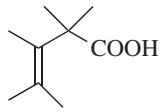
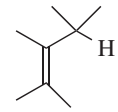
22

In such compounds, the six-membered cyclic transition state cannot form for steric reasons,[726] and formation of the intermediate enol would violate *Bredt's rule* (Sec. 4.Q.iii). Some of the structural features observed for the decarboxylation of acids are shown in Table 12.1.

For decarboxylation of aromatic acids, see **11-35**. Decarboxylation of an α-cyano acid can give a nitrile or a carboxylic acid, since the cyano group may or may not be hydrolyzed in the course of the reaction. In addition to the compounds listed in Table 12.1,

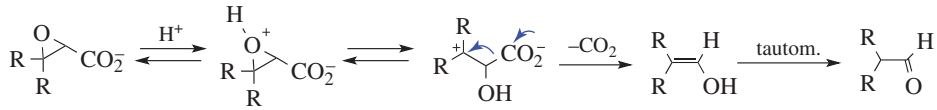
[717] Zara, C.L.; Jin, T.; Giguere, R.J. *Synth. Commun.* ***2000***, *30*, 2099.
[718] Kluger, R. *Acc. Chem. Res.* ***2015***, *48*, 2843.
[719] See Jencks, W.P. *Catalysis in Chemistry and Enzmology*, McGraw-Hill, NY, ***1969***, pp. 116–120.
[720] Bigley, D.B.; Clarke, M.J. *J. Chem. Soc., Perkin Trans. 2* ***1982***, 1, and references cited therein. For a review, see Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* ***1971***, *8*, 75 (pp. 150–153).
[721] See Buncel, E.; Venkatachalam, T.K.; Menon, B.C. *J. Org. Chem.* ***1984***, *49*, 413.
[722] Hunter, D.H.; Patel, V.; Perry, R.A. *Can. J. Chem.* ***1980***, *58*, 2271, and references cited therein.
[723] Graul, S.T.; Squires, R.R. *J. Am. Chem. Soc.* ***1988***, *110*, 607.
[724] Bigley, D.B. *J. Chem. Soc.* ***1964***, 3897.
[725] Wasserman, H.H. in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, p. 352. See also, Buchanan, G.L.; Kean, N.B.; Taylor, R. *Tetrahedron* ***1975***, *31*, 1583.
[726] Sterically hindered β-keto acids decarboxylate more slowly: Meier, H.; Wengenroth, H.; Lauer, W.; Krause, V. *Tetrahedron Lett.* ***1989***, *30*, 5253.

TABLE 12.1 Some acids that undergo decarboxylation fairly readily[a]

	Acid type	Decarboxylation product
Malonic		
Cyano		
Nitro		
Aryl		
Trihalo	$X_3C-COOH$	X_3C-H
Keto		
Unsaturated		

[a]Others are described in the text.

decarboxylation can be carried out on α,β-unsaturated[727] and α,β-acetylenic acids. Glycidic acids give aldehydes on decarboxylation. The mechanism shown has been suggested.[728]



The direct product is an enol that tautomerizes to the aldehyde.[729] This is the usual last step in the *Darzens reaction* (**16-40**).

Krapcho and co-workers developed a mild decarboxylation procedure of esters[730] that involved heating with LiCl in aqueous DMSO. This mild procedure is an S_N2-type reaction and is referred to as *Krapcho decarboxylation*.[731] A microwave-assisted decarboxylation procedure has been reported.[732]

[727] See Roy, S.C.; Guin, C.; Maiti, G. *Tetrahedron Lett.* ***2001***, *42*, 9253.
[728] Singh, S.P.; Kagan, J. *J. Org. Chem.* ***1970***, *35*, 2203.
[729] Shiner Jr., V.J.; Martin, B. *J. Am. Chem. Soc.* ***1962***, *84*, 4824.
[730] Krapcho, A.P.; Weimaster, J.F.; Eldridge, J.M.; Jahngen Jr., E.G.E.; Lovey, A.J.; Stephens, W.P. *J. Org. Chem.* ***1978***, *43*, 138; Krapcho, A.P. *Synthesis* ***1982***, 805, 893.
[731] *The Merck Index*, 14th ed., Merck & Co., Inc., Whitehouse Station, NJ, ***2006***, p ONR-53; Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis*, 2nd ed., Wiley-Interscience, NJ, ***2005***, pp. 380–381.
[732] Mason, J.D.; Murphree, S.S. *Synlett* ***2013***, *24*, 1391.

β-Keto acids[733] are easily decarboxylated, but such acids are usually prepared from β-keto esters, and the esters are easily decarboxylated themselves on hydrolysis without isolation of the acids.[734] This decarboxylation of β-keto esters involving cleavage on the carboxyl side of the substituted methylene group is carried out under acidic, neutral, or slightly basic conditions to yield a ketone. When strongly basic conditions are used, cleavage occurs on the other side of the CR_2 group (**12-42**). β-Keto esters can be decarboxylated without passing through the free-acid stage by treatment with boric anhydride B_2O_3 at 150 °C.[735] The alkyl portion of the ester (R′) is converted to an alkene or, if it lacks a β hydrogen, to an ether R′OR′. Another method for the decarbalkoxylation of β-keto esters, malonic esters, and α-cyano esters consists of heating the substrate in wet DMSO containing NaCl, Na_3PO_4, or some other simple salt.[736] In this method, too, the free acid is probably not an intermediate, but here the alkyl portion of the substrate is converted to the corresponding alcohol. α-Amino acids have been decarboxylated by treatment with a catalytic amount of cyclohexen-2-one.[737] Amino acids are decarboxylated by sequential treatment with NBS at pH 5 followed by $NaBH_4$ and $NiCl_2$.[738] Certain decarboxylations can also be accomplished photochemically.[739] See also, the decarbonylation of acyl halides, mentioned in **14-26**. In some cases, decarboxylations can give organometallic compounds:[740]

$$RCOOM \rightarrow RM + CO_2$$

The Cu-catalyzed decarboxylation of 2-alkynoic acids to terminal alkynes has been reported.[741]

Research continues for decarboxylation techniques. Fatty acids were decarboxylated to give terminal alkenes by treatment with Cytochrome P450 $OleT_{JE}$.[742] An Fe-catalyzed decarbonylation of aliphatic carboxylic acids has been reported, leading to an alkene.[743] The reaction of N-Boc amino acids with aryl halides under photoredox and Ni catalysis led to decarboxylation with the formation of α-arylamines.[744] Aliphatic carboxylic acids were treated with TMS and Me_3SiBr, with a catalytic amount of $InBr_3$, and gave the alkyl bromide, whereas the reaction with I_2 under the same conditions led to the alkyl iodide.[745] A Ag-catalyzed decarboxylative bromination from aliphatic carboxylic acids has been reported.[746] Allylic carboxylic acids reacted with $PhI(OAc)_2$ to give the allylic acetate via decarboxylation, and reacted with hypervalent iodine reagents containing an

[733] See Oshry, L.; Rosenfeld, S.M. *Org. Prep. Proced. Int.* ***1982***, *14*, 249.

[734] For a list of examples, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1542–1543. See Yu, Y.; Zhang, Y. *Synth. Commun.* ***1999***, *29*, 243.

[735] Lalancette, J.M.; Lachance, A. *Tetrahedron Lett.* ***1970***, 3903.

[736] See Krapcho, A.P. *Synthesis* ***1982***, 805, 893. For other methods, see Dehmlow, E.V.; Kunesch, E. *Synthesis* ***1985***, 320; Taber, D.F.; Amedio Jr., J.C.; Gulino, F. *J. Org. Chem.* ***1989***, *54*, 3474.

[737] Hashimoto, M.; Eda, Y.; Osanai, Y.; Iwai, T.; Aoki, S. *Chem. Lett.* ***1986***, 893.

[738] Laval, G.; Golding, B.T. *Synlett* ***2003***, 542.

[739] See Okada, K.; Okubo, K.; Oda, M. *Tetrahedron Lett.* ***1989***, *30*, 6733.

[740] See Deacon, G.B. *Organomet. Chem. Rev. A* ***1970***, 355; Deacon, G.B.; Faulks, S.J.; Pain, G.N. *Adv. Organomet. Chem.* ***1986***, *25*, 237.

[741] Kolarovi, A.; Fberov, Z. *J. Org. Chem.* ***2009***, *74*, 7199.

[742] Grant, J.L.; Hsieh, C.H.; Makris, T.M. *J. Am. Chem. Soc.* ***2015***, *137*, 4940.

[743] Maetani, S.; Fukuyama, T.; Suzuki, N.; Ishihara, D.; Ryu, I. *Chem. Commun.* ***2012***, *48*, 2552.

[744] Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G.C.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2016***, *138*, 1832.

[745] Moriya, T.; Yoneda, S.; Kawana, K.; Ikeda, R.; Konakahara, T.; Sakai, N. *J. Org. Chem.* ***2013***, *78*, 10642.

[746] Tan, X.; Song, T.; Wang, Z.; Chen, H.; Cui, L.; Li, C. *Org. Lett.* ***2017***, *19*, 1634. Also see Candish, L.; Standley, E.A.; Gómez-Suárez, A.; Mukherjee, S.; Glorius, F. *Chem. Eur. J.* ***2016***, *22*, 9971.

amine unit to give allylic amines.[747] Conjugated ketones were produced by the reaction of α-oxocarboxylic acids with allyl α-oxocarboxylates and a Pd catalyst via decarboxylative allylation.[748] Propiolic acids reacted with alkyl halides in the presence of CuI as a catalyst to give the alkyne via decarboxylative alkylation.[749] The mechanism of the silver-catalyzed decarboxylative fluorination has been discussed.[750] *Barton decarboxylation* using ultrasonic flow conditions (Sec. 7.D) has been reported.[751]

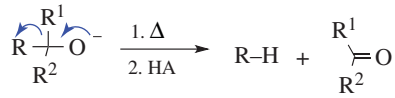
Some carboxylic acids that cannot form a six-membered transition state in accord with the six-centered transition state shown above can still be decarboxylated, presumably via an S_E1 or S_E2 mechanism.[752] Further evidence for the cyclic mechanism is that the reaction rate varies very little with a change from a nonpolar to a polar solvent (even from benzene to water[753]), and is not subject to acid catalysis.[754] The rate of decarboxylation of a β,γ-unsaturated acid was increased $\sim 10^5$–10^6 times by introduction of a β-methoxy group, indicating that the cyclic transition state has dipolar character.[755] Rate constants for decarboxylation reactions have been calculated using no barrier theory.[756]

Decarboxylative alkylation and arylation reactions are known. In the presence of a Ru catalyst and a *B*-phenyl borinate, decarboxylation of proline esters leads to 2-phenylpyrrolidine derivatives.[757] In the presence of a Pd catalyst, esters undergo decarboxylation with coupling between the alkyl groups on the carbonyl and the ester oxygen to give the corresponding hydrocarbon fragment.[758]

With ester or nitrile hydrolysis: OS **I**, 290, 451, 523; **II**, 200, 391; **III**, 281, 286, 313, 326, 510, 513, 591; **IV**, 55, 93, 176, 441, 664, 708, 790, 804; **V**, 76, 288, 572, 687, 989; **VI**, 615, 781, 873, 932; **VII**, 50, 210, 319; **VIII**, 263.

Simple decarboxylations: OS **I**, 351, 401, 440, 473, 475; **II**, 21, 61, 93, 229, 302, 333, 368, 416, 474, 512, 523; **III**, 213, 425, 495, 705, 733, 783; **IV**, 234, 254, 278, 337, 555, 560, 597, 630, 731, 857; **V**, 251, 585; **VI**, 271, 965; **VII**, 249, 359; **VIII**, 235, 444, 536; **75**, 195. Also see, OS **IV**, 633.

12-40 Cleavage of Alkoxides



Alkoxides of tertiary alcohols can be cleaved in a reaction that is essentially the reverse of addition of carbanions to ketones (**16-22**).[759] The reaction is unsuccessful when the R

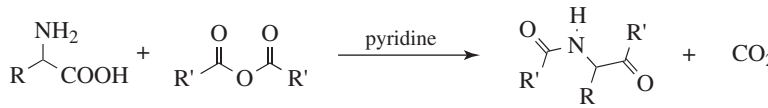
[747] Kiyokawa, K.; Yahata, S.; Kojima, T.; Minakata, S. *Org. Lett.* ***2014***, *16*, 4646.
[748] Manjolinho, F.; Grünberg, M.F.; Rodríguez, N.; Gooßen, L.J. *Eur. J. Org. Chem.* ***2012***, 4680.
[749] Li, T.; Sun, P.; Yang, H.; Zhu, Y.; Yan, H.; Lu, L.; Mao, J. *Tetrahedron* ***2012***, *68*, 6413.
[750] Patel, N.R.; Flowers II, R.A. *J. Org. Chem.* ***2015***, *80*, 5834.
[751] Banaszak-Léonard, E.; Mangin, F.; Len, C. *New J. Chem.* ***2016***, 7414.
[752] See Ferris, J.P.; Miller, N.C. *J. Am. Chem. Soc.* ***1966***, *88*, 3522.
[753] Swain, C.G.; Bader, R.F.W.; Esteve Jr., R.M.; Griffin, R.N. *J. Am. Chem. Soc.* ***1961***, *83*, 1951.
[754] Noyce, D.S.; Metesich, M.A. *J. Org. Chem.* ***1967***, *32*, 3243.
[755] Bigley, D.B.; Al-Borno, A. *J. Chem. Soc., Perkin Trans. 2* ***1982***, 15.
[756] Guthrie, J.P.; Peiris, S.; Simkin, M.; Wang, Y. *Can. J. Chem.* ***2010***, *88*, 79.
[757] Gribkov, D.V.; Pastine, S.J.; Schnürch, M.; Sames, D. *J. Am. Chem. Soc.* ***2007***, *129*, 11750.
[758] Waetzig, S.R.; Tunge, J.A. *J. Am. Chem. Soc.* ***2007***, *129*, 14860.
[759] Benkeser, R.A.; Siklosi, M.P.; Mozdzen, E.C. *J. Am. Chem. Soc.* ***1978***, *100*, 2134.

groups are simple unbranched alkyl groups, for example, the alkoxide of triethylcarbinol. Cleavage is accomplished with branched alkoxides, such as the alkoxides of diisopropylneopentylcarbinol or tri-*tert*-butylcarbinol.[760] Allylic,[761] benzylic,[762] and aryl groups also cleave; for example, the alkoxide of triphenylcarbinol gives benzene and benzophenone. Studies in the gas phase show that the cleavage is a simple one, giving the carbanion and ketone directly in one step.[763] However, with some substrates in solution, substantial amounts of dimer R—R have been found, indicating a radical pathway.[764] Hindered alcohols (not the alkoxides) also lose one R group by cleavage, also by a radical pathway.[765]

The retro-aldol (see **16-34**) is another example. The reaction has been used for extensive mechanistic studies (Sec. 12.A.ii).

OS **VI**, 268.

12-41 Replacement of a Carboxyl Group by an Acyl Group



When an α-amino acid is treated with an anhydride in the presence of pyridine, the carboxyl group is replaced by an acyl group and the NH_2 becomes acylated. This decarboxylation is called the *Dakin-West reaction*.[766] The mechanism involves formation of an oxazolone.[767] The reaction sometimes takes place on carboxylic acids even when an α-amino group is not present. A number of *N*-substituted amino acids, RCH(NHR′)COOH, give the corresponding *N*-alkylated products.

OS **IV**, 5; **V**, 27.

B. Acyl Cleavages

Formally, these reactions could be placed in Chapter 16, but because carbanion leaving groups are involved the reactions are placed here. In these reactions (**12-42** to **12-45**), a carbonyl group is attacked by a hydroxide ion (or an amide ion), giving an intermediate that undergoes cleavage to a carboxylic acid (or an amide). With respect to the leaving group, the carbanion must be stabilized. This is nucleophilic substitution at a carbonyl group and

[760] Arnett, E.M.; Small, L.E.; McIver Jr., R.T.; Miller, J.S. *J. Org. Chem.* ***1978***, *43*, 815. See also, Lomas, J.S.; Dubois, J.E. *J. Org. Chem.* ***1984***, *49*, 2067.

[761] See Snowden, R.L.; Linder, S.M.; Muller, B.L.; Schulte-Elte, K.H. *Helv. Chim. Acta* ***1987***, *70*, 1858, 1879.

[762] Partington, S.M.; Watt, C.I.F. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 983.

[763] Tumas, W.; Foster, R.F.; Brauman, J.I. *J. Am. Chem. Soc.* ***1988***, *110*, 2714; Ibrahim, S.; Watt, C.I.F.; Wilson, J.M.; Moore, C. *J. Chem. Soc., Chem. Commun.* ***1989***, 161.

[764] Paquette, L.A.; Gilday, J.P.; Maynard, G.D. *J. Org. Chem.* ***1989***, *54*, 5044; Paquette, L.A.; Maynard, G.D. *J. Org. Chem.* ***1989***, *54*, 5054.

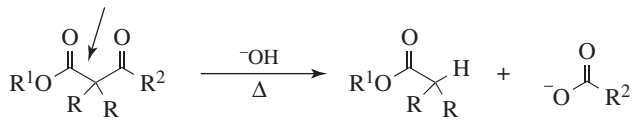
[765] See Lomas, J.S.; Fain, D.; Briand, S. *J. Org. Chem.* ***1990***, *55*, 1052, and references cited therein.

[766] See Buchanan, G.L. *Chem. Soc. Rev.* ***1988***, *17*, 91. See Behbahani, F.K.; Daloee, T.S. *Monatsh. Chem.* ***2014***, *145*, 683.

[767] Allinger, N.L.; Wang, G.L.; Dewhurst, B.B. *J. Org. Chem.* ***1974***, *39*, 1730; Dalla-Vechia, L.; Santos, V.G.; Godoi, M.N.; Cantillo, D.; Kappe, C.O.; Eberlin, M.N.; de Souza, R.O.M.A.; Miranda, L.S.M. *Org. Biomol. Chem.* ***2012***, *10*, 9013.

the mechanism is the tetrahedral one discussed in Sec. 16.A.i. With respect to R this is of course electrophilic substitution. The mechanism is usually S_E1.

12-42 Basic Cleavage of β-Keto Esters and β-Diketones



When β-keto esters are treated with concentrated base, cleavage occurs, but on the keto side of the CR_2 group in contrast to the acid cleavage mentioned in **12-39**. The products are a carboxylic ester and the salt of an acid. However, the utility of the reaction is somewhat limited by the fact that decarboxylation is a side reaction, even under basic conditions. β-Diketones behave similarly to give a ketone and the salt of a carboxylic acid. With both β-keto esters and β-diketones, $^-$OEt can be used instead of $^-$OH, in which case the ethyl esters of the corresponding acids are obtained instead of the salts. In the case of β-keto esters, this is the reverse of the *Claisen condensation* (**16-81**). The related cleavage of cyclic α-cyano ketones, in an intramolecular fashion, has been used in a synthesis of macrocyclic lactones.[768] Activated F^- (from KF and a crown ether) has been used as the base to cleave an α-cyano ketone.[769] Treatment with ceric ammonium nitrate led to cleavage of β-diketones to give a carboxylic acid.[770]

OS **II**, 266, 531; **III**, 379; **IV**, 415, 957; **V**, 179, 187, 277, 533, 747, 767.

12-43 Haloform Reaction

In the *haloform reaction*, methyl ketones (and the only methyl aldehyde, acetaldehyde) are cleaved with halogen and a base.[771] The halogen can be bromine, chlorine, or iodine. What takes place is actually a combination of two reactions. The first is an example of **12-4**, in which, under the basic conditions employed, the methyl group is trihalogenated. Then the resulting trihalo ketone is attacked by hydroxide ion to give tetrahedral intermediate **23**.[772] The X_3C^- group is a sufficiently good leaving group (not HX_2C^- or H_2XC^-) that a carboxylic acid is formed, which quickly reacts with the carbanion to give the final products. Primary or secondary methylcarbinols also give the reaction, because they are oxidized to the carbonyl compounds under the conditions employed.

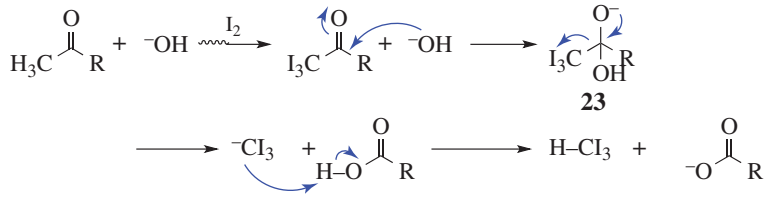
[768] Milenkov, B.; Hesse, M. *Helv. Chim. Acta* ***1987***, *70*, 308. For a similar preparation of lactams, see Wälchli, R.; Bienz, S.; Hesse, M. *Helv. Chim. Acta* ***1985***, *68*, 484.

[769] Beletskaya, I.P.; Gulyukina, N.S.; Borodkin, V.S.; Solov'yanov, A.A.; Reutov, O.A. *Doklad. Chem.* ***1984***, *276*, 202. See also, Mignani, G.; Morel, D.; Grass, F. *Tetrahedron Lett.* ***1987***, *28*, 5505.

[770] Zhang, Y.; Jiao, J.; Flowers II, R.A. *J. Org. Chem.* ***2006***, *71*, 4516.

[771] See Chakrabartty, S.K. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 343–370.

[772] See Zucco, C.; Lima, C.F.; Rezende, M.C.; Vianna, J.F.; Nome, F. *J. Org. Chem.* ***1987***, *52*, 5356.

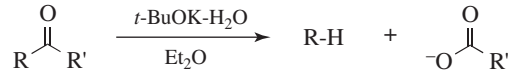


23

As with **12-4**, the rate-determining step is the preliminary enolization of the methyl ketone.[773] A side reaction is α-halogenation of the nonmethyl R group. Sometimes these groups are also cleaved.[774] The reaction cannot be applied to F_2, but ketones of the form $RCOCF_3$ (R = alkyl or aryl) give fluoroform and $RCOO^-$ when treated with base.[775] Rate constants for cleavage of X_3CCOPh (X = F, Cl, Br) were found to be in the ratio $1:5.3\times10^{10}:2.2\times10^{13}$, showing that an F_3C^- group cleaves much more slowly than the others.[776] In the past, the haloform reaction was used as a test for methylcarbinols and methyl ketones. Iodine was most often used as the test reagent, since iodoform (HCI_3) is an easily identifiable yellow solid. The reaction can be used for synthetic purposes. Methyl ketones $RCOCH_3$ can be converted directly to methyl esters RCO_2CH_3 by an electrochemical reaction.[777] Trifluoromethyl ketones have been converted to ethyl esters via treatment with NaH in aqueous DMF followed by reaction with bromoethane.[778]

OS **I**, 526; **II**, 428; **III**, 302; **IV**, 345; **V**, 8. Also see, OS **VI**, 618.

12-44 Cleavage of Nonenolizable Ketones



Ordinary ketones are generally much more difficult to cleave than trihalo ketones or β-diketones. However, nonenolizable ketones can be cleaved by treatment with a 10:3 mixture of *t*-BuOK-H_2O in an aprotic solvent such as ether, DMSO, 1,2-dimethoxyethane (glyme),[779] or with solid *t*-BuOK in the absence of a solvent.[780] When the reaction is applied to monosubstituted diaryl ketones, the aryl group that preferentially cleaves comes off as the more stable carbanion, except that aryl groups substituted in the *ortho* position are more readily cleaved than otherwise because of the steric effect (relief of strain).[780,781] In certain cases, cyclic ketones can be cleaved by base treatment, even if they are enolizable.[782]

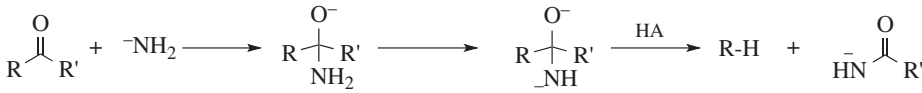
OS **VI**, 625. See also, OS **VII**, 297.

[773] Pocker, Y. *Chem. Ind. (London)* ***1959***, 1383.
[774] Levine, R.; Stephens, J.R. *J. Am. Chem. Soc.* ***1950***, *72*, 1642.
[775] See Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, ***1976***, pp. 276–278.
[776] Guthrie, J.P.; Cossar, J. *Can. J. Chem.* ***1990***, *68*, 1640.
[777] Nikishin, G.I.; Elinson, M.N.; Makhova, I.V. *Tetrahedron* ***1991***, *47*, 895.
[778] Delgado, A.; Clardy, J. *Tetrahedron Lett.* ***1992***, *33*, 2789.
[779] Gassman, P.G.; Lumb, J.T.; Zalar, F.V. *J. Am. Chem. Soc.* ***1967***, *89*, 946.
[780] March, J.; Plankl, W. *J. Chem. Soc., Perkin Trans. 1* ***1977***, 460.
[781] Davies, D.G.; Derenberg, M.; Hodge, P. *J. Chem. Soc. C* ***1971***, 455.
[782] See Hoffman, T.D.; Cram, D.J. *J. Am. Chem. Soc.* ***1969***, *91*, 1009.

12-45 The Haller-Bauer Reaction

Cleavage of ketones with sodium amide is called the *Haller-Bauer reaction*.[783] As with **12-44**, which is exactly analogous, the reaction is usually applied only to nonenolizable ketones, most often to ketones of the form $ArCOCR_3$, where the products R_3CCONH_2 (after hydrolysis) are not easily attainable by other methods. However, many other ketones have been used, although benzophenone is virtually unaffected.

It has been shown that the configuration of optically active alkyl groups (R) is retained.[784] The NH_2 loses its proton from the tetrahedral intermediate **24** before the R group is cleaved.[785]



24

An extension of this cleavage process involves the reaction of α-nitro ketones ($RCOCHRNO_2$) with a primary amine, neat, to give the corresponding amide, RCONHR′.[786]

OS **V**, 384, 1074.

C. Other Cleavages

12-46 The Cleavage of Alkanes

$$(CH_3)_4C \xrightarrow{FSO_3H-SbF_5} CH_4 + (CH_3)_3C^+$$

The C—C bonds of alkanes can be cleaved by treatment with superacids (Sec. 5.A.ii). For example, neopentane in FSO_3H/SbF_5 can cleave to give methane and the *tert*-butyl cation. A competing reaction of C—H cleavage (see **12-1**), for example of neopentane, can give H_2 and the *tert*-pentyl carbocation (formed by rearrangement of the initially formed neopentyl cation) by this pathway. In general, the order of reactivity is tertiary C—H > C—C > secondary C—H ≫ primary C—H, although steric factors cause a shift in favor of C—C cleavage in such a hindered compound as tri-*tert*-butylmethane. The mechanism is similar to that shown in **12-1** and **12-20** and involves attack by H^+ on the C—C bond to give a pentavalent cation.

Catalytic hydrogenation seldom breaks unactivated C—C bonds, i.e.,

$$R{-}R' + H_2 \rightarrow RH + R'H$$

[783] See Gilday, J.P.; Paquette, L.A. *Org. Prep. Proced. Int.* ***1990***, *22*, 167.
[784] See Paquette, L.A.; Ra, C.S. *J. Org. Chem.* ***1988***, *53*, 4978.
[785] Bunnett, J.F.; Hrutfiord, B.F. *J. Org. Chem.* ***1962***, *27*, 4152.
[786] Ballini, R.; Bosica, G.; Fiorini, D. *Tetrahedron* ***2003***, *59*, 1143.

but methyl and ethyl groups have been cleaved from substituted adamantanes by hydrogenation with a Ni/Al_2O_3 catalyst at about 250 °C.[787] Certain C—C bonds have been cleaved by alkali metals.[788]

12-47 Decyanation

$$RCN \xrightarrow{Na-NH_3 \text{ or } Na-Fe(acac)_3} RH$$

The cyano group of alkyl nitriles can be removed[789] by treatment with metallic Na, either in liquid ammonia,[790] or together with tris(acetylacetonato)iron(III) [$Fe(acac)_3$].[791] The two procedures are complementary. Although both can be used to decyanate many kinds of nitriles, the Na/NH_3 method gives high yields with R groups such as trityl, benzyl, phenyl, and tertiary alkyl, but lower yields (~35–50%) when R = primary or secondary alkyl. On the other hand, primary and secondary alkyl nitriles are decyanated in high yields by the $Na/Fe(acac)_3$ procedure. Sodium in liquid ammonia is known to be a source of solvated electrons, and the reaction may proceed through the free radical R• that would then be reduced to the carbanion R^-, which by abstraction of a proton from the solvent, would give RH. The mechanism with $Fe(acac)_3$ is presumably different. Another procedure,[792] which is successful for R = primary, secondary, or tertiary, involves the use of potassium metal and the crown ether dicyclohexano-18-crown-6 in toluene.[793]

α-Amino nitriles [$RCH(CN)NR'_2$] and α-amido nitriles [RCH(CN)NHCOR′] can be decyanated in high yield by treatment with $NaBH_4$.[794]

12.C.v. Electrophilic Substitution At Nitrogen

In most of the reactions in this section, an electrophile bonds with the unshared electron pair of a nitrogen atom. The electrophile may be a free positive ion or a positive species attached to a carrier that breaks off in the course of the attack or shortly after:

$$R_3N + Y{-}Z \rightarrow R_3N^+{-}Y + Z$$

Further reaction of the ammonium ion depends on the nature of Y and of the other groups attached to the nitrogen.

[787] Grubmüller, P.; Schleyer, P.v.R.; McKervey, M.A. *Tetrahedron Lett.* ***1979***, 181.

[788] See Grovenstein Jr., E.; Bhatti, A.M.; Quest, D.E.; Sengupta, D.; VanDerveer, D. *J. Am. Chem. Soc.* ***1983***, *105*, 6290.

[789] For a list of procedures, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley-VCH, NY, ***1999***, pp. 75.

[790] Birch, A.J.; Hutchinson, E.G. *J. Chem. Soc., Perkin Trans. 1* ***1972***, 1546; Yamada, S.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* ***1976***, 61.

[791] van Tamelen, E.E.; Rudler, H.; Bjorklund, C. *J. Am. Chem. Soc.* ***1971***, *93*, 7113.

[792] See Berkoff, C.E.; Rivard, D.E.; Kirkpatrick, D.; Ives, J.L. *Synth. Commun.* ***1980***, *10*, 939; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* ***1980***, *45*, 3227; Ozawa, F.; Iri, K.; Yamamoto, A. *Chem. Lett.* ***1982***, 1707.

[793] Ohsawa, T.; Kobayashi, T.; Mizuguchi, Y.; Saitoh, T.; Oishi, T. *Tetrahedron Lett.* ***1985***, *26*, 6103.

[794] Fabre, C.; Hadj Ali Salem, M.; Welvart, Z. *Bull. Soc. Chim. Fr.* ***1975***, 178. See also, Ogura, K.; Shimamura, Y.; Fujita, M. *J. Org. Chem.* ***1991***, *56*, 2920.

12-48 The Conversion of Hydrazines to Azides

$$RNHNH_2 + HONO \longrightarrow R{-}N{=}\overset{+}{N}{=}N^-$$

Monosubstituted hydrazines treated with nitrous acid give azides in a reaction exactly analogous to the formation of aliphatic diazo compounds mentioned in **13-19**. Examples of reagents used for this conversion are N_2O_4[795] and nitrosyl tetrafluoroborate ($NOBF_4$).[796]

OS **III**, 710; **IV**, 819; **V**, 157.

12-49 *N*-Nitrosation

$$R_2NH + HONO \longrightarrow R_2N{-}NO$$

When secondary amines are treated with nitrous acid (typically formed from sodium nitrite and a mineral acid),[797] *N*-nitroso compounds (also called nitrosamines) are formed.[798] The reaction can be accomplished with dialkyl-, diaryl-, or alkylarylamines, and even with mono-*N*-substituted amides:[799]

$$RCONHR' + HONO \rightarrow RCON(NO)R'$$

Tertiary amines have also been *N*-nitrosated, but in these cases one group cleaves, so that the product is the nitroso derivative of a secondary amine.[800] The group that cleaves appears as an aldehyde or ketone product. Other reagents have also been used, for example, NOCl, which is useful for amines or amides that are not soluble in an acidic aqueous solution or where the *N*-nitroso compounds are highly reactive. *N*-Nitroso compounds can be prepared in basic solution by treatment of secondary amines with gaseous N_2O_3, N_2O_4,[801] or alkyl nitrites,[802] and, in aqueous or organic solvents, by treatment with $BrCH_2NO_2$.[803] Secondary amines are converted to the *N*-nitroso compound with H_5IO_6 on wet silica.[804]

The mechanism of nitrosation is essentially the same as in **13-19** up to the point where Ar(R)N—N=O is formed. Since this species cannot lose a proton, it is stable and the reaction ends there. The attacking entity can be any of those mentioned in **13-19**. The mechanism suggested for the reaction with tertiary amines involves reaction with HONO to give the

[795] Kim, Y.H.; Kim, K.; Shim, S.B. *Tetrahedron Lett.* ***1986***, *27*, 4749.
[796] Pozsgay, V.; Jennings, H.J. *Tetrahedron Lett.* ***1987***, *28*, 5091.
[797] See Zolfigol, M.A.; Ghaemi, E.; Madrikian, E.; Kiany-Burazjani, M. *Synth. Commun.* ***2000***, *30*, 2057.
[798] See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 95–109; Kostyukovskii, Ya.L.; Melamed, D.B. *Russ. Chem. Rev.* ***1988***, *57*, 350; Saavedra, J.E. *Org. Prep. Proced. Int.* ***1987***, *19*, 83; Challis, B.C.; Challis, J.A. in Patai, S.; Rappoport, Z. *The Chemistry of the Functional Groups, Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 1151–1223. Also see Zyranov, G.V.; Rudkevich, D.M. *Org. Lett.* ***2003***, *5*, 1253.
[799] Castro, A.; Iglesias, E.; Leis, J.R.; Peña, M.E.; Tato, J.V. *J. Chem. Soc., Perkin Trans. 2* ***1986***, 1725.
[800] Hein, G.E. *J. Chem. Educ.* ***1963***, *40*, 181. See also, Verardo, G.; Giumanini, A.G.; Strazzolini, P. *Tetrahedron* ***1990***, *46*, 4303.
[801] Challis, B.C.; Kyrtopoulos, S.A. *J. Chem. Soc., Perkin Trans. 1* ***1979***, 299.
[802] Casado, J.; Castro, A.; Lorenzo, F.M.; Meijide, F. *Monatsh. Chem.* ***1986***, *117*, 335.
[803] Challis, B.C.; Yousaf, T.I. *J. Chem. Soc., Chem. Commun.* ***1990***, 1598.
[804] Zolfigol, M.A.; Choghamarani, A.G.; Shivini, F.; Keypour, H.; Salehzadeh, S. *Synth. Commun.* ***2001***, *31*, 359. See Zolfigol, M.A.; Bagherzadeh, M.; Choghamarani, A.G.; Keypour, H.; Salehzadeh, S. *Synth. Commun.* ***2001***, *31*, 1161.

N-nitrosoamine, which loses HNO to give an iminium salt.[805] The iminium salt fragments to a ketone and an ammonium salt, and final reaction with HONO gives the final product, $R_2N{-}N{=}O$.[805] The evidence for this mechanism includes the facts that nitrous oxide is a product (formed by $2HNO \rightarrow H_2O + N_2O$) and that quinuclidine, where the nitrogen is at a bridgehead and cannot give elimination, does not react. Tertiary amines have also been converted to nitrosamines with nitric acid in Ac_2O[806] and with N_2O_4.[807]

Amines and amides can be *N*-nitrated[808] with nitric acid,[809] or NO_2^+,[810] and aromatic amines can be converted to triazenes with diazonium salts. Aliphatic primary amines can also be converted to triazenes if the diazonium salts contain electron-withdrawing groups.[811]

OS **I**, 177, 399, 417; **II**, 163, 211, 290, 460, 461, 462, 464 (Also see, **V**, 842); **III**, 106, 244; **IV**, 718, 780, 943; **V**, 336, 650, 797, 839, 962; **VI**, 542, 981. Also see, OS **III**, 711.

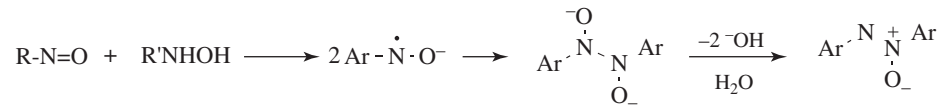
12-50 Conversion of Nitroso Compounds to Azoxy Compounds

In a reaction similar to **13-24**, azoxy compounds can be prepared by the condensation of a nitroso compound with a hydroxylamine.[812] The position of the oxygen in the final product is determined by the nature of the R groups, not by which R groups came from which starting compound. Both R and R′ can be alkyl or aryl, but when two different aryl groups are involved, mixtures of azoxy compounds (ArNONAr, ArNONAr′, and Ar′NONAr′) are obtained[813] and the unsymmetrical product (ArNONAr′) is likely to be formed in the smallest amount. This behavior is probably caused by an equilibration between the starting compounds prior to the actual reaction:[814]

$$ArNO + Ar'NHOH \rightarrow Ar'NO + ArNHOH$$

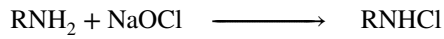
The mechanism[815] has been investigated in the presence of base. Under these conditions both reactants are converted to radical anions, which couple:

[805] Gowenlock, B.G.; Hutchison, R.J.; Little, J.; Pfab, J. *J. Chem. Soc., Perkin Trans. 2* ***1979***, 1110. See also, Loeppky, R.N.; Outram, J.R.; Tomasik, W.; Faulconer, J.M. *Tetrahedron Lett.* ***1983***, *24*, 4271.
[806] Boyer, J.H.; Pillai, T.P.; Ramakrishnan, V.T. *Synthesis* ***1985***, 677.
[807] Boyer, J.H.; Kumar, G.; Pillai, T.P. *J. Chem. Soc., Perkin Trans. 1* ***1986***, 1751.
[808] See Suri, S.C.; Chapman, R.D. *Synthesis* ***1988***, 743; Carvalho, E.; Iley, J.; Norberto, F.; Rosa, E. *J. Chem. Res. (S)* ***1989***, 260.
[809] Cherednichenko, L.V.; Dmitrieva, L.G.; Kuznetsov, L.L.; Gidaspov, B.V. *J. Org. Chem. USSR* ***1976***, *12*, 2101, 2105.
[810] Andreev, S.A.; Lededev, B.A.; Tselinskii, I.V. *J. Org. Chem. USSR* ***1980***, *16*, 1166, 1170, 1175, 1179.
[811] See Vaughan, K.; Stevens, M.F.G. *Chem. Soc. Rev.* ***1978***, *7*, 377.
[812] Boyer, J.H. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, ***1969***, pp. 278–283.
[813] See Ogata, Y.; Tsuchida, M.; Takagi, Y. *J. Am. Chem. Soc.* ***1957***, *79*, 3397.
[814] Knight, G.T.; Saville, B. *J. Chem. Soc., Perkin Trans. 2* ***1973***, 1550.
[815] For discussions of the mechanism in the absence of base, see Becker, A.R.; Sternson, L.A. *J. Org. Chem.* ***1980***, *45*, 1708. See also, Pizzolatti, M.G.; Yunes, R.A. *J. Chem. Soc., Perkin Trans. 1* ***1990***, 759.



These radical anions have been detected by ESR.[816] This mechanism is consistent with the following result: when nitrosobenzene and phenylhydroxylamine are coupled, ^{18}O and ^{15}N labeling show that the two nitrogen atoms and the two oxygen atoms become equivalent.[817] Unsymmetrical azoxy compounds can be prepared[818] by combination of a nitroso compound with an *N*,*N*-dibromoamine. Symmetrical and unsymmetrical azo and azoxy compounds are produced when aromatic nitro compounds react with aryliminodimagnesium reagents $ArN(MgBr)_2$.[819]

12-51 *N*-Halogenation



The use of *N*-haloamines in organic synthesis has been reviewed.[820] Treatment with sodium hypochlorite or hypobromite converts primary amines into *N*-halo- or *N*,*N*-dihaloamines. Secondary amines can be converted to *N*-halo secondary amines. Similar reactions can be carried out on unsubstituted and *N*-substituted amides and on sulfonamides. With unsubstituted amides, the *N*-halogen product is seldom isolated but usually rearranges (see **18-13**); however, *N*-halo-*N*-alkyl amides and *N*-halo imides are quite stable. The important reagents NBS and NCS are made in this manner. *N*-Halogenation has also been accomplished with other reagents (e.g., sodium bromite $NaBrO_2$),[821] benzyltrimethylammonium tribromide ($PhCH_2NMe_3{}^+Br_3{}^-$),[822] NaCl with Oxone,[823] and NCS.[824] Sodium hypohalite in the presence of *tert*-butanol and acetic acid is an efficient method for the preparation of *N*-haloamines.[825] The mechanisms of these reactions[826] involve attack by a positive halogen and are probably similar to those of **13-19** and **12-49**.[827] *N*-Fluorination can be accomplished by direct treatment of amines[828] or amides[829] with F_2. Trichloroisocyanuric acid converts primary amines to the *N*,*N*-dichloroamine.[830] Amides are *N*-chlorinated with

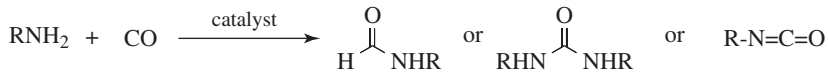
[816] Russell, G.A.; Geels, E.J.; Smentowski, F.J.; Chang, K.; Reynolds, J.; Kaupp, G. *J. Am. Chem. Soc.* ***1967***, *89*, 3821.
[817] Oae, S.; Fukumoto, T.; Yamagami, M. *Bull. Chem. Soc. Jpn.* ***1963***, *36*, 728.
[818] Zawalski, R.C.; Kovacic, P. *J. Org. Chem.* ***1979***, *44*, 2130. Also see Moriarty, R.M.; Hopkins, T.E.; Prakash, I.; Vaid, B.K.; Vaid, R.K. *Synth. Commun.* ***1990***, *20*, 2353.
[819] Okubo, M.; Matsuo, K.; Yamauchi, A. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 915, and other papers in this series.
[820] Veisi, H.; Ghorbani-Vaghei, R.; Ali-Zolfigol, M. *Org. Prep. Proceed. Int.* ***2011***, *43*, 489.
[821] Kajigaeshi, S.; Nakagawa, T.; Fujisaki, S. *Chem. Lett.* ***1984***, 2045.
[822] Kajigaeshi, S.; Murakawa, K.; Asano, K.; Fujisaki, S.; Kakinami, T. *J. Chem. Soc., Perkin Trans. 1* ***1989***, 1702.
[823] Curini, M.; Epifano, F.; Marcotullio, M.C.; Rosati, O.; Tsadjout, A. *Synlett* ***2000***, 813.
[824] See Guillemin, J.; Denis, J.N. *Synthesis* ***1985***, 1131.
[825] Zhong, Y.-L.; Zhou, H.; Gauthier, D.R.; Lee, J.; Askin, D.; Dolling, U.H.; Volante, R.P. *Tetrahedron Lett.* ***2005***, *46*, 1099.
[826] See Matte, D.; Solastiouk, B.; Merlin, A.; Deglise, X. *Can. J. Chem.* ***1989***, *67*, 786.
[827] See Thomm, E.W.C.W.; Wayman, M. *Can. J. Chem.* ***1969***, *47*, 3289; Higuchi, T.; Hussain, A.; Pitman, I.H. *J. Chem. Soc. B* ***1969***, 626.
[828] Sharts, C.M. *J. Org. Chem.* ***1968***, *33*, 1008.
[829] Grakauskas, V.; Baum, K. *J. Org. Chem.* ***1969***, *34*, 2840; ***1970***, *35*, 1545.
[830] DeLuca, L.; Giacomelli, G. *Synlett* ***2004***, 2180.

trichloroisocyanuric acid.[831] *N*-Heteroaromatic halides were prepared using Cl_3CCN/PPh_3 or CBr_4/PPh_3.[832] The *N*-chlorination of primary amines used $FeCl_3$ and mcpba.[833]

The synthesis of dichlorophosphines has been reported,[834] as well as of dibromophosphines.[835]

OS **III**, 159; **IV**, 104, 157; **V**, 208, 663, 909; **VI**, 968; **VII**, 223; **VIII**, 167, 427.

12-52 The Reaction of Amines With Carbon Monoxide or Carbon Dioxide



Three types of product can be obtained from the reaction of amines with carbon monoxide, depending on the catalyst.

1. Both primary and secondary amines react with CO in the presence of various catalysts [e.g., $Cu(CN)_2$, $Me_3N\text{-}H_2Se$, and Rh or Ru complexes] to give *N*-substituted and *N*,*N*-disubstituted formamides, respectively.[836] Primary aromatic amines react with ammonium formate to give the formamide.[837] Tertiary amines react with CO and a Pd catalyst to give an amide.[838]
2. Symmetrically substituted ureas can be prepared by treatment of a primary amine (or ammonia) with CO[839] in the presence of Se[840] or S.[841] R can be alkyl or aryl. The same thing can be done with secondary amines, using $Pd(OAc)_2\text{-}I_2\text{-}K_2CO_3$.[842] Treatment of a secondary amine with nitrobenzene, selenium, and carbon monoxide leads to the unsymmetrical urea.[843]
3. When $PdCl_2$ is the catalyst, primary amines yield isocyanates.[844] Isocyanates can also be obtained by treatment of CO with azides:[845]

$$RN_3 + CO \rightarrow RNCO$$

or with an aromatic nitroso or nitro compound and a Rh complex catalyst.[846]

[831] De Luca, L.; Giacomelli, G.; Nieddu, G. *Synlett* ***2005***, 223.
[832] Kijrungphaiboon, W.; Chantarasriwong, O.; Chavasiri, W. *Tetrahedron Lett.* ***2012***, *53*, 674.
[833] Liu, J.; Xu, J.; Ren, J.; Zeng, B.-B. *Chem. Lett.* ***2014***, *43*, 190.
[834] Tavtorkin, A.N.; Toloraya, S.A.; Nifant'ev, E.E.; Nifant'ev, I.E. *Tetrahedron Lett.* ***2011***, *52*, 824.
[835] Wang, L.; Zhang, L.; Shi, H.; Duan, Z.; Mathey, F. *Synlett* ***2013***, *24*, 2006.
[836] See Bitsi, G.; Jenner, G. *J. Organomet. Chem.* ***1987***, *330*, 429.
[837] Reddy, P.G.; Kumar, D.K.; Baskaran, S. *Tetrahedron Lett.* ***2000***, *41*, 9149.
[838] Troisi, L.; Granito, C.; Rosato, F.; Videtta, V. *Tetrahedron Lett.* ***2010***, *51*, 371; Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Eur. J.* ***2010***, *16*, 9750.
[839] See Gabriele, B.; Salerno, G.; Mancuso, R.; Costa, M. *J. Org. Chem.* ***2004***, *69*, 4741.
[840] Sonoda, N.; Yasuhara, T.; Kondo, K.; Ikeda, T.; Tsutsumi, S. *J. Am. Chem. Soc.* ***1971***, *93*, 6344.
[841] Franz, R.A.; Applegath, F.; Morriss, F.V.; Baiocchi, F.; Bolze, C. *J. Org. Chem.* ***1961***, *26*, 3309.
[842] Pri-Bar, I.; Alper, H. *Can. J. Chem.* ***1990***, *68*, 1544.
[843] Yang, Y.; Lu, S. *Tetrahedron Lett.* ***1999***, *40*, 4845.
[844] Stern, E.W.; Spector, M.L. *J. Org. Chem.* ***1966***, *31*, 596.
[845] Bennett, R.P.; Hardy, W.B. *J. Am. Chem. Soc.* ***1968***, *90*, 3295.
[846] Unverferth, K.; Tietz, H.; Schwetlick, K. *J. Prakt. Chem.* ***1985***, *327*, 932. See also, Kunin, A.J.; Noirot, M.D.; Gladfelter, W.L. *J. Am. Chem. Soc.* ***1989***, *111*, 2739.

Lactams are converted to the corresponding *N*-chloro lactam with $Ca(OCl)_2$ with moist alumina in dichloromethane.[847] Ring-expanded lactams are obtained from cyclic amines via a similar reaction[848] (see also, **16-20**). Intramolecular carbonylation of amines also leads to lactams.[849]

Another type of product, a carbamate (RNHCOOR′), can be obtained from primary or secondary amines, if these are treated with CO, O_2, and an alcohol (R′OH) in the presence of a catalyst.[850] Primary amines react with dimethyl carbonate in supercritical CO_2 (Sec. 9.D.ii) to give a carbamate.[851] Carbamates can also be obtained from nitroso compounds, by treatment with CO, R′OH, $Pd(OAc)_2$, and $Cu(OAc)_2$,[852] and from nitro compounds.[853] When allylic amines ($R_2C{=}CHRCHRNR'_2$) are treated with CO and a Pd-phosphine catalyst, the CO inserts to produce the β,γ-unsaturated amides ($R_2C{=}CHRCHRCONR'_2$) in good yields.[854] Silyloxy carbamates ($RNHCO_2SiR'_3$) can be prepared by the reaction of a primary amine with carbon dioxide and triethylamine, followed by reaction with triisopropylsilyl triflate and tetrabutylammonium fluoride.[855]

Carbon dioxide reacts with amines ($ArNH_2$) and alkyl halides, under electrolysis conditions, to give the corresponding carbamate ($ArNHCO_2Et$).[856] Secondary amines react with all halides and an onium salt in supercritical CO_2 (Sec. 9.D.ii) to give the carbamate.[857] *N*-Phenylthioamines react with CO and a Pd catalyst to give a thiocarbamate ($ArSCO_2NR'_2$).[858] Urea derivatives were obtained from amines, CO_2, and an Sb catalyst.[859]

Aziridines can be converted to cyclic carbamates (oxazolidinones) by heating with carbon dioxide and a Cr-salen catalyst.[860] The reaction of aziridines with LiI and then CO_2 also generates oxazolidinones.[861]

[847] Larionov, O.V.; Kozhushkov, S.I.; de Meijere, A. *Synthesis* ***2003***, 1916.
[848] Wang, M.D.; Alper, H. *J. Am. Chem. Soc.* ***1992***, *114*, 7018.
[849] Lu, S.-M.; Alper, H. *J. Am. Chem. Soc.* ***2005***, *127*, 14776.
[850] Feroci, M.; Inesi, A.; Rossi, L. *Tetrahedron Lett.* ***2000***, *41*, 963.
[851] Selva, M.; Tundo, P.; Perosa, A. *Tetrahedron Lett.* ***2002***, *43*, 1217. Also see Selva, M.; Tundo, P.; Perosa, A.; Dall'Acqua, F. *J. Org. Chem.* ***2005***, *70*, 2771.
[852] Alper, H.; Vasapollo, G. *Tetrahedron Lett.* ***1987***, *28*, 6411.
[853] Cenini, S.; Crotti, C.; Pizzotti, M.; Porta, F. *J. Org. Chem.* ***1988***, *53*, 1243; Reddy, N.P.; Masdeu, A.M.; El Ali, B.; Alper, H. *J. Chem. Soc., Chem. Commun.* ***1994***, 863.
[854] Murahashi, S.; Imada, Y.; Nishimura, K. *J. Chem. Soc., Chem. Commun.* ***1988***, 1578.
[855] Lipshutz, B.H.; Papa, P.; Keith, J.M. *J. Org. Chem.* ***1999***, *64*, 3792.
[856] Feroci, M.; Casadei, M.A.; Orsini, M.; Palombi, L.; Inesi, A. *J. Org. Chem.* ***2003***, *68*, 1548.
[857] Yoshida, M.; Hara, N.; Okuyama, S. *Chem. Commun.* ***2000***, 151.
[858] Kuniyasu, H.; Hiraike, H.; Morita, M.; Tanaka, A.; Sugoh, K.; Kurosawa, H. *J. Org. Chem.* ***1999***, *64*, 7305.
[859] Nomura, R.; Hasegawa, Y.; Ishimoto, M.; Toyosaki, T.; Matsuda, H. *J. Org. Chem.* ***1992***, *57*, 7339.
[860] Miller, A.W.; Nguyen, S.T. *Org. Lett.* ***2004***, *6*, 2301.
[861] Hancock, M.T.; Pinhas, A.R. *Tetrahedron Lett.* ***2003***, *44*, 5457.

CHAPTER 13

Aromatic Substitution: Nucleophilic and Organometallic

In Sec. 10.G, category 2, it was pointed out that nucleophilic substitutions proceed so slowly at an aromatic carbon that the reactions of Chapter 10 are not feasible for aromatic substrates. There are, however, exceptions to this statement, and these exceptions form the subject of this chapter.[1] Reactions that *are* successful at an aromatic substrate are largely of five kinds: (i) reactions activated by electron-withdrawing groups *ortho* and *para* to the leaving group; (ii) reactions catalyzed by very strong bases and proceeding through aryne intermediates; (iii) reactions initiated by electron donors; (iv) reactions in which the nitrogen of a diazonium salt is replaced by a nucleophile; and (v) coupling reactions[2] catalyzed by transition metals,[3] primarily Pd,[4] Cu, Ni, Pt,[5] Co,[6] Mo,[7] Fe,[8] etc. There are also transition metal-free coupling reactions.[9] It is noted that solvent effects can be important.[10] The transition metal-catalyzed coupling reactions are included because they involve replacement of a leaving group on an aromatic ring.

[1] See Zoltewicz, J.A. *Top. Curr. Chem.* ***1975***, *59*, 33.
[2] Arancon, R.A.D.; Lin, C.S.K.; Vargas, C.; Luque, R. *Org. Biomol. Chem.* ***2014***, *12*, 10.
[3] Mo, J.; Wang, L.; Liu, Y.; Cui, X. *Synthesis* ***2015***, *47*, 439; Li, H.; Sun, C.-L.; Yu, M.; Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Chem. Eur. J.* ***2011***, *17*, 3593; Chan, T.L.; Wu, Y.; Choy, P.Y.; Kwong, F.Y. *Chem. Eur. J.* ***2013***, *19*, 15802; Yang, J. *Org. Biomol. Chem.* ***2015***, *13*, 1930. See Ackermann, L. *Chem. Rev.* ***2011***, *111*, 1315. Also see Gulevich, A.V.; Dudnik, A.S.; Chernyak, N.; Gevorgyan,V. *Chem. Rev.* ***2013***, *113*, 3084.
[4] See Wu, Y.; Wang, J.; Mao, F.; Kwong, F.Y. *Chem. Asian J.* ***2014***, *9*, 26. Neufeldt, S.R.; Sanford, M.S. *Acc. Chem. Res.* ***2012***, *45*, 936; Froese, R.D.J.; Lombardi, C.; Pompeo, M.; Rucker, R.P.; Organ, M.G. *Acc. Chem. Res.* ***2017***, *50*, 2244.
[5] Labinger, J.A. *Chem. Rev.* ***2017***, *117*, 8483.
[6] Yoshikai, N. *Bull. Chem. Soc. Jpn.* ***2014***, *87*, 843; Röse, P.; Hilt, G. *Synthesis* ***2016***, *48*, 463.
[7] Schubert, M.; Waldvogel, S.R. *Eur. J. Org. Chem.* ***2016***, 1921.
[8] Kuzmina, O.M.; Steib, A.K.; Moyeux, A.; Cahiez, G.; Knochel, P. *Synthesis* ***2015***, *47*, 1696. Sun, C.-L.; Li, B.-J.; Shi, Z.J. *Chem. Rev.* ***2011***, *111*, 1293.
[9] Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* ***2014***, *114*, 9219.
[10] Acevedo, O.; Jorgensen, W.L. *Org. Lett.* ***2004***, *6*, 2881.

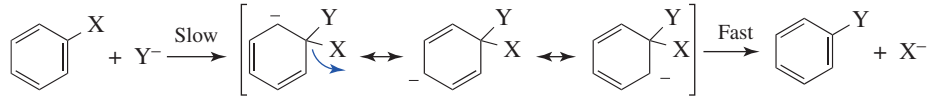
March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

13.A. MECHANISMS

There are four principal mechanisms for aromatic nucleophilic substitution.[11] Each of the four is similar to one of the aliphatic nucleophilic substitution mechanisms discussed in Chapter 10.

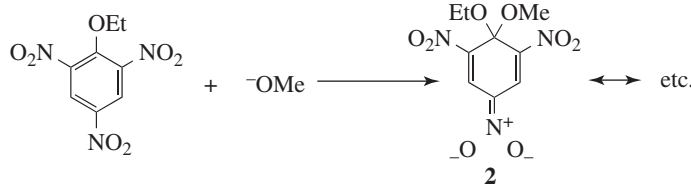
13.A.i. The S_NAr Mechanism[12]

By far the most important mechanism for nucleophilic aromatic substitution consists of two steps: (i) attack of the nucleophilic species at the *ipso* carbon of the aromatic ring (the carbon bearing the leaving group in this case), followed (ii) by elimination of the leaving group and regeneration of the aromatic ring.[13]



1

The reaction with the nucleophilic Y^- is usually, but not always, rate determining because an electron-rich species donating electrons to an electron-rich aromatic ring should be slow. The attacking species forms a bond with the substrate, giving an intermediate such as **1**, and then the leaving group departs. This is the S_NAr mechanism.[14] The IUPAC designation is $A_N + D_N$ (the same as for the tetrahedral mechanism; compare the designation $A_E + D_E$ for the arenium ion mechanism). This mechanism is generally found where activating groups are present on the ring (Sec. 13.B.i).



2

There is a great deal of evidence for the mechanism.[11] Probably the most convincing evidence was the isolation, as long ago as 1902, of the intermediate **2** in the reaction between 2,4,6-trinitrophenetole and methoxide ion.[15] Intermediates of this type are stable

[11] See Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***. For reviews, see Bernasconi, C.F. *Chimia* ***1980***, *34*, 1; *Acc. Chem. Res.* ***1978***, *11*, 147; Ross, S.D. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 407–431; Bunnett, J.F. *Tetrahedron* ***1993***, *49*, 4477; Zoltewicz, J.A. *Top. Curr. Chem.* ***1975***, *59*, 33. See Drapeau, M.P.; Ollevier, T.; Taillefer, M. *Chem. Eur. J.* ***2014***, *20*, 5231.

[12] See Barrett, I.C.; Kerr, M.A. *Tetrahedron Lett.* ***1999***, *40*, 2439. Terrier, F. *Modern Nucleophilic Aromatic Substitution*, Wiley-VCH, Weinheim, ***2013***; Ormazábal-Toledo, R.; Contreras, R.; Campodónico, P.R. *J. Org. Chem.* ***2013***, *78*, 1091.

[13] Wubbels, G.G. *Tetrahedron Lett.* ***2014***, *55*, 5066. For a discussion of regioselectivity with aromatic fluorides, see Liljenberg, M.; Brinck, T.; Herschend, B.; Rein, T.; Rockwell, G.; Svensson, M. *Tetrahedron Lett.* ***2011***, *52*, 3150.

[14] Also see Wu, Z.; Glaser, R. *J. Am. Chem. Soc.* ***2004***, *126*, 10632.

[15] Meisenheimer, J. *Liebigs Ann. Chem.* ***1902***, *323*, 205; see Jackson, C.L.; Gazzolo, F.H. *Am. Chem. J.* ***1900***, *23*, 376; Jackson, C.L.; Earle, R.B. *Am. Chem. J.* ***1903***, *29*, 89. The aromatic nucleophilic substitution pathway has been questioned for nitroarenes, see Błaziak, K.; Danikiewicz, W.; Mąkosza, M. *J. Am. Chem. Soc.* ***2016***, *138*, 7276. For base-dependent selectivity, see Chan, L.C.; Cox, B.G.; Jones, I.C.; Tomasi, S. *J. Phys. Org. Chem.* ***2011***, *24*, 751.

salts, called *Meisenheimer* or *Meisenheimer-Jackson salts*,[16] and many more have been isolated.[17] The structures of several of these intermediates have been proved by NMR[18] and by X-ray crystallography.[19] Further evidence comes from studies of the effect of the leaving group on the reaction. If the mechanism were similar to either the S_N1 or S_N2 mechanisms described in Chapter 10, the Ar—X bond would be broken in the rate-determining step. In the S_NAr mechanism this bond is not broken until after the rate-determining step (i.e., if step 1 is rate determining). There is some evidence that electron transfer may be operative during this process.[20] If the S_NAr mechanism is operating, a change in leaving group should not have much effect on the reaction rate. In the reaction of dinitro compounds such as **3** with piperidine, when X was Cl, Br, I, SOPh, SO_2Ph, or *p*-nitrophenoxy, the rates differed only by a factor of ~5.[21]

3

This behavior would not be expected in a reaction in which the Ar—X bond is broken in the rate-determining step. The rates are not expected to be *identical*, because the nature of X affects the rate at which Y attacks.[22] An increase in the electronegativity of X causes a decrease in the electron density at the site of attack, resulting in a faster attack by a nucleophile. Thus, in the reaction just mentioned, when X = F, the relative rate was 3300 (compared with I = 1). The very fact that fluoro is the best leaving group among the halogens in most aromatic nucleophilic substitutions is good evidence that the mechanism is different from the S_N1 and the S_N2 mechanisms, where fluoro is by far the poorest leaving group of the halogens. This is an example of the element effect (Sec. 10.F).

The pattern of base catalysis of reactions with amine nucleophiles provides additional evidence. Bases only catalyze these reactions when a relatively poor leaving group (e.g., OR) is present (not Cl or Br) and only when relatively bulky amines are nucleophiles.[23] Bases could not catalyze step 1, but if amines are nucleophiles, bases can catalyze step 2. Base catalysis is found precisely in those cases where the amine moiety cleaves easily but X does not, so that k_1 is large and step 2 is rate determining. This is evidence for the S_NAr mechanism because it implies two steps. Furthermore, in cases where bases *are* catalysts, they catalyze only at low base concentrations: a plot of the rate against the base concentration shows that small increments of base rapidly increase the rate until a certain

[16] For a probable hydrogen bonded complex, see Imoto, M.; Matsui, Y.; Takeda, M.; Tamaki, A.; Taniguchi, H.; Mizuno, K.; Ikeda, H. *J. Org. Chem.* ***2011***, *76*, 6356. For heteroatom nucleophiles see Gallardo, I.; Guirado, G.; Marquet, J. *J. Org. Chem.* ***2002***, *67*, 2548.

[17] See Buncel, E.; Crampton, M.R.; Strauss, M.J.; Terrier, F. *Electron Deficient Aromatic- and Heteroaromatic-Base Interactions*, Elsevier, NY, ***1984***; Illuminati, G.; Stegel, F. *Adv. Heterocycl. Chem.* ***1983***, *34*, 305; Terrier, F. *Chem. Rev.* ***1982***, *82*, 77; Strauss, M.J. *Acc. Chem. Res.* ***1974***, *7*, 181.

[18] Crampton, M.R.; Gold, V. *J. Chem. Soc. B* ***1966***, 893. See Buncel, E.; Crampton, M.R.; Strauss, M.J.; Terrier, F. *Electron Deficient Aromatic- and Heteroaromatic-Base Interactions*, Elsevier, NY, ***1984***, pp. 15–133.

[19] Destro, R.; Gramaccioli, C.M.; Simonetta, M. *Acta Crystallogr.* ***1968***, *24*, 1369; Messmer, G.G.; Palenik, G.J. *Chem. Commun.* ***1969***, 470.

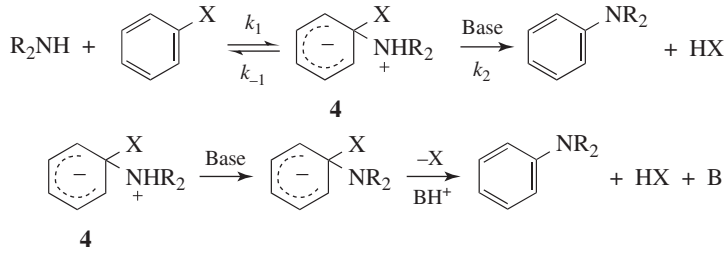
[20] Grossi, L. *Tetrahedron Lett.* ***1992***, *33*, 5645.

[21] Bunnett, J.F.; Garbisch Jr., E.W.; Pruitt, K.M. *J. Am. Chem. Soc.* ***1957***, *79*, 385. See Gandler, J.R.; Setiarahardjo, I.U.; Tufon, C.; Chen, C. *J. Org. Chem.* ***1992***, *57*, 4169.

[22] See Fernndez, I.; Frenking, G.; Uggerud, E. *J. Org. Chem.* ***2010***, *75*, 2971.

[23] Chiacchiera, S.M.; Singh, J.O.; Anunziata, J.D.; Silber, J.J. *J. Chem. Soc., Perkin Trans. 2* ***1987***, 987.

concentration of base is reached, after which further base addition no longer greatly affects the rate. This behavior, based on a partitioning effect (Sec. 11.A.i), is also evidence for the S_NAr mechanism. At low base concentration, each increment of base, by increasing the rate of step 2, increases the fraction of intermediate that goes to product rather than reverting to reactants. At high base concentration the process is virtually complete: there is very little reversion to reactants and the rate becomes dependent on step 1. Just how bases catalyze step 2 has been investigated. For protic solvents two proposals have been presented. One is that step 2 consists of two steps: rate-determining deprotonation of **4** followed by rapid loss of X, and that bases catalyze the reaction by increasing the rate of the deprotonation step.[24] According to the other proposal, loss of X assisted by BH^+ is rate determining.[25]



Two mechanisms, both based on kinetic evidence, have been proposed for aprotic solvents, such as benzene.[26] In both proposals the ordinary S_NAr mechanism operates, but in one the attacking species involves two molecules of the amine (the *dimer mechanism*),[27] while in the other there is a cyclic transition state.[28] Further evidence for the S_NAr mechanism has been obtained from $^{18}O/^{16}O$ and $^{15}N/^{14}N$ isotope effects.[29] The S_NAr reaction has been reported in water by micellar catalysis.[30]

The S_NAr mechanism has been studied for the reaction between picryl chloride (as well as other substrates) and ^-OH ions (**13-1**), and spectral evidence has been reported[31] for two intermediates, one a π complex (Sec. 11.A.i), and the other a radical ion–radical pair.

As with the tetrahedral mechanism at an acyl carbon, nucleophilic catalysis (Sec. 16.A.i) has been demonstrated with an aryl substrate, in certain cases.[32] There is also evidence of an interaction of anions with the π cloud of aromatic compounds.[33] Nucleophilic aromatic substitution of heterocycles has been reported using flow conditions (Sec.7.D).[34]

[24] Bernasconi, C.F.; de Rossi, R.H.; Schmid, P. *J. Am. Chem. Soc.* ***1977***, *99*, 4090.
[25] Bunnett, J.F.; Sekiguchi, S.; Smith, L.A. *J. Am. Chem. Soc.* ***1981***, *103*, 4865.
[26] For studies in different solvents, see Vlasov, V.M.; Kornakova, T.A. *J. Phys. Org. Chem.* ***2013***, *26*, 131.
[27] See Nudelman, N.S. *J. Phys. Org. Chem.* ***1989***, *2*, 1. See also, Nudelman, N.S.; Montserrat, J.M. *J. Chem. Soc., Perkin Trans. 2* ***1990***, 1073.
[28] Jain, A.K.; Gupta, V.K.; Kumar, A. *J. Chem. Soc., Perkin Trans. 2* ***1990***, 11.
[29] Ayrey, G.; Wylie, W.A. *J. Chem. Soc. B* ***1970***, 738.
[30] Isley, N.A.; Linstadt, R.T.H.; Kelly, S.M.; Gallou, F.; Lipshutz, B.H. *Org. Lett.* ***2015***, *17*, 4734.
[31] Bacaloglu, R.; Blaskó, A.; Bunton, C.A.; Dorwin, E.; Ortega, F.; Zucco, C. *J. Am. Chem. Soc.* ***1991***, *113*, 238.
[32] See Muscio Jr., O.J.; Rutherford, D.R. *J. Org. Chem.* ***1987***, *52*, 5194.
[33] Quiñonero, D.; Garau, C.; Rotger, C.; Frontera, A.; Ballester, P.; Costa, A.; Deyà, P.M. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3389.
[34] Charaschanya, M.; Bogdan, A.R.; Wang, Y.; Djuric, S.W. *Tetrahedron Lett.* ***2016***, *57*, 1035; Alam, M.P.; Jagodzinska, B.; Campagna, J.; Spilman, P.; John,V. *Tetrahedron Lett.* ***2016***, *57*, 2059.

13.A.ii. The S_N1 Mechanism

For aryl halides and sulfonates, even active ones, a unimolecular S_N1 mechanism (IUPAC: $D_N + A_N$) is very rare; it has only been observed for aryl triflates in which both *ortho* positions contain bulky groups (*tert*-butyl or SiR_3).[35] This mechanism seems to be observed in reactions with diazonium salts,[36] with slow loss of N_2 to give an aryl cation that reacts with the nucleophile, Y^-.[37] Among the evidence for the S_N1 mechanism[38] with aryl cations as intermediates,[39,40] is the following:[41]

1. The reaction rate is first order in diazonium salt and independent of the concentration of Y.
2. When high concentrations of halide salts are added, the product is an aryl halide but the rate is independent of the concentration of the added salts.
3. The effects of ring substituents on the rate are consistent with a unimolecular rate-determining cleavage.[42]
4. When reactions were run with substrate deuterated in the *ortho* position, isotope effects of ~1.22 were obtained.[43] It is difficult to account for such high secondary isotope effects in any other way except that an incipient phenyl cation is stabilized by hyperconjugation (Sec. 2.M),[44] which is diminished when hydrogen is replaced by deuterium.
5. The first step is reversible cleavage,[45] demonstrated by the observation that when $Ar^{15}N^+{\equiv}N$ was the reacting species, recovered starting material contained not only $Ar^{15}N^+{\equiv}N$ but also $ArN^+{\equiv}{}^{15}N$.[46,47] This observation could arise only if the nitrogen breaks away from the ring and then returns. Additional evidence was obtained by treating $PhN^+{\equiv}{}^{15}N$ with unlabeled N_2 at various pressures. At 300 atm, the recovered product had lost ~3% of the labeled nitrogen, indicating that PhN_2^+ was exchanging with atmospheric N_2.[47]

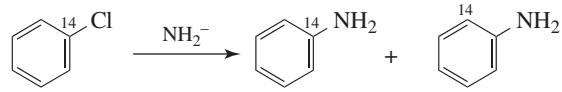
There is kinetic and other evidence[48] that the first step is more complicated and involves two steps, both reversible, where ArN_2^+ is in equilibrium with $[Ar^+\ N_2]$, which is in

[35] Himeshima, Y.; Kobayashi, H.; Sonoda, T. *J. Am. Chem. Soc.* ***1985***, *107*, 5286.
[36] See Glaser, R.; Horan, C.J.; Nelson, E.D.; Hall, M.K. *J. Org. Chem.* ***1992***, *57*, 215.
[37] Aryl iodonium salts Ar_2I^+ also undergo substitutions by this mechanism (and by a free-radical mechanism).
[38] Also see Lorand, J.P. *Tetrahedron Lett.* ***1989***, *30*, 7337.
[39] See Ambroz, H.B.; Kemp, T.J. *Chem. Soc. Rev.* ***1979***, *8*, 353.
[40] Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*, Academic Press, NY, 1979. See Hanack, M. *Pure Appl. Chem.* ***1984***, *56*, 1819; Rappoport, Z. *Reactiv. Intermed. (Plenum)* ***1983***, *3*, 427; Ambroz, H.B.; Kemp, T.J. *Chem. Soc. Rev.* ***1979***, *8*, 353. See also, Charton, M. *Mol. Struct. Energ.* ***1987***, *4*, 271; Glaser, R.; Horan, C.J.; Lewis, M.; Zollinger, H. *J. Org. Chem.* ***1999***, *64*, 902.
[41] See Zollinger, H. *Angew. Chem. Int. Ed.* ***1978***, *17*, 141; Richey Jr., H.G.; Richey, J.M. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 922–931; Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***, pp. 29–40.
[42] Lewis, E.S.; Miller, E.B. *J. Am. Chem. Soc.* ***1953***, *75*, 429.
[43] Swain, C.G.; Sheats, J.E.; Gorenstein, D.G.; Harbison, K.G. *J. Am. Chem. Soc.* ***1975***, *97*, 791.
[44] See Apeloig, Y.; Arad, D. *J. Am. Chem. Soc.* ***1985***, *107*, 5285.
[45] See Williams, D.L.H.; Buncel, E. *Isot. Org. Chem.* Vol. 5, Elsevier, Amsterdam, The Netherlands, ***1980***, pp. 147, 212; Zollinger, H. *Pure Appl. Chem.* ***1983***, *55*, 401.
[46] Lewis, E.S.; Kotcher, P.G. *Tetrahedron* ***1969***, *25*, 4873; Lewis, E.S.; Holliday, R.E. *J. Am. Chem. Soc.* ***1969***, *91*, 426; Tröndlin, F.; Medina, R.; Rüchardt, C. *Chem. Ber.* ***1979***, *112*, 1835.
[47] Bergstrom, R.G.; Landell, R.G.M.; Wahl Jr., G.H.; Zollinger, H. *J. Am. Chem. Soc.* ***1976***, *98*, 3301.
[48] Szele, I.; Zollinger, H. *Helv. Chim. Acta* ***1981***, *64*, 2728.

equilibrium with $Ar^+ + N_2$. The $[Ar^+\ N_2]$ intermediate, which is probably some kind of a tight ion–molecule pair, has been trapped with carbon monoxide.[49]

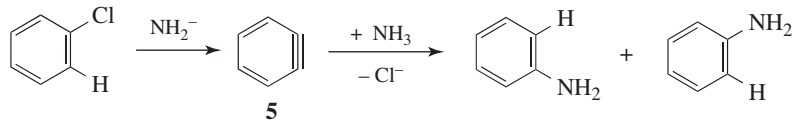
13.A.iii. The Benzyne Mechanism[50]

Some aromatic nucleophilic substitutions are clearly different in character from those that occur by the S_NAr mechanism (or the S_N1 mechanism). These substitutions occur with aryl halides that have no activating groups; stronger bases are required than those normally used and the incoming group does not always take the position vacated by the leaving group. The validity of the latter statement was elegantly demonstrated by the reaction of 1-^{14}C-chlorobenzene with potassium amide:



The product consisted of almost equal amounts of aniline labeled in the 1 position and in the 2 position.[51]

A mechanism that can explain all these facts involves elimination followed by addition. A suitable base removes the *ortho* hydrogen, with subsequent (or concomitant) loss of the chlorine (leaving group) to generate a symmetrical intermediate **5** called *benzyne.*[52] Subsequently, benzyne is attacked by the NH_3 at either of two positions, which explains why about half of the aniline produced from the radioactive chlorobenzene was labeled at the 2 position.[53] The fact that the 1 and 2 positions were not labeled equally is the result of a small isotope effect.



5

Other evidence for this mechanism is the following:

1. If the aryl halide contains two *ortho* substituents, the reaction should not be able to occur. This is indeed the case.[49]
2. It had been known many years earlier that aromatic nucleophilic substitution occasionally results in substitution at a different position. This is called *cine substitution*[54] and can be illustrated by the conversion of *o*-bromoanisole to *m*-aminoanisole.[55] In

[49] Ravenscroft, M.D.; Skrabal, P.; Weiss, B.; Zollinger, H. *Helv. Chim. Acta* ***1988***, *71*, 515.

[50] See Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, ***1967***; Gilchrist, T.L. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wiley, NY, ***1983***, pp. 383–419; Bryce, M.R.; Vernon, J.M. *Adv. Heterocycl. Chem.* ***1981***, *28*, 183; Levin, R.H. *React. Intermed. (Wiley)* ***1985***, *3*, 1; Fields, E.K. in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 449–508.

[51] Roberts, J.D.; Semenow, D.A.; Simmons, H.E.; Carlsmith, L.A. *J. Am. Chem. Soc.* ***1956***, *78*, 601.

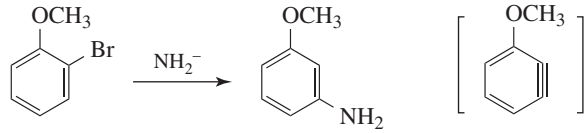
[52] See Hess Jr., B.A. *Eur. J. Org. Chem.* ***2001***, 2185; Wentrup, C. *Austr. J. Chem.* ***2010***, *63*, 979.

[53] The electrophilicity of benzyne and related intermediates has been quantified, see Nathel, N.F.F.; Morrill, L.A.; Mayr, H.; Garg, N.K. *J. Am. Chem. Soc.* ***2016***, *138*, 10402.

[54] See Suwinski, J.; Swierczek, K. *Tetrahedron* ***2001***, *57*, 1639.

[55] See Gilman, H.; Avakian, S. *J. Am. Chem. Soc.* ***1945***, *67*, 349. For a table of many such examples, see Bunnett, J.F.; Zahler, R.E. *Chem. Rev.* ***1951***, *49*, 273 (pp. 385).

this particular case, only the *meta* isomer is formed. The reason a 1 : 1 mixture is not formed is that the intermediate **6** is not symmetrical and the methoxy group directs the incoming group *meta*, but not *ortho* (Sec. 13.B.i). However, not all *cine* substitutions proceed by this kind of mechanism (see **13-31**). A study of the influence of structure on the formation of substituted benzynes, along with rate studies, has been reported.[56]



6

3. The fact that the order of halide reactivity is Br > I > Cl > F (when the reaction is performed with KNH_2 in liquid NH_3) shows that the S_NAr mechanism is not operating here.[51]

In the conversion of the substrate to **6**, either proton removal or subsequent loss of halide ion can be rate determining. In fact, the unusual leaving-group order just mentioned (Br > I > Cl) stems from a change in the rate-determining step. When the leaving group is Br or I, proton removal is rate determining and the rate order for this step is F > Cl > Br > I. When Cl or F is the leaving group, cleavage of the C—X bond is rate determining and the order for this step is I > Br > Cl > F. Confirmation of the latter order was found in a direct competitive study. *meta*-Dihalobenzenes in which the two halogens are different were treated with $^-NH_2$.[57] In such compounds, the most acidic hydrogen is the one between the two halogens; when it leaves, the remaining anion can lose either halogen. Therefore a study of which halogen is preferentially lost provides a direct measure of leaving-group ability. The order was found to be I > Br > Cl.[57,58]

Species such as **5** and **6** are *benzynes* (sometimes dehydrobenzenes) but the more general term is *arynes*,[59] and the mechanism in which such species are intermediates is known as the *benzyne mechanism*. Benzynes are very reactive, and neither benzyne nor any other aryne has yet been isolated under ordinary conditions,[60] but benzyne has been isolated in an argon matrix at 8 K,[61] and its IR spectrum observed. In addition, benzynes can be trapped; for example, they undergo the *Diels-Alder reaction* (**15-56**). Note that the extra pair of electrons does not affect the aromaticity. However, evaluation by a series of aromaticity indicators, including magnetic susceptibility anisotropies and exaltations,

[56] Riggs, J.C.; Ramirez, A.; Cremeens, M.E.; Bashore, C.G.; Candler, J.; Wirtz, M.C.; Coe, J.C.; Collum, D.B. *J. Am. Chem. Soc.* ***2008***, *130*, 3406.

[57] Bunnett, J.F.; Kearley Jr., F.J. *J. Org. Chem.* ***1971***, *36*, 184.

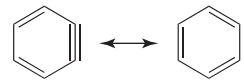
[58] See Kalendra, D.M.; Sickles, B.R. *J. Org. Chem.* ***2003***, *68*, 1594.

[59] See Pellissier, H.; Santelli, M. *Tetrahedron* ***2003***, *59*, 701. For the use of arynes in chemical synthesis, see Goetz, A.E.; Garg, N.K. *J. Org. Chem.* ***2014***, *79*, 846; Bhojgude, S.S.; Biju, A.T. *Angew. Chem. Int. Ed.* ***2012***, *51*, 1520. For a study of 3-silylarynes, see Bronner, S.M.; Mackey, J.L.; Houk, K.N.; Garg, N.K. *J. Am. Chem. Soc.* ***2012***, *134*, 13966; Yoshida, S.; Hosoya, T. *Chem. Lett.* ***2015***, *44*, 1450.

[60] See Gaviña, F.; Luis, S.V.; Costero, A.M.; Gil, P. *Tetrahedron* ***1986***, *42*, 155.

[61] Chapman, O.L.; Mattes, K.; McIntosh, C.L.; Pacansky, J.; Calder, G.V.; Orr, G. *J. Am. Chem. Soc.* ***1973***, *95*, 6134. For the IR spectrum of pyridyne trapped in a matrix, see Nam, H.; Leroi, G.E. *J. Am. Chem. Soc.* ***1988***, *110*, 4096. See Brown, R.D.; Godfrey, P.D.; Rodler, M. *J. Am. Chem. Soc.* ***1986***, *108*, 1296.

nucleus-independent chemical shifts (NICS), aromatic stabilization energies, and valence bond Pauling resonance energies point to the *o*-benzyne > *m*-benzyne > *p*-benzyne aromaticity order.[62] The relative order with respect to benzene depends on the aromaticity criterion.[58] It is noted that tunable reactivity for *meta*-benzynes has been demonstrated.[63] The aromatic sextet from the aromatic precursor functions as a closed ring, and the two additional electrons are merely located in a π orbital that covers only two carbons. Benzynes do not have a formal triple bond, since two canonical forms (**A** and **B**) contribute to the hybrid. The IR spectrum, mentioned above, indicates that **A** contributes more than **B**.



A **B**

Not only benzene rings but also other aromatic rings,[64] and even nonaromatic rings (Sec. 10.F), can react through this kind of intermediate. Of course, the nonaromatic rings do have a formal triple bond. When a benzyne unit is fused to a small ring, strain-induced regioselectivity is observed in its reactions.[65] 2-(Trimethylsilyl)phenyl trimethylsilyl ethers have been used as benzyne precursors.[66] The reaction of alcohols with *ortho*-benzynes has been studied.[67] Insertion reactions into C—C,[68] C—O, O—H,[69] C—I,[70] and I—I bonds[71] have been observed.[72] A photo-induced, benzyne click reaction has been reported.[73]

13.A.iv. The $S_{RN}1$ Mechanism

When 5-iodo-1,2,4-trimethylbenzene was treated with KNH_2 in NH_3, 2,3,5-trimethylaniline and 2,4,5-trimethylaniline were formed in the ratio 0.63 : 1. The presence of an unactivated substrate, a strong base, and the occurrence of *cine* substitution along with normal substitution are strong indications of a benzyne mechanism. Yet if that were so, 6-iodo-2,4-trimethylbenzene should have given 2,3,5-trimethylaniline and 2,4,5-trimethylaniline in the same ratio (because the same aryne intermediate would be formed in both cases), but in this case the ratio of 2,3,5-trimethylaniline and 2,4,5-trimethylaniline

[62] DeProft, F.; Schleyer, P.v.R.; van Lenthe, J.H.; Stahl, F.; Geerlings, P. *Chem. Eur. J.* ***2002***, *8*, 3402.
[63] Nash, J.J.; Nizzi, K.E.; Adeuya, A.; Yurkovich, M.J.; Cramer, C.J.; Kenttämaa, H.I. *J. Am. Chem. Soc.* ***2005***, *127*, 5760.
[64] For reviews of *hetarynes*, see van der Plas, H.C.; Roeterdink, F. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wiley, NY, ***1983***, pp. 421–511; Reinecke, M.G. *Tetrahedron* ***1982***, *38*, 427; den Hertog, H.J.; van der Plas, H.C. *Adv. Heterocycl. Chem.* ***1971***, *40*, 121; Kauffmann, T.; Wirthwein, R. *Angew. Chem. Int. Ed.* ***1971***, *10*, 20.
[65] Hamura, T.; Ibusuki, Y.; Sato, K.; Matsumoto, T.; Osamura, Y.; Suzuki, K. *Org. Lett.* ***2003***, *5*, 3551; Mirzaei, S.; Khosravi, H. *Tetrahedron. Lett.* ***2017***, *58*, 3362.
[66] Ikawa, T.; Masuda, S.; Nakajima, H.; Akai, S. *J. Org. Chem.* ***2017***, *82*, 4242.
[67] Willoughby, P.H.; Niu, D.; Wang, T.; Haj, M.K.; Cramer, C.J.; Hoye, T.R. *J. Am. Chem. Soc.* ***2014***, *136*, 13657.
[68] Rao, B.; Tang, J.; Zeng, X. *Org. Lett.* ***2016***, *18*, 1678; Ahire, M.M.; Khan, R.; Mhaske, S.B. *Org. Lett.* ***2017***, *19*, 2134; Yoshida, H.; Takaki, K. *Synlett* ***2012***, *23*, 1725.
[69] Wen, C.; Chen, Q.; He, Z.; Yan, X.; Zhang, C.; Du, Z.; Zhang, K. *Tetrahedron Lett.* ***2015***, *56*, 5470.
[70] Zeng, Y.; Hu, J. *Chem. Eur. J.* ***2014***, *20*, 6866.
[71] Lojo, D.R.; Cobas, A.; Peña, D.; Pérez, D.; Guitián, E. *Org. Lett.* ***2012***, *14*, 1363.
[72] Łączkowski, K.Z.; García, D.; Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Org. Lett.* ***2011***, *13*, 960.
[73] Gann, A.W.; Amoroso, J.W.; Einck, V.J.; Rice, W.P.; Chambers, J.J.; Schnarr, N.A. *Org. Lett.* ***2014***, *16*, 2003.

was 5.9 : 1 (the chloro and bromo analogs did give the same ratio, 1.46 : 1, showing that the benzyne mechanism may be taking place there). To explain the iodo result, it has been proposed[74] that in addition to the benzyne mechanism, a free-radical mechanism is also operating:

$$ArI \xrightarrow[\text{donor}]{\text{Electron}} ArI^{\bullet -} \longrightarrow Ar\bullet + I^-$$

$$Ar\bullet + NH_2^- \longrightarrow ArNH_2^{\bullet -} + ArI \longrightarrow ArNH_2 + ArI^{\bullet -}$$

Followed by termination steps

This sequence is called the $S_{RN}1$ mechanism,[75] and many other examples are known (**13-2**, **13-3**, **13-5**, **13-15**). The IUPAC designation is $T + D_N + A_N$.[76] Note that the last step of the mechanism produces $ArI^{\bullet -}$ radical ions, so the process is a chain mechanism[77] (Sec. 14.A.i). An electron donor is required to initiate the reaction, and in the case above it was solvated electrons from KNH_2 in NH_3. Evidence for the mechanism was that the addition of potassium metal (a good producer of solvated electrons in ammonia) completely suppressed the *cine* substitution. Further evidence for the $S_{RN}1$ mechanism was that addition of radical scavengers (which would suppress a free-radical mechanism) led to 2,3,5-trimethylaniline and 2,4,5-trimethylaniline ratios much closer to 1.46 : 1. Numerous other observations of $S_{RN}1$ mechanisms that were stimulated by solvated electrons and inhibited by radical scavengers have also been recorded.[78] Further evidence for the $S_{RN}1$ mechanism in the case above was that some 1,2,4-trimethylbenzene was found among the products. This could easily be formed by abstraction by Ar• of H from the solvent NH_3. Besides initiation by solvated electrons,[79] $S_{RN}1$ reactions have been initiated photochemically,[80] electrochemically,[81] and even thermally.[82]

The $S_{RN}1$ reactions have a fairly wide scope. The efficiency of the reaction has been traced to the energy level of the radical anion of the substitution product.[83] There is no requirement for activating groups or strong bases, but in DMSO haloarenes are less reactive as the stability of the anion increases.[84] The reaction has also been done in liquid ammonia,

[74] Kim, J.K.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1970***, *92*, 7463, 7464.

[75] See Rossi, R.A.; de Rossi, R.H. *Aromatic Substitution by the SRN1 Mechanism*, American Chemical Society, Washington, ***1983***; Savéant, J. *Adv. Phys. Org. Chem.* ***1990***, *26*, 1; Norris, R.K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 1, Wiley, NY, ***1983***, pp. 681–701; Chanon, M.; Tobe, M.L. *Angew. Chem. Int. Ed.* ***1982***, *21*, 1; Rossi, R.A. *Acc. Chem. Res.* ***1982***, *15*, 164. Also see Rossi, R.A.; Pierini, A.B.; Palacios, S.M. *Adv. Free Radical Chem. (Greenwich, Conn.)* ***1990***, *1*, 193; Costentin, C.; Hapiot, P.; Médebielle, M.; Savéant, J.-M. *J. Am. Chem. Soc.* ***1999***, *121*, 4451. See Roche, M.; Terme, T.; Vanelle, P. *Tetrahedron Lett.* ***2012***, *53*, 4184; Peisino, L.E.; Pierini, A.B. *J. Org. Chem.* ***2013***, *78*, 4719.

[76] The symbol T is used for electron transfer.

[77] See Amatore, C.; Pinson, J.; Savéant, J.; Thiébault, A. *J. Am. Chem. Soc.* ***1981***, *103*, 6930.

[78] Bunnett, J.F. *Acc. Chem. Res.* ***1978***, *11*, 413.

[79] Savéant, J.-M. *Tetrahedron* ***1994***, *50*, 10117.

[80] See Cornelisse, J.; de Gunst, G.P.; Havinga, E. *Adv. Phys. Org. Chem.* ***1975***, *11*, 225; Cornelisse, J. *Pure Appl. Chem.* ***1975***, *41*, 433; Pietra, F. *Q. Rev. Chem. Soc.* ***1969***, *23*, 504 (pp. 519).

[81] See Savéant, J. *Acc. Chem. Res.* ***1980***, *13*, 323. See also, Alam, N.; Amatore, C.; Combellas, C.; Thiébault, A.; Verpeaux, J.N. *J. Org. Chem.* ***1990***, *55*, 6347.

[82] Swartz, J.E.; Bunnett, J.F. *J. Org. Chem.* ***1979***, *44*, 340, and references cited therein.

[83] Galli, C.; Gentili, P.; Guarnieri, A. *Gazz. Chim. Ital.* ***1995***, *125*, 409.

[84] Borosky, G.L.; Pierini, A.B.; Rossi, R.A. *J. Org. Chem.* ***1992***, *57*, 247.

promoted by ultrasound (Sec. 7.B),[85] and ferrous ion has been used as a catalyst.[86] Alkyl, alkoxy, aryl, and COO^- groups do not interfere, although Me_2N, O^-, and NO_2 groups do interfere. *Cine* substitution is not found.

13.A.v. Other Mechanisms

There is no clearcut proof that a one-step S_N2 mechanism, so important at a saturated carbon, ever actually occurs with an aromatic substrate. The hypothetical aromatic S_N2 process is sometimes called the *one-stage* mechanism to distinguish it from the *two-stage* S_NAr mechanism. A "clean" example of a $S_{RN}2$ reaction has been reported, the conversion of 2,3,4,5,6-pentafluoronitrobenzene to 2,3,5,6-tetrafluoro-4-nitroanisole in methanol.[87] Both $S_{RN}1$ and $S_{RN}2$ reactions have been reviewed.[88]

Some of the reactions in this chapter operate by still other mechanisms, among them an addition–elimination mechanism (see **13-12**). A new mechanism has been reported in aromatic chemistry, a reductively activated "polar" nucleophilic aromatic substitution.[89] The reaction of phenoxide with *p*-dinitrobenzene in DMF shows radical features that cannot be attributed to a radical anion, and it is not $S_{RN}2$. The new designation was proposed to account for these results.

13.B. REACTIVITY

13.B.i. The Effect of Substrate Structure

In the discussion of electrophilic aromatic substitution (Chapter 11) equal attention was paid to the effect of substrate structure on reactivity (activation or deactivation) and on orientation. The question of orientation was important because in a typical substitution there are four or five hydrogen atoms that could serve as leaving groups. This type of question is much less important for aromatic nucleophilic substitution, since in most cases there is only one potential leaving group in a molecule. Therefore attention is largely focused on the reactivity of one molecule compared with another and not on the comparison of the reactivity of different positions within the same molecule.

S_NAr Mechanism

These substitutions are accelerated by electron-withdrawing groups, especially in positions *ortho* and *para* to the leaving group[90] and are hindered by electron-attracting groups. This is, of course, opposite to the effects of these groups on electrophilic substitutions, and the reasons are similar to those discussed in Sec. 11.A.i. When attached to a benzene ring, the rate of reaction depends on the substituent.[91] Activating groups include

[85] Manzo, P.G.; Palacios, S.M.; Alonso, R.A. *Tetrahedron Lett.* ***1994***, *35*, 677.
[86] Galli, C.; Gentili, P. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 1135.
[87] Marquet, J.; Jiang, Z.; Gallardo, I.; Batlle, A.; Cayón, E. *Tetrahedron Lett.* ***1993***, *34*, 2801. Also see, Keegstra, M.A. *Tetrahedron* ***1992***, *48*, 2681.
[88] Rossi, R.A.; Palacios, S.M. *Tetrahedron* ***1993***, *49*, 4485.
[89] Marquet, J.; Casado, F.; Cervera, M.; Espín, M.; Gallardo, I.; Mir, M.; Niat, M. *Pure Appl. Chem.* ***1995***, *67*, 703.
[90] With *meta* substituents, electron-withdrawing groups also increase the rate: see Nurgatin, V.V.; Sharnin, G.P.; Ginzburg, B.M. *J. Org. Chem. USSR* ***1983***, *19*, 343.
[91] See Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***, pp. 61–136.

2-nitro,[92,93] N_2^+, NO, or C=N units with strong nucleophiles. When a nitro group is attached SO_2Me, NMe_3, CF_3, CN, CHO, COR, CO_2H, SO_3, halogen, H, Me, or OMe activate.[91] Nitrogen atoms are also strongly activating (especially to the α and γ positions) and are even more so when quaternized.[94] Both 2- and 4-chloropyridine, for example, are often used as substrates. Heteroaromatic amine *N*-oxides are readily attacked by nucleophiles in the 2 and 4 positions, but the oxygen is generally lost in these reactions.[95] The most highly activating group, N_2^+, is seldom deliberately used to activate a reaction, but it sometimes happens that in the diazotization of a compound such as *p*-nitroaniline or *p*-chloroaniline, the group *para* to the diazonium group is replaced by OH from the solvent or by X from $ArN_2^+ X^-$ untouched. By far the most common activating group is the nitro group and the most common substrates are 2,4-dinitrophenyl halides and 2,4,6-trinitrophenyl halides (also called picryl halides).[96] Polyfluorobenzenes[97] (see **11**) also undergo aromatic nucleophilic substitution quite well.[98] Benzene rings that lack activating substituents are generally not useful substrates for the S_NAr mechanism, because the two extra electrons in **1** are in an antibonding orbital (Sec. 2.A). Activating groups, by withdrawing electron density, are able to stabilize the intermediates and the transition states leading to them. Reactions taking place by the S_NAr mechanism are also accelerated when the aromatic ring is coordinated with a transition metal.[99]

Just as electrophilic aromatic substitutions were found more or less to follow the *Hammett relationship* (with σ^+ instead of σ; Sec. 9.C) so do nucleophilic substitutions, with σ^- instead of σ for electron-withdrawing groups.[100]

Benzyne Mechanism

Two factors affect the position of the incoming group, the first being the direction in which the aryne forms.[101] When there are groups *ortho* or *para* to the leaving group, there is no choice:

[92] For reviews of reactivity of nitrogen-containing heterocycles, see Illuminati, G. *Adv. Heterocycl. Chem.* ***1964***, *3*, 285; Shepherd, R.G.; Fedrick, J.L. *Adv. Heterocycl. Chem.* ***1965***, *4*, 145.

[93] See Albini, A.; Pietra, S. *Heterocyclic N-Oxides*, CRC Press, Boca Raton, FL, ***1991***, pp. 142–180; Katritzky, A.R.; Lagowski, J.M. *Chemistry of the Heterocyclic N-Oxides*, Academic Press, NY, ***1971***, pp. 258–319, 550–553.

[94] Miller, J.; Parker, A.J. *Aust. J. Chem.* ***1958***, *11*, 302.

[95] Berliner, E.; Monack, L.C. *J. Am. Chem. Soc.* ***1952***, *74*, 1574.

[96] See de Boer, T.J.; Dirkx, I.P. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, ***1970***, pp. 487–612.

[97] Fluorine significantly activates *ortho* and *meta* positions, and slightly deactivates *para* positions. See Chambers, R.D.; Seabury, N.J.; Williams, D.L.H.; Hughes, N. *J. Chem. Soc., Perkin Trans. 1* ***1988***, 255.

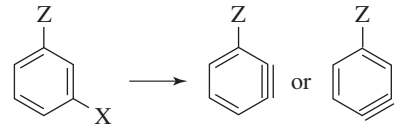
[98] See Yakobson, G.G.; Vlasov, V.M. *Synthesis* ***1976***, 652; Kobrina, L.S. *Fluorine Chem. Rev.* ***1974***, *7*, 1.

[99] See Balas, L.; Jhurry, D.; Latxague, L.; Grelier, S.; Morel, Y.; Hamdani, M.; Ardoin, N.; Astruc, D. *Bull. Soc. Chim. Fr.* ***1990***, 401.

[100] See Bartoli, G.; Todesco, P.E. *Acc. Chem. Res.* ***1977***, *10*, 125; there is a list of σ− values in Table 9.4 in Sec. 9.C.

[101] From Roberts, J.D.; Vaughan, C.W.; Carlsmith, L.A.; Semenow, D.A. *J. Am. Chem. Soc.* ***1956***, *78*, 611. See Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, ***1973***, pp. 134–150.

but when a *meta* group is present, the aryne can form in two different ways:



In such cases, the more acidic hydrogen is removed. Since acidity is related to the field effect of Z, it can be stated that an electron-attracting Z favors removal of the *ortho* hydrogen while an electron-donating Z favors removal of the *para* hydrogen. The second factor is that the aryne, once formed, can be attacked at two positions. The favored position for nucleophilic attack is the one that leads to the more stable carbanion intermediate, and this in turn also depends on the field effect of Z. For $-I$ groups, the more stable carbanion is the one in which the negative charge is closer to the substituent.

These principles are illustrated by the reaction of the three dichlorobenzenes (**13-16**) with alkali metal amides to give the predicted products shown. In each case, the predicted product was the one chiefly formed.[102] The observation that *m*-aminoanisole is obtained, mentioned in Sec. 13.A.iii, is also in accord with these predictions.

13.B.ii. The Effect of the Leaving Group[103]

The common leaving groups in aliphatic nucleophilic substitution (halide, sulfate, sulfonate, NR_3^+, etc.) are also common leaving groups in aromatic nucleophilic substitutions, but the groups NO_2, OR, OAr, SO_2R,[104] and SR, which are not generally lost in aliphatic systems, *are* leaving groups when attached to aromatic rings. Surprisingly, NO_2 is a particularly good leaving group.[105] An approximate order of leaving-group ability[106] is $F > NO_2 > OTs > SOPh > Cl,\ Br,\ I > N_3 > NR_3^+ > OAr,\ OR,\ SR,\ NH_2$. However, this depends greatly on the nature of the nucleophile, as illustrated by the fact that $C_6Cl_5OCH_3$ treated with NH_2^- gives mostly $C_6Cl_5NH_2$; that is, the one methoxy group is replaced in preference to the five chlorines.[107] As usual, OH can be a leaving group if it is converted to an inorganic ester. Among the halogens, fluoro is generally a much better leaving group than the other halogens, which have reactivities fairly close together. The order is usually $Cl > Br > I$, but not always.[108] The leaving-group order is quite different from that for the S_N1 or S_N2 mechanisms. The most likely explanation is that the first step of the S_NAr mechanism is usually rate determining, and this step is promoted by groups with strong $-I$ effects. This would explain why fluoro and nitro are such good leaving groups when this mechanism is operating. Fluoro is the poorest leaving group of the halogens when the second step of the S_NAr mechanism is rate determining or when the benzyne mechanism is

[102] Wotiz, J.H.; Huba, F. *J. Org. Chem.* ***1959***, *24*, 595. See also, Biehl, E.R.; Razzuk, A.; Jovanovic, M.V.; Khanapure, S.P. *J. Org. Chem.* ***1986***, *51*, 5157.

[103] See Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***, pp. 137–179.

[104] See Furukawa, N.; Ogawa, S.; Kawai, T.; Oae, S. *J. Chem. Soc., Perkin Trans. 1* ***1984***, 1839.

[105] See Beck, J.R. *Tetrahedron* ***1978***, *34*, 2057. See also, Effenberger, F.; Koch, M.; Streicher, W. *Chem. Ber.* ***1991***, *24*, 163.

[106] Loudon, J.D.; Shulman, N. *J. Chem. Soc.* ***1941***, 772; Suhr, H. *Chem. Ber.* ***1963***, *97*, 3268.

[107] Kobrina, L.S.; Yakobson, G.G. *J. Gen. Chem. USSR* ***1963***, *33*, 3238.

[108] Reinheimer, J.D.; Taylor, R.C.; Rohrbaugh, P.E. *J. Am. Chem. Soc.* ***1961***, *83*, 835; Ross, S.D. *J. Am. Chem. Soc.* ***1959***, *81*, 2113; Litvinenko, L.M.; Shpan'ko, L.V.; Korostylev, A.P. *Doklad. Chem.* ***1982***, *266*, 309.

operating. The four halogens, as well as SPh, NMe_3^+, and $OPO(OEt)_2$, have been shown to be leaving groups in the $S_{RN}1$ mechanism.[77] The only important leaving group in the S_N1 mechanism is N_2^+.

13.B.iii. The Effect of the Attacking Nucleophile[109]

It is not possible to construct an invariant nucleophilicity order because different substrates and different conditions lead to different orders of nucleophilicity, but an overall approximate order is $^-NH_2 > Ph_3C^- > PhNH^-$ (aryne mechanism) $> ArS^- > RO^- > R_2NH > ArO^- > {}^-OH > ArNH_2 > NH_3 > I^- > Br^- > Cl^- > H_2O > ROH$.[110] As with aliphatic nucleophilic substitution, nucleophilicity is generally dependent on base strength and nucleophilicity increases as the attacking atom moves down a column of the periodic table, but there are some surprising exceptions; for example, ^-OH, a stronger base than ArO^-, is a poorer nucleophile.[111] In a series of similar nucleophiles, such as substituted anilines, nucleophilicity *is* correlated with base strength. Oddly, the cyanide ion is not a nucleophile for aromatic systems, except for sulfonic acid salts and in the *von Richter* (**13-31**) and *Rosenmund-von Braun* (**13-8**) reactions, which are special cases. Studies on the nature of the nucleophile continue. Indeed, the second-order rate constants for vicarious nucleophilic substitution reactions of some carbanions were measured to define electrophilicity parameters for electron-deficient heteroarenes.[112]

13.C. REACTIONS

In the first part of this section, reactions are classified according to the attacking species, with all leaving groups considered together, except for hydrogen and N_2^+, which are treated subsequently. Finally, a few rearrangement reactions are discussed.

13.C.i. All Leaving Groups Except Hydrogen And N_2^+

A. Oxygen Nucleophiles

13-1 Hydroxylation of Aromatic Compounds

$$ArBr + OH^- \longrightarrow ArOH$$

Direct hydroxylation of aryl halides to give phenols generally requires the presence of activating groups or exceedingly strenuous reaction conditions.[113] When the reaction is carried out at high temperatures, *cine* substitution is observed, indicating a benzyne

[109] See Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***, pp. 180–233.
[110] From Bunnett, J.F.; Zahler, R.E. *Chem. Rev.* ***1951***, *49*, 273 (p. 340); Sauer, J.; Huisgen, R. *Angew. Chem.* ***1960***, *72*, 294 (p. 311); Bunnett, J.F. *Annu. Rev. Phys. Chem.* ***1963***, *14*, 271.
[111] See Amatore, C.; Combellas, C.; Robveille, S.; Savéant, J.; Thiébault, A. *J. Am. Chem. Soc.* ***1986***, *108*, 4754, and references cited therein.
[112] Seeliger, F.; Błażej, S.; Bernhardt, S.; Mąkosza, M.; Mayr, H. *Chem. Eur. J.* ***2008***, *14*, 6108.
[113] See Fyfe, C.A. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 83–124.

mechanism.[114] However, phenols are prepared from aryl halides using KOH and a Pd catalyst at 100 °C.[115] Formation of phenols is possible using $AgNO_3$ with microwave irradiation,[116] or CuI.[117] Other microwave-promoted phenol-forming reactions are known.[118] A slightly related reaction involves the amino group of naphthylamines, which can be replaced by a hydroxyl group by treatment with aqueous bisulfite.[119]

Continuous flow techniques (Sec. 7.D) have been applied to the synthesis of phenols.[120] Phenols have been obtained from unactivated aryl halides by treatment with borane and a metal such as lithium, followed by oxidation with alkaline H_2O_2.[121] Arylboronic acids, $ArB(OH)_2$, are oxidized by aqueous hydrogen peroxide to give the corresponding phenol.[122] Aryllithium reagents have been converted to phenols by treatment with oxygen.[123] Arylboronic acids reacted with aqueous hydrogen peroxide and acidic alumina to give phenols,[124] or with iron(III) oxide as a photocatalyst to give phenols.[125] Benzene was converted to phenol by reaction with O_2 and a NADH analog,[126] or by using H_2O_2 and a specialized molecular sieve.[127] The oxidative hydroxylation of arylboronic acids by visible light photoredox catalysis has been reported.[128] Metal-free conversion of aryl halides to phenols have been reported.[129]

[114] For a discussion of ^{14}C labeling experiments: Bottini, A.T.; Roberts, J.D. *J. Am. Chem. Soc.* ***1957***, *79*, 1458; Dalman, G.W.; Neumann, F.W. *J. Am. Chem. Soc.* ***1968***, *90*, 1601.

[115] Anderson, K.W.; Ikawa, T.; Tundel, R.E.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2006***, *128*, 10694. Also see Sergeev, A.G.; Schulz, T.; Torborg, C.; Spannenberg, A.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* ***2009***, *48*, 7595.

[116] Hashemi, M.M.; Akhbari, M. *Synth. Commun.* ***2004***, *34*, 2783.

[117] Maurer, S.; Liu, W.; Zhang, X.; Jiang, Y.; Ma, D. *Synlett* ***2010***, 976. See also Jing, L.; Wei, J.; Zhou, L.; Huang, Z.; Li, Z.; Zhou, X. *Chem. Commun.* ***2010***, 4767.

[118] Kormos, C.M.; Leadbeater, N.E. *Tetrahedron* ***2006***, *62*, 4728.

[119] See Seeboth, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 307; Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 166–169.

[120] He, Z.; Jamison, T.F. *Angew. Chem. Int. Ed.* ***2014***, *53*, 3353; Cyr, P.; Charette, A.B. *Synlett* ***2014***, *25*, 1409.

[121] Pickles, G.M.; Thorpe, F.G. *J. Organomet. Chem.* ***1974***, *76*, C23.

[122] Simon, J.; Salzbrunn, S.; Prakash, G.K.S.; Petasis, N.A.; Olah, G.A. *J. Org. Chem.* ***2001***, *66*, 633. Also see Xu, J.; Wang, X.; Shao, C.; Su, D.; Cheng, G.; Hu, Y. *Org. Lett.* ***2010***, *12*, 1964.

[123] Parker, K.A.; Koziski, K.A. *J. Org. Chem.* ***1987***, *52*, 674. See Einhorn, J.; Luche, J.; Demerseman, P. *J. Chem. Soc., Chem. Commun.* ***1988***, 1350.

[124] Gogoi, A.; Bora, U. *Tetrahedron Lett.* ***2013***, *54*, 1821.

[125] Sawant, S.D.; Hudwekar, A.D.; Kumar, K.A.A.; Venkateswarlu, V.; Singh, P.P.; Vishwakarma, R.A. *Tetrahedron Lett.* ***2014***, *55*, 811. See Yang, D.; An, B.; Wei, W.; Jiang, M.; You, J.; Wang, H. *Tetrahedron* ***2014***, *70*, 3630.

[126] Hirose, K.; Ohkubo, K.; Fukuzumi, S. *Chem. Eur. J.* ***2016***, *22*, 12904.

[127] Jiang, T.; Wang, W.; Han, B. *New J. Chem.* ***2013***, 1654.

[128] Pitre, S.P.; McTiernan, C.D.; Ismaili, H.; Scaiano, J.C. *J. Am. Chem. Soc.* ***2013***, *135*, 13286; Zou, Y.-Q.; Chen, J.-R.; Liu, X.-P.; Lu, L.-Q.; Davis, R.L.; Jørgensen, K.A.; Xiao, W.-J. *Angew. Chem. Int. Ed.* ***2012***, *51*, 784; Zhu, C.; Wang, R.; Falck, J.R. *Org. Lett.* ***2012***, *14*, 3494. Amberlite IR-120 has been for the synthesis of phenols from arylboronic acids: see Mulakayala, N.; Ismail, Kumar, K.M.; Rapolu, R.K.; Kandagatla, B.; Rao, P.; Oruganti, S.; Pal, M. *Tetrahedron Lett.* ***2012***, *53*, 6004. For a reaction that used iodine and aqueous hydrogen peroxide, see Gogoi, A.; Bora, U. *Synlett* ***2012***, *23*, 1079. For a reaction that used mcpba, see Chen, D.-S.; Huang, J.-M. *Synlett* ***2013***, *24*, 499. For a reaction that used *t*-butylhydroperoxide, see Guo, S.; Lu, L.; Cai, H. *Synlett* ***2013***, *24*, 1712. For a Cu-catalyzed micellar system, see Inamoto, K.; Nozawa, K.; Yonemoto, M.; Kondo, Y. *Chem. Commun.* ***2011***, *47*, 11775. For a reaction using sodium chlorite, see Gogoi, P.; Bezboruah, P.; Gogoi, J.; Boruah, R.C. *Eur. J. Org. Chem.* ***2013***, 7291.

[129] Fier, P.S.; Maloney, K.M. *Org. Lett.* ***2016***, *18*, 2244; Gohain, M.; du Plessis, M.; van Tonder, J.H.; Bezuidenhoudt, B.C.B. *Tetrahedron Lett.* ***2014***, *55*, 2082. For the transformation of arylboronic acid to phenols by reaction with benzophenone in the presence of air and water, see Cheng, G.; Zeng, X.; Cui, X. *Synthesis* ***2014***, *46*, 295.

Many metal-catalyzed transformations that produce phenols have been reported. The Cu-catalyzed reaction of aryl halides with CsOH in aqueous DMSO gave phenols.[130] Aryl and heteroaryl halides reacted with KOH or CsOH in the presence of a Pd catalyst[131] to give the hydroxylated derivative.[132] Benzene derivatives were hydroxylated to give the phenol by reaction with H_2O_2 and a Mn complex incorporated into mesoporous silica alumina.[133]

OS **I**, 455; **II**, 451; **V**, 632. Also see, OS **V**, 918.

$$ArSO_3^- \xrightarrow[300-320\ ^\circ C]{\text{NaOH Fusion}} ArO^-$$

Aryl sulfonic acids can be converted, through their salts, to phenols, by alkali fusion. In spite of the extreme conditions, the reaction gives fairly good yields, except when the substrate contains other groups that are attacked by alkali at the fusion temperatures. Milder conditions can be used when the substrate contains activating groups, but the presence of deactivating groups hinders the reaction. The mechanism is not clear, but a benzyne intermediate has been ruled out by the finding that *cine* substitution does not occur.[134]

OS **I**, 175; **III**, 288.

13-2 Replacement by OR or OAr

$$ArBr + RO^- \longrightarrow ArOR$$

This reaction is similar to **13-1** and so generally requires activated substrates.[113,135] With unactivated substrates, side reactions predominate, although aryl methyl ethers have been prepared from unactivated chlorides by treatment with MeO^- in HMPA.[136] This reaction gives better yields than **13-1** and is used more often. A good solvent is liquid ammonia. Aryl chlorides react with phenol and KOH with microwave irradiation to give the diaryl ether.[137] The metal-free preparation of aryl ethers has been reported in water.[138] Phenols reacted with alcohols in the presence of Phenofluor and TMS-imidazole to give the corresponding ether.[139]

Phenols reacted with aryl fluorides[140] or aryl chlorides[141] to give the diaryl ether. Intramolecular versions are known that produce benzofurans.[142] Heating aryl iodides and

[130] Yang, K.; Li, Z.; Wang, Z.; Yao, Z.; Jiang, S. *Org. Lett.* ***2011***, *13*, 4340. See Jia, J.; Jiang, C.; Zhang, X.; Jiang, Y.; Ma, D. *Tetrahedron Lett.* ***2011***, *52*, 5593.
[131] See Felpin, F.-X. *Synlett* ***2014***, *25*, 1055.
[132] Cheung, C.W.; Buchwald, S.L. *J. Org. Chem.* ***2014***, *79*, 5351. See Yu, C.-W.; Chen, G.S.; Huang, C.-W.; Chern, J.-W. *Org. Lett.* ***2012***, *14*, 3688.
[133] Aratani, Y.; Yamada, Y.; Fukuzumi, S. *Chem. Commun.* ***2015***, *51*, 4662.
[134] Buzbee, L.R. *J. Org. Chem.* ***1966***, *31*, 3289; Oae, S.; Furukawa, N.; Kise, M.; Kawanishi, M. *Bull. Chem. Soc. Jpn.* ***1966***, *39*, 1212.
[135] See Gujadhur, R.; Venkataraman, D. *Synth. Commun.* ***2001***, *31*, 2865. Thirunavukkarasu, V.S.; Kozhushkov, S.I.; Ackermann, L. *Chem. Commun.* ***2014***, *50*, 29.
[136] Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Tetrahedron* ***1983***, *39*, 193.
[137] Rebeiro, G.L.; Khadilkar, B.M. *Synth. Commun.* ***2003***, *33*, 1405.
[138] Lindstedt, E.; Ghosh, R.; Olofsson, B. *Org. Lett.* ***2013***, *15*, 6070.
[139] Shen, X.; Neumann, C.N.; Kleinlein, C.; Goldberg, N.W.; Ritter, T. *Angew. Chem. Int. Ed.* ***2015***, *54*, 5662.
[140] See Agejas, J.; Bueno, A.B. *Tetrahedron Lett.* ***2006***, *47*, 5661.
[141] Chaouchi, M.; Loupy, A.; Marque, S.; Petit, A. *Eur. J. Org. Chem.* ***2002***, 1278.
[142] Chen, C.-y.; Dormer, P.G. *J. Org. Chem.* ***2005***, *70*, 6964.

phenols in an ionic liquid forms ethers.[143] Aniline has been alkoxylated using an iodine(III)-mediated reaction with alcohols.[144] Benzoxazoles have been prepared using flow conditions (Sec. 7.D).[145]

Copper-catalyzed coupling is known using ligand-free and additive-free conditions.[146] Aryl halides are converted to aryl ethers with aliphatic alcohols in the presence of suitable Cu salts.[147] Phase-transfer catalysis has also been used.[148] High yields of ethers can be obtained by reaction of ROCu or ArOCu with aryl halides.[149] Benzamide derivatives have been converted to the *ortho*-alkoxy derivative using CuCl in air at 130 °C.[150] Treatment of the potassium salts of benzoic acids with $Si(OR)_4$ and $Cu(OAc)_2/Ag_2CO_3$ in the presence of oxygen gave the ether.[151] The intramolecular aerobic reaction of 2-arylphenols gave benzofurans with a Cu catalyst.[152] Aryl and heteroaryl iodides reacted with alcohols in the presence of magnetic $CuFe_2O_4$ to give the corresponding alkoxyarene.[153]

Reactions have been reported that produce diaryl ethers using Pd,[154] Bi,[155] or Cu catalysts.[156] Ligand effects are important in such reactions.[157] A related Pd-catalyzed reaction of alcohols and anilides gave the *ortho*-alkoxyanilide.[158] A Pd-catalyzed, intramolecular displacement of an aryl halide with a pendant alkoxide unit leads to dihydrobenzofurans.[159]

Nickel catalysts have also been used.[160] An Fe-catalyzed etherification reaction is known.[161] Diaryl ethers have been prepared by the reaction of aryl bromides and phenols

[143] Luo, Y.; Wu, J.X.; Ren, R.X. *Synlett* ***2003***, 1734.
[144] Jiang, Q.; Wang, J.-Y.; Guo, C. *J. Org. Chem.* ***2014***, *79*, 8768.
[145] Sedelmeier, J.; Lima, F.; Litzler, A.; Martin, B.; Venturoni, F. *Org. Lett.* ***2013***, *15*, 5546.
[146] Chang, J.W.W.; Chee, S.; Mak, S.; Buranaprasertsuk, P.; Chavasiri, W.; Chan, P.W.H. *Tetrahedron Lett.* ***2008***, *49*, 2018.
[147] See Maiti, D.; Buchwald, S.L. *J. Org. Chem.* ***2010***, ***75***, 1791; Tlili, A.; Monnier, F.; Taillefer, M. *Chem. Eur. J.* ***2010***, *16*, 12299. For reactions with aroxide nucleophiles, see Hosseinzadeh, R.; Tajbakhsh, M.; Mohadjerani, M.; Alikarami, M. *Synlett* ***2005***, 1101. *Copper-Mediated Cross-Coupling Reactions*, Evano, G.; Blanchard, N. (Eds.), Wiley, Hoboken, ***2013***.
[148] Artamanova, N.N.; Seregina, V.F.; Shner, V.F.; Salov, B.V.; Kokhlova, V.M.; Zhdamarova, V.N. *J. Org. Chem. USSR* ***1989***, *25*, 554.
[149] Whitesides, G.M.; Sadowski, J.S.; Lilburn, J. *J. Am. Chem. Soc.* ***1974***, *96*, 2829.
[150] Zhang, L.-B.; Hao, X.-Q.; Zhang, S.-K.; Liu, K.; Ren, B.; Gong, J.-F.; Niu, J.-L.; Song, M.-P. *J. Org. Chem.* ***2014***, *79*, 10399.
[151] Bhadra, S.; Dzik, W.I.; Gooßen, L.J. *Synthesis* ***2013***, *45*, 2387.
[152] Zhao, J.; Wang, Y.; He, Y.; Liu, L.; Zhu, Q. *Org. Lett.* ***2012***, *14*, 1078. Also see Priyadarshini, S.; Joseph, P.J.A.; Kantam, M.L.; Sreedhar, B. *Tetrahedron* ***2013***, *69*, 6409.
[153] Yang, S.; Xie, W.; Zhou, H.; Wu, C.; Yang, Y.; Niu, J.; Yang, W.; Xu, J. *Tetrahedron* ***2013***, *69*, 3415. See Swapna, K.; Murthy, S.N.; Jyothi, M.T.; Nageswar, Y.V.D. *Org. Biomol. Chem.* ***2011***, *9*, 5989.
[154] See Cheung, C.W.; Buchwald, S.L. *Org. Lett.* ***2013***, *15*, 3998; Wu, X.; Fors, B.P.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***2011***, *50*, 9943.
[155] Murai, M.; Origuchi, K.; Takai, K. *Org. Lett.* ***2014***, *16*, 3828. Crifar, C.; Petiot, P.; Ahmad, T.; Gagnon, A. *Chem. Eur. J.* ***2014***, *20*, 2755.
[156] Bhadra, S.; Matheis, C.; Katayev, D.; Gooßen, L.J. *Angew. Chem. Int. Ed.* ***2013***, *52*, 9279; Fan, M.; Zhou, W.; Jiang, Y.; Ma, D. *Angew. Chem. Int. Ed.* ***2016***, *55*, 6211. For the use of colloidal Cu nanoparticles, see Isomura, Y.; Naarushima, T.; Kawasaki, H.; Yonezawa, T.; Obora, Y. *Chem. Commun.* ***2012***, *48*, 3784. For a microwave-assisted reaction, see Navarro, L.; Pujol, M.D. *Tetrahedron Lett.* ***2015***, *56*, 1812.
[157] Burgos, C.H.; Barder, T.E.; Huang, X.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***2006***, *45*, 4321.
[158] Jiang, T.-S.; Wang, G.-W. *J. Org. Chem.* ***2012***, *77*, 9504.
[159] Kuwabe, S.-i.; Torraca, K.E.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2001***, *123*, 12202.
[160] Manolikakes, G.; Dastbaravardeh, N.; Knochel, P. *Synlett* ***2007***, 2077.
[161] Bistri, O.; Correa, A.; Bolm, C. *Angew. Chem. Int. Ed.* ***2008***, *47*, 586.

in the presence of a Rh catalyst and *N*-heterocyclic ligands.[162] Phenols reacted with aryl halides using nano cerium oxide (CeO_2) as a catalyst, to give the diaryl ether.[163]

Potassium aryltrifluoroborates reacted with KOTFA and a Cu catalyst to give aryl trifluoroacetates.[164] In a related reaction, acid salts, $RCOO^-$, are sometimes used as nucleophiles.[165] Unactivated substrates have been converted to carboxylic esters in low-to-moderate yields under oxidizing conditions.[166] A chain mechanism, called the $S_{ON}2$ mechanism,[167] has been suggested.[166]

OS **I**, 219; **II**, 445; **III**, 293, 566; **V**, 926; **VI**, 150; **X**, 418.

B. Sulfur Nucleophiles

13-3 Replacement by SH or SR

$$ArBr + SH^- \longrightarrow ArSH$$
$$ArBr + SR^- \longrightarrow ArSR$$

Aryl thiols (mercaptans) and thioethers (sulfides) can be prepared by reactions that are similar to **13-1** and **13-2**.[168] Activated aryl halides generally give good results, but side reactions are occasionally important. Some reagents give the thiol directly. 4-Bromonitrobenzene reacts with Na_3SPO_3, in refluxing methanol, to give 4-nitrothiophenol, for example.[169] Thiophenols have been prepared by the reaction of formate anion via transfer hydrogenation of aryl sulfonamides and sulfonyl chlorides.[170]

Diaryl sulfides can also be prepared (in high yields) by treatment of unactivated aryl iodides with ArS^- in liquid ammonia under irradiation.[171] Even unactivated aryl halides react with ArS^- if polar aprotic solvents, for example, DMF,[172] DMSO,[173] or HMPA,[174] are used. Aryl halides reacted with aryl thiols in the presence of Cs_2CO_3 and visible light to give the diaryl sulfide.[175] Aryl sulfides were formed by the reaction of thiols with diaryliodonium salts.[176] The reaction of dialkyl, diaryl, or alkyl aryl sulfides with diaryliodonoium salt, in the presence of trifluoroacetic acid, gave aryl thioethers.[177] Alkyl thiols reacted with alkyldiazonium tetrafluoroborates in the presence of a catalytic amount of Eosin Y (an acidic

[162] Kim, H.J.; Kim, M.; Chang, S. *Org. Lett.* ***2011***, *13*, 2368.
[163] Agawane, S.M.; Nagarkar, J.M. *Tetrahedron Lett.* ***2011***, *52*, 5220.
[164] Schimler, S.D.; Sanford, M.S. *Synlett* ***2016***, *27*, 2279.
[165] See Desai, L.V.; Stowers, K.J.; Sanford, M.S. *J. Am. Chem. Soc.* ***2008***, *130*, 13285.
[166] Jönsson, L.; Wistrand, L. *J. Org. Chem.* ***1984***, *49*, 3340.
[167] First proposed by Alder, R.W. *J. Chem. Soc., Chem. Commun.* ***1980***, 1184.
[168] See Peach, M.E. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 735–744.
[169] Bieniarz, C.; Cornwell, M.J. *Tetrahedron Lett.* ***1993***, *34*, 939.
[170] Zhou, S.; Qian, C.; Chen, X. *Synth. Commun.* ***2012***, *42*, 2432.
[171] Bunnett, J.F.; Creary, X. *J. Org. Chem.* ***1974***, *39*, 3173, 3611. See Palomo, C.; Oiarbide, M.; López, R.; Gómez-Bengoa, E. *Tetrahedron Lett.* ***2000***, *41*, 1283.
[172] Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Synthesis* ***1983***, 751. See Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D.; Montanucci, M. *J. Org. Chem.* ***1983***, *48*, 4289.
[173] Bradshaw, J.S.; South, J.A.; Hales, R.H. *J. Org. Chem.* ***1972***, *37*, 2381.
[174] Cogolli, P.; Maiolo, F.; Testaferri, L.; Tingoli, M.; Tiecco, M. *J. Org. Chem.* ***1979***, *44*, 2642. See also, Testaferri, L.; Tingoli, M.; Tiecco, M. *Tetrahedron Lett.* ***1980***, *21*, 3099; Suzuki, H.; Abe, H.; Osuka, A. *Chem. Lett.* ***1980***, 1363.
[175] Liu, B.; Lim, C.-H.; Miyake, G.M. *J. Am. Chem. Soc.* ***2017***, *139*, 13616.
[176] Wang, D.; Yu, X.; Zhao, K.; Li, L.; Ding, Y. *Tetrahedron Lett.* ***2014***, *55*, 5739.
[177] Wagner, A.M.; Sanford, M.S. *J. Org. Chem.* ***2014***, *79*, 2263.

red stain for highlighting cytoplasmic material) and also air and green LEDs to give the corresponding sulfide.[178] Aryl diazonium salts were reduced by ascorbic acid to generate an aryl radical, which reacted with disulfides to yield aryl sulfides.[179]

Metal-catalyzed reactions of aromatic compounds give thioethers, and such reactions have been reviewed.[180] Catalysis in aqueous media has been reported.[181] The more common metals used are Pd,[182] Cu,[183] Rh,[184] Ni,[185] or In catalysts.[186]

A significant amount of work continues with Cu catalysts. Arylboronic acids, $ArB(OH)_2$, react with thiols and copper(II) acetate to give the corresponding alkyl aryl sulfide.[187] Diaryl sulfides have been prepared by the photo-induced, Cu-catalyzed coupling of aryl thiols with aryl halides, using CuI as a precatalyst.[188] Diaryl sulfides were prepared by the reaction of triarylbismuth reagents with diaryl sulfides in the presence of a Cu catalyst.[189] Aryl- and alkenylboronic acids reacted with thiosulfonates using a Cu catalyst to give the aryl thioether.[190] Heating aryl thiols and aryl halides with a Cu catalyst gave the diaryl sulfide.[191] The Cu-catalyzed reaction of aryl halides and potassium thiocyanate gave diaryl sulfides.[192]

Other metals are continuing to be examined as catalysts. Aryl thioethers have been prepared by the reaction of thiols and Grignard reagents, promoted by NCS.[193] A Mn-catalyzed cross-coupling reaction of thiols with aryl iodides gave the aryl thioether.[194] In the presence of a Pd catalyst, thiophenols react with diaryliodonium salts, Ar_2I^{+-} BF_4, to give the unsymmetrical diaryl sulfide.[195] The reaction of aniline derivatives with thiols using a Ru photoredox catalyst and *t*-BuONO gave the aryl sulfide under flow conditions (Sec.7.D).[196] Aryl chlorides reacted with thiophenols to give the corresponding sulfide using an Ir catalyst.[197]

Other sulfur nucleophiles also react with activated aryl halides. Aryl sulfones have been prepared from sulfinic acid salts, aryl iodides, and CuI.[198] The Cu-catalyzed reaction of

[178] Hong, B.; Lee, J.; Lee, A. *Tetrahedron. Lett.* ***2017***, *58*, 2809.
[179] Bu, M.; Lu, G.; Cai, C. *Synlett* ***2015***, *26*, 1841.
[180] Ghaderi, A. *Tetrahedron* ***2016***, *72*, 4758.
[181] Rout, L.; Saha, P.; Jammi, S.; Punniyamurthy, T. *Eur. J. Org. Chem.* ***2008***, 640.
[182] Fernández-Rodríguez, M.A.; Shen, Q.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2006***, *128*, 2180.
[183] See Feng, Y.-S.; Li, Y.-Y.; Tang, L.; Wu, W.; Xu, H.-J. *Tetrahedron Lett.* ***2010***, *51*, 2489; Feng, Y.; Wang, H.; Sun, F.; Li,Y.; Fu, X.; Jin, K. *Tetrahedron* ***2009***, *65*, 9737. For reactions with arylboronic acids, see Lin, Y.; Cai, M.; Fang, Z.; Zhao, H. *Tetrahedron* ***2016***, *72*, 3335. Also see Su, K.; Qiu, Y.; Yao, Y.; Zhang, D.; Jiang, S. *Synlett* ***2012***, *23*, 2853.
[184] Timpa, S.D.; Pell, C.J.; Ozerov, O.V. *J. Am. Chem. Soc.* ***2014***, *136*, 14772; Lai, C.-S.; Kao, H.-L.; Wang, Y.-J.; Lee, C.-F. *Tetrahedron Lett.* ***2012***, *53*, 4365. See Prasad, D.J.C.; Sekar, G. *Org. Lett.* ***2011***, *13*, 1008.
[185] See Gogoi, P.; Hazarika, S.; Sarma, M.J.; Sarma, K.; Barman, P. *Tetrahedron* ***2014***, *70*, 7484.
[186] Reddy, V.P.; Swapna, K.; Kumar, A.V.; Rama Rao, K. *J. Org. Chem.* ***2009***, *74*, 3189.
[187] Herradua, P.S.; Pendola, K.A.; Guy, R.K. *Org. Lett.* ***2000***, *2*, 2019.
[188] Uyeda, C.; Tan, Y.; Fu, G.C.; Peters, J.C. *J. Am. Chem. Soc.* ***2013***, *135*, 9548. Also see Thomas, A.M.; Asha, S.; Sindhu, K.S.; Anilkumar, G. *Tetrahedron Lett.* ***2015***, *56*, 6560.
[189] Yasuike, S.; Nishioka, M.; Kakusawa, N.; Kurita, J. *Tetrahedron Lett.* ***2011***, *52*, 6403.
[190] Yoshida, S.; Sugimura, Y.; Hazama, Y.; Nishiyama, Y.; Yano, T.; Shimizu, S.; Hosoya, T. *Chem. Commun.* ***2015***, *51*, 16613.
[191] Chen, C.-W.; Chen, Y.-L.; Reddy, D.M.; Du, K.; Li, C.-E.; Shih, B.-H.; Xue, Y.-J.; Lee, C.-F. *Chem. Eur. J.* ***2017***, *23*, 10087.
[192] Ke, F.; Qu, Y.; Jiang, Z.; Li, Z.; Wu, D.; Zhou, X. *Org. Lett.* ***2011***, *13*, 454.
[193] Cheng, J.-H.; Ramesh, C.; Kao, H.-L.; Wang, Y.-J.; Chan, C.-C.; Lee, C.-F. *J. Org. Chem.* ***2012***, *77*, 10369.
[194] Liu, T.-J.; Yi, C.-L.; Chan, C.-C.; Lee, C.-F. *Chem. Asian J.* ***2013***, *8*, 1029.
[195] Wang, L.; Chen, Z.-C. *Synth. Commun.* ***2001***, *31*, 1227.
[196] Wang, X.; Cuny, G.D.; Noël, T. *Angew. Chem. Int. Ed.* ***2013***, *52*, 7860.
[197] Jiang, M.; Li, H.; Yang, H.; Fu, H. *Angew. Chem. Int. Ed.* ***2017***, *56*, 874.
[198] Suzuki, H.; Abe, H. *Tetrahedron Lett.* ***1995***, *36*, 6239.

NaO_2SMe and aryl iodides give the aryl methyl sulfone,[199] and aryl sulfones have been prepared from arylboronic acids using a Cu catalyst.[200] A similar synthesis of diaryl sulfones has been reported using a Pd catalyst.[201]

$$2ArX + S_2^{2-} \longrightarrow Ar{-}S{-}S{-}Ar \qquad ArX + SCN^- \longrightarrow ArSCN$$
$$ArX + SO_3^{2-} \longrightarrow Ar{-}SO_3^- \qquad ArX + RSO_2^- \longrightarrow Ar{-}SO_2{-}R$$

Aryl selenides (ArSeAr and ArSeAr′) can be prepared by similar methodology. Symmetrical diaryl selenides were prepared by the reaction of iodobenzene with diphenyl diselenide (PhSeSePh), in the presence of Mg and a Cu catalyst.[202] Aryl halides reacted with tin selenides ($ArSeSnR_3$), with a Cu catalyst, to give the diaryl selenide,[203] and a CuS/Fe catalyst was also used.[204] Diaryl selenides have been prepared from arenediazonium salts with aryl selenenols.[205] Diaryl tellurides have been prepared from arylboronic acids.[206] Aryl selenides have been prepared using selenenyl chlorides and diselenides with a Rh catalyst.[207] Aryl iodides react with elemental selenium in the presence of KOH and a Cu_2O catalyst to give diaryl selenides.[208] A Cu-catalyzed reaction of arylboronic acids and diphenyl diselenide has been reported,[209] as has a Ag-catalyzed reaction of diaryl selenides and arylboronic acids.[210]

OS **I**, 220; **III**, 86, 239, 667; **V**, 107, 474; **VI**, 558, 824. Also see, OS **V**, 977.

C. Nitrogen Nucleophiles

13-4 Replacement of Halogen by NH_2, NHR, or NR_2

$$R_3N + Ar{-}X \xrightarrow[R = H,\ alkyl(1^\circ \text{ and } 2^\circ)]{} R_2N{-}Ar$$

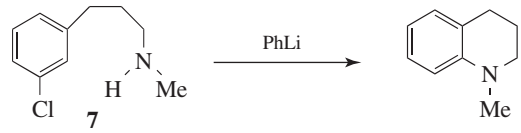
Aryl halides can be converted to amines by the use of $NaNH_2$, NaNHR, or $NaNR_2$.[211] The reaction of an amine, an aryl halide, and potassium *tert*-butoxide generates the *N*-arylamine.[212] Activated aryl halides react with ammonia and with primary and secondary amines to give the corresponding arylamines.[213] Primary and secondary amines usually give better results than ammonia, with piperidine especially reactive. Lithium dialkylamides

[199] Baskin, J.M.; Wang, Z. *Org. Lett.* ***2002***, *4*, 4423.
[200] Kar, A.; Sayyed, I.A.; Lo, W.F.; Kaiser, H.M.; Beller, M.; Tse, M.K. *Org. Lett.* ***2007***, *9*, 3405.
[201] Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L.M.; Bernini, R. *J. Org. Chem.* ***2004***, *69*, 5608.
[202] Taniguchi, N.; Onami, T. *J. Org. Chem.* ***2004***, *69*, 915; Taniguchi, N.; Onami, T. *Synlett* ***2003***, 829.
[203] Beletskaya, I.P.; Sigeev, A.S.; Peregudov, A.S.; Petrovskii, P.V. *Tetrahedron Lett.* ***2003***, *44*, 7039.
[204] Li, Y.; Wang, H.; Li, X.; Chen, T.; Zhao, D. *Tetrahedron* ***2010***, *66*, 8583.
[205] Balaguez, R.A.; Ricordi, V.G.; Freitas, C.S.; Perin, G.; Schumacher, R.F.; Alves, D. *Tetrahedron Lett.* ***2014***, *55*, 1057.
[206] Mohan, B.; Hwang, S.; Jang, S.; Park, K.H. *Synlett* ***2014***, *25*, 2078.
[207] Yu, S.; Wan, B.; Li, X. *Org. Lett.* ***2015***, *17*, 58.
[208] Zhang, S.; Karra, K.; Heintz, C.; Kleckler, E.; Jin, J. *Tetrahedron Lett.* ***2013***, *54*, 4753.
[209] Zheng, B.; Gong, Y.; Xu, H.-J. *Tetrahedron* ***2013***, *69*, 5342. Also see Dandapat, A.; Korupalli, C.; Prasad, D.J.C.; Singh, R.; Sekar, G. *Synthesis* ***2011***, *43*, 2297.
[210] Goldani, B.; Ricordi, V.G.; Seus, N.; Lenardão, E.J.; Schumacher, R.F.; Alves, D. *J. Org. Chem.* ***2016***, *81*, 11472.
[211] See Heaney, H. *Chem. Rev.* ***1962***, *62*, 81 (see p. 83).
[212] Shi, L.; Wang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q. *Org. Lett.* ***2003***, *5*, 3515.
[213] Gao, L.; Xiong, S.; Wan, C.; Wang, Z. *Synlett* ***2013***, *24*, 1322.

also react with aryl halides to give the *N*-arylamine.[214] With amide base reagents, the benzyne mechanism generally operates, so *cine* substitution (Sec. 13.A.iii, category 2) is often found. Triarylamines have been prepared in a similar manner from ArI and Ar'_2NLi, even with unactivated ArI.[215] Arylation of amines with aryl halides has also been done in ionic liquids[216] and in supercritical CO_2.[217] Flow reactor technology (Sec. 7.D) has been used for the direct, uncatalyzed amination of 2-chloropyridine.[218] Aryl triflates react directly with secondary amines in *N*-methylpyrrolidine solvent using microwave irradiation.[219]

Aryl fluorides react with amines in the presence of potassium carbonate/DMSO and ultrasound,[220] and aryl chlorides react on basic alumina with microwave irradiation.[221] Aryl fluorides react in the presence of KF-alumina and 18-crown-6 in DMSO.[222]

Intramolecular versions of this reaction generate bicyclic or polycyclic amines.[223] An example is the conversion of **7** to the tetrahydroquinoline.[224] Larger ring amines can be prepared using this approach, giving 8- and even 12-membered products.



7

Organometallics are important intermediates for the preparation of arylamines. Aryl halides can be converted to the corresponding Grignard reagent (**12-37**) and subsequent reaction with allyl azide followed by hydrolysis leads to the corresponding aniline derivative.[225] Aryl Grignard reagents react with nitroaryl compounds to give, after reduction with $FeCl_3/NaBH_4$, a diaryl amine.[226]

Both aliphatic amines and aniline derivatives and amide bases have been coupled to aryl halides using Pd catalysts and an appropriate ligand. This Pd-catalyzed amination has come to be called the *Buchwald-Hartwig cross-coupling reaction*.[227] A considerable amount of

[214] Tripathy, S.; Le Blanc, R.; Durst, T. *Org. Lett.* ***1999***, *1*, 1973. See Kanth, J.V.B.; Periasamy, M. *J. Org. Chem.* ***1993***, *58*, 3156.
[215] Neunhoeffer, O.; Heitmann, P. *Chem. Ber.* ***1961***, *94*, 2511.
[216] Yadav, J.S.; Reddy, B.V.S.; Basak, A.K.; Narsaiah, A.V. *Tetrahedron Lett.* ***2003***, *44*, 2217.
[217] Smith, C.J.; Tsang, M.W.S.; Holmes, A.B.; Danheiser, R.L.; Tester, J.W. *Org. Biomol. Chem.* ***2005***, *3*, 3767.
[218] Hamper, B.C.; Tesfu, E. *Synlett* ***2007***, 2257.
[219] Xu, G.; Wang, Y.-G. *Org. Lett.* ***2004***, *6*, 985.
[220] Magdolen, P.; Mečiarová, M.; Toma, S. *Tetrahedron* ***2001***, *57*, 4781.
[221] Kidwai, M.; Sapra, P.; Dave, B. *Synth. Commun.* ***2000***, *30*, 4479.
[222] Smith III, W.J.; Sawyer, J.S. *Tetrahedron Lett.* ***1996***, *37*, 299.
[223] See Jordan-Hore, J.A.; Johansson, C.C.C.; Gulias, M.; Beck, E.M.; Gaunt, M.J. *J. Am. Chem. Soc.* ***2008***, *130*, 16184; Kuwahara, A.; Nakano, K.; Nozaki, K. *J. Org. Chem.* ***2005***, *70*, 413.
[224] See Bunnett, J.F.; Hrutfiord, B.F. *J. Am. Chem. Soc.* ***1961***, *83*, 1691. Also see Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, ***1973***, pp. 150–164.
[225] Kabalka, G.W.; Li, G. *Tetrahedron Lett.* ***1997***, *38*, 5777.
[226] Sapountzis, I.; Knochel, P. *J. Am. Chem. Soc.* ***2002***, *124*, 9390.
[227] Ali, M.H.; Buchwald, S.L. *J. Org. Chem.* ***2001***, *66*, 2560; Kuwano, R.; Utsunomiya, M.; Hartwig, J.F. *J. Org. Chem.* ***2002***, *67*, 6479; Shen, Q.; Hartwig, J.F. *Org. Lett.* ***2008***, *10*, 4109. Harris, M.C.; Huang, X.; Buchwald, S.L. *Org. Lett.* ***2003***, *4*, 2885. See Shen, Q.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2006***, *128*, 10028. See Anderson, K.W.; Tundel, R.E.; Ikawa, T.; Altman, R.A.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***2006***, *45*, 6523; Topchiy, M.A.; Dzhevakov, P.B.; Rubina, M.S.; Morozov, O.S.; Asachenko, A.F.; Nechaev, M.S. *Eur. J. Org. Chem.* ***2016***, 1908.

work[228] has been done to vary the nature of the ligand and the Pd catalyst, as well as the base.[229] Ligands have been prepared that facilitate the dynamic kinetic asymmetric version of the Buchwald-Hartwig reaction.[230] Other ligands have been developed that are important in this reaction.[231] The role of the base in the amination reaction has been discussed.[232] The reaction has been done in water using surfactants.[233] Work to discern the mechanism of this reaction has also received considerable attention.[234] The metal-catalyzed reaction with ammonia or amines likely proceeds by the S_NAr mechanism,[235] although, in certain cases, the $S_{RN}1$ mechanism has been found (**10-26**). When the substrate is a heterocyclic aromatic nitrogen compound, a different mechanism still [the S_N(ANRORC) mechanism], involving opening and reclosing of the aromatic ring, has been shown to take place.[236]

Polymer-supported Pd catalysts,[237] polymer-bound phosphine ligands used in conjunction with a Pd catalyst,[238] and polymer-bound amines[239] have been used for *N*-arylation. These reactions have been carried out in ionic liquids using a Pd catalyst,[240] and with microwave irradiation.[241] Catalysts are available for the amination of aryl halides in aqueous media.[242] The Pd-catalyzed amination of aryl substrates is not limited to halides, and the reaction with mesylates lead to arylamines.[243] Arylamines with chiral substituents on nitrogen can be prepared using a Pd catalyst with optically active ligands.[244]

Aryl tosylates reacted with secondary amines to give the corresponding arylamine in the presence of a Pd catalyst.[245] The Pd-catalyzed coupling of aryl halides with ammonia and gaseous amines as their ammonium salts gave arylamines.[246] Amines react with

[228] See Huang, X.; Anderson, K.W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2004***, *125*, 6653; Smith, C.J.; Early, T.R.; Holmes, A.B.; Shute, R.E. *Chem. Commun.* ***2004***, 1976.

[229] See Singh, U.K.; Strieter, E.R.; Blackmond, D.G.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 14104. For a study of rate enhancement by the added base, see Meyers, C.; Maes, B.U.W.; Loones, K.T.J.; Bal, G.; Lemière, G.L.F.; Dommisse, R.A. *J. Org. Chem.* ***2004***, *69*, 6010.

[230] Ramírez-López, P.; Ros, A.; Romero-Arenas, A.; Iglesias-Sigüenza, J.; Fernández, R.; Lassaletta, J.M. *J. Am. Chem. Soc.* ***2016***, *138*, 12053.

[231] Raders, S.M.; Moore, J.N.; Parks, J.K.; Miller, A.D.; Leißing, T.M.; Kelley, S.P.; Rogers, R.D.; Shaughnessy, K.H. *J. Org. Chem.* ***2013***, *78*, 4649; Prabhu, R.N.; Ramesh, R. *Tetrahedron Lett.* ***2013***, *54*, 1120; Nagao, S.; Matsumoto, T.; Koga, Y.; Matsubara, K. *Chem. Lett.* ***2011***, *40*, 1036; Tardiff, B.J.; Stradiotto, M. *Eur. J. Org. Chem.* ***2012***, 3972; Zhang, Y.; César, V.; Lavigne, G. *Eur. J. Org. Chem.* ***2015***, 2042. Also see Mitra, A.W.; Hansen, M.M.; Laurila, M.E.; Kolis, S.P.; Martinelli, J.R. *Tetrahedron Lett.* ***2013***, *54*, 6580.

[232] Sunesson, Y.; Limé, E.; Lill, S.O.N.; Meadows, R.E.; Norrby, P.-O. *J. Org. Chem.* ***2014***, *79*, 11961.

[233] Salomé, C.; Wagner, P.; Bollenbach, M.; Bihel, F.; Bourguignon, J.-J.; Schmitt, M. *Tetrahedron* ***2014***, *70*, 3413.

[234] See Strieter, E.R.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***2006***, *45*, 925; Fors, B.P.; Davis, N.R.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2009***, *131*, 5766.

[235] See Paine, A.J. *J. Am. Chem. Soc.* ***1987***, *109*, 1496. See Um, I.-H.; Im, L.-R.; Kang, J.-S.; Bursey, S.S.; Dust, J.M. *J. Org. Chem.* ***2012***, *77*, 9738.

[236] See van der Plas, H.C. *Tetrahedron* ***1985***, *41*, 237; *Acc. Chem. Res.* ***1978***, *11*, 462.

[237] Guinó, M.; Hii, K.K. *Tetrahedron Lett.* ***2005***, *46*, 7363. See Inasaki, T.; Ueno, M.; Miyamoto, S.; Kobayashi, S. *Synlett* ***2007***, 3209.

[238] Parrish, C.A.; Buchwald, S.L. *J. Org. Chem.* ***2001***, *66*, 3820.

[239] Weigand, K.; Pelka, S. *Org. Lett.* ***2002***, *4*, 4689.

[240] See Grasa, G.A.; Viciu, M.S.; Huang, J.; Nolan, S.P. *J. Org. Chem.* ***2001***, *66*, 7729.

[241] See Loones, K.T.J.; Maes, B.U.W.; Rombouts, G.; Hostyn, S.; Diels, G. *Tetrahedron* ***2005***, *61*, 10338.

[242] Xu, C.; Gong, J.-F.; Wu, Y.-J. *Tetrahedron Lett.* ***2007***, *48*, 1619.

[243] So, C.M.; Zhou, Z.; Lau, C.P.; Kwong, F.Y. *Angew. Chem. Int. Ed.* ***2008***, *47*, 6402.

[244] Tagashira, J.; Imao, D.; Yamamoto, T.; Ohta, T.; Furukawa, I.; Ito, Y. *Tetrahedron: Asymmetry* ***2005***, *16*, 230.

[245] Zhang, Y.; Lavigne, G.; César, V. *J. Org. Chem.* ***2015***, *80*, 7666.

[246] Green, R.A.; Hartwig, J.F. *Org. Lett.* ***2014***, *16*, 4388.

Ph_2I^+ BF_4^-, in the presence of Pd catalysts[247] or a CuI catalyst,[248] to give the *N*-phenylamine. Aminoalkylation of heteroaromatic rings is possible, as in the reaction of 3-bromothiophene with a primary amine and a Pd catalyst.[249] 2-Halopyridines react to give the 2-aminoalkyl pyridine.[250]

Copper catalysts have been extensively explored for this coupling reaction.[251] The selectivity of *O*- versus *N*-arylation for reactions of amino alcohols has been discussed.[252] The Cu-catalyzed reaction of aryl halides and amines,[253] or of aryl halides and α-amino acids, led to the formation of arylamines.[254] The Cu-catalyzed *N*-arylation of indoles has been reported.[255] The *N*-arylation of amines used a Cu catalyst in water.[256] Aryl halides in liquid ammonia gave the primary aromatic amine when catalyzed by a Cu-salt/ascorbate system.[257]

Arylboronic acids react with aliphatic amines[258] or aqueous ammonia[259] in the presence of a Cu catalyst. The Cu-catalyzed reaction of an arylboronic acid (BPin) (Pin = pinacolato) and secondary amines gave arylamines.[260] The *N*-arylation of imidazolines has been reported using arylboronic acids and a Cu catalyst.[261] Arylboronic acids reacted with aryl azides in the presence of indium and $Cu(OAc)_2$ to give diarylamines.[262] The S_NAr amination of functionalized pyrimidines has been reported.[263]

Nickel catalysts have been used in the reaction of aryl halides with *N*-alkyl aniline derivatives[264] and also with aliphatic amines.[265] An intramolecular reaction of a pendant aminoalkyl unit with an aryl chloride moiety, catalyzed by Ni(0), gave a dihydroindole.[266]

[247] Kang, S.-K.; Lee, H.-W.; Choi, W.-K.; Hong, R.-K.; Kim, J.-S. *Synth. Commun.* ***1996***, *26*, 4219. See Carroll, M.A.; Wood, R.A. *Tetrahedron* ***2007***, *63*, 11349.

[248] Kang, S.-K.; Lee, S.-H.; Lee, D. *Synlett* ***2000***, 1022.

[249] Ogawa, K.; Radke, K.R.; Rothstein, S.D.; Rasmussen, S.C. *J. Org. Chem.* ***2001***, *66*, 9067.

[250] See Basu, B.; Jha, S.; Mridha, N.K.; Bhuiyan, Md.M.H. *Tetrahedron Lett.* ***2002***, *43*, 7967.

[251] See Wang, H.; Li, Y.; Sun, F.; Feng, Y.; Jin, K.; Wang, X. *J. Org. Chem.* ***2008***, *73*, 8639. For a ligand-free reaction, see Yong, F.F.; Teo, Y.-C. *Synlett* ***2010***, 3068.

[252] Shafir, A.; Lichtor, P.A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2007***, *129*, 3490. For an amination using aqueous ammonia, see Meng, F.; Zhu, X.; Li, Y.; Xie, J.; Wang, B.; Yao, J.; Wan, Y. *Eur. J. Org. Chem.* ***2010***, 6149.

[253] Jiao, J.; Zhang, X.-R.; Chang, N.-H.; Wang, J.; Wei, J.-F.; Shi, X.-Y.; Chen, Z.-G. *J. Org. Chem.* ***2011***, *76*, 1180; Zhang, C.; Zhan, Z.; Lei, M.; Hu, L. *Tetrahedron* ***2014***, *70*, 8817; Güell, I.; Ribas, X. *Eur. J. Org. Chem.* ***2014***, 3188.

[254] Thomas, C.; Wu, M.; Billingsley, K.L. *J. Org. Chem.* ***2016***, *81*, 330.

[255] Xiao, R.; Zhao, H.; Cai, M. *Tetrahedron* ***2013***, *69*, 5444. Also see Besandre, R.; Jaimes, M.; May, J.A. *Org. Lett.* ***2013***, *15*, 1666; Nagashima, S.; Sasaki, T.; Kamiguchi, S.; Chihara, T. *Chem. Lett.* ***2015***, *44*, 764.

[256] Wang, D.; Zheng, Y.; Yang, M.; Zhang, F.; Mao, F.; Yu, J.; Xa, X. *Org. Biomol. Chem.* ***2017***, *15*, 8009.

[257] Ji, P.; Atherton, J.H.; Page, M.I. *J. Org. Chem.* ***2012***, *77*, 7471.

[258] Chiang, G.C.H.; Olsson, T. *Org. Lett.* ***2004***, *6*, 3079; Lan, J.-B.; Zhang, G.-L.; Yu, X.-Q.; You, J.-S.; Chen, L.; Yan, M.; Xie, R.-G. *Synlett* ***2004***, 1095.

[259] Jiang, Z.; Wu, Z.; Wang, L.; Wu, D.; Zhou, X. *Can. J. Chem.* ***2010***, *88*, 964.

[260] Vantourout, J.C.; Miras, H.N.; Isidro-Llobet, A.; Sproules, S.; Watson, A.J.B. *J. Am. Chem. Soc.* ***2017***, *139*, 4769.

[261] Dar'in, D.; Krasavin, M. *J. Org. Chem.* ***2016***, *81*, 12514.

[262] Reddy, B.V.S.; Reddy, N.S.; Reddy, Y.J.; Reddy, Y.V. *Tetrahedron Lett.* ***2011***, *52*, 2547.

[263] Lee, M.; Rucil, T.; Hesek, D.; Oliver, A.G.; Fisher, J.F.; Mobashery, S. *J. Org. Chem.* ***2015***, *80*, 7757.

[264] Wolfe, J.P.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1997***, *119*, 6054; Lipshutz, B.H.; Ueda, H. *Angew. Chem. Int. Ed.* ***2000***, *39*, 4492; Chen, C.; Yang, L.-M. *J. Org. Chem.* ***2007***, *72*, 6324.

[265] See Gao, C.-Y.; Cao, X.; Yang, L.-M. *Org. Biomol. Chem.* ***2009***, ***7***, 3922.

[266] Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett.* ***2003***, *5*, 2311.

Aryl ethers reacted with imines, in the presence of a Ni catalyst, to give arylamines after acid hydrolysis.[267]

Several other transition metal-catalyzed reactions have been examined. The amination of arenes with phthalimide used an iodine(III) oxidant in the presence of a Au(I) catalyst, to give phthalimide-substituted aniline derivatives.[268] The Au-catalyzed direct amination of arenes with azodicarboxylates gave *N*-arylhydrazine derivatives.[269] Indoles have been prepared by intramolecular C—H amination using an Fe catalyst.[270] The reaction of arenes with azide in water used an Fe catalyst and DDQ and gave the amides.[271] 2-Chloropyridine reacted with *N*-(MgCl)-pyrrolidine in the presence of a Cr catalyst to give 2-pyrrolidinopyridine.[272] A $Mo(CO)_6$-mediated, Pd-catalyzed reaction is known for allylamines and aryl halides.[273]

Amides react with aryl halides in the presence of a Pd[274] or a Cu catalyst.[275] *N*-Aryl lactams are prepared by the reaction of a lactam with an aryl halide in the presence of a Pd catalyst.[276] β-Lactams also react.[277] The Ru-catalyzed amidation of heteroaryl arenes has been reported.[278] *N*-Aryl imides have been prepared, using a Cu catalyst, from arylboronic acids.[279] In the *Goldberg reaction*, an aryl bromide reacts with an acetanilide in the presence of K_2CO_3 and CuI to give an *N*-acetyldiarylamine, which can be hydrolyzed to a diarylamine:[280]

$$\mathrm{ArBr + Ar'NHAc \rightarrow ArAr'NAc}$$

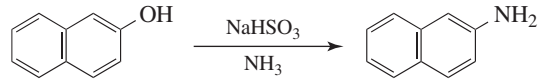
N-Arylation of urea is possible using a Cu catalyst.[281] The Pd-catalyzed amidation of aryl halides by reaction with isocyanides has been reported.[282] The Cu-catalyzed, intramolecular amidation of benzamide derivatives led to isoindolinones.[283] Functionalized arenes reacted with phthalimide in the presence of oxygen and a Cu catalyst to give the *ortho* amide derivative.[284] Arylamines were produced by the Ir-catalyzed *ortho* C—H amidation of arenes by reaction of arenes with sulfonyl and aryl azides.[285]

[267] Yue, H.; Guo, L.; Liu, X.; Rueping, M. *Org. Lett.* ***2017***, *19*, 1788.
[268] Marchetti, L.; Kantak, A.; Davis, R.; DeBoef, B. *Org. Lett.* ***2015***, *17*, 358.
[269] Gu, L.; Neo, B.S.; Zhang, Y. *Org. Lett.* ***2011***, *13*, 1872.
[270] Bonnamour, J.; Bolm, C. *Org. Lett.* ***2011***, *13*, 2012.
[271] Qin, C.; Zhou, W.; Chen, F.; Ou, Y.; Jiao, N. *Angew. Chem. Int. Ed.* ***2011***, *50*, 12595.
[272] Steib, A.K.; Fernandez, S.; Kuzmina, O.M.; Corpet, M.; Gosmini, C.; Knochel, P. *Synlett* ***2015***, *26*, 1049.
[273] Appukkuttan, P.; Axelsson, L.; van der Eycken, E.; Larhed, M. *Tetrahedron Lett.* ***2008***, *49*, 5625.
[274] Fors, B.P.; Dooleweerdt, K.; Zeng, Q.; Buchwald, S.L. *Tetrahedron* ***2009***, *65*, 6576. For an intramolecular reaction, see Yang, B.H.; Buchwald, S.L. *Org. Lett.* ***1999***, *1*, 35.
[275] Hosseinzadeh, R.; Tajbakhsh, M.; Mohadjerani, M.; Mehdinejad, H. *Synlett* ***2004***, 1517.
[276] Browning, R.G.; Badaringarayana, V.; Mahmud, H.; Lovely, C.J. *Tetrahedron* ***2004***, *60*, 359; Deng, W.; Wang, Y.-F.; Zou, Y.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* ***2004***, *45*, 2311. Also see Klapars, A.; Huang, X.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 74219.
[277] Klapars, A.; Parris, S.; Anderson, K.W.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2004***, *126*, 3529.
[278] Thirunavukkarasu, V.S.; Raghuvanshi, K.; Ackermann, L. *Org. Lett.* ***2013***, *15*, 3286. Also see Besson, T.; Fruit, C. *Synthesis* ***2016***, *48*, 3879.
[279] Chernick, E.T.; Ahrens, M.J.; Scheidt, K.A.; Wasielewski, M.R. *J. Org. Chem.* ***2005***, *70*, 1486.
[280] See Renger, B. *Synthesis* ***1985***, 856.
[281] Nandakumar, M.V. *Tetrahedron Lett.* ***2004***, *45*, 1989.
[282] Jiang, H.; Liu, B.; Li, Y.; Wang, A.; Huang, H. *Org. Lett.* ***2011***, *13*, 1028.
[283] Yamamoto, C.; Takamatsu, K.; Hirano, K.; Miura, M. *J. Org. Chem.* ***2016***, *81*, 7675.
[284] Xu, H.; Qiao, X.; Yang, S.; Shen, Z. *J. Org. Chem.* ***2014***, *79*, 4414.
[285] Lee, D.; Kim, Y.; Chang, S. *J. Org. Chem.* ***2013***, *78*, 11102.

The transition metal-catalyzed couplings of primary or secondary phosphines with aryl halides or sulfonate esters to give arylphosphines is known.[286] Diphenylphosphine reacts with aryl iodides and a Cu catalyst to give the triarylphosphine.[287] The Pd-catalyzed conversion of aryl halides to arylphosphines using (trimethylsilyl)diphenylphosphine tolerates many functional groups, but it is mainly limited to aryl iodides.[288] The *P*-arylation of secondary phosphine oxides, with a Pd catalyst, has been reported.[289] The α-arylation of benzylic phosphine oxides used a Pd catalyst.[290] The Pd-catalyzed *ortho* arylation of aryl phosphates and aryl hydrogenphosphates has been reported.[291] Phenylboronic acids reacted with H-phosphonate diesters using a Cu catalyst.[292] Benzothiazole/thiazole derivatives reacted with phosphine oxides, phosphinate ester, or phosphonate diesters under ball-milling conditions and a Mn catalyst to give the corresponding 2-phosphonylated derivatives.[293]

OS **I**, 544; **II**, 15, 221, 228; **III**, 53, 307, 573; **IV**, 336, 364; **V**, 816, 1067; **VII**, 15. OS **III**, 664. **OS X**, 423.

13-5 Replacement of a Hydroxy Group by an Amino Group



The reaction of naphthols with ammonia and sodium bisulfite is called the *Bucherer reaction*. Primary amines can be used instead of ammonia, in which case *N*-substituted naphthylamines are obtained. The mechanism of the Bucherer reaction amounts to a kind of overall addition–elimination, via initial sulfonation at C-3 to give an enol and loss of proton with dearomatization to give the 1-oxo-3-sodium sulfonate. Addition of the amine to the ketone moiety gives the imine, which tautomerizes to the enamine and aromatization then gives the 1-naphthylamine derivative.[294]

Evidence for this mechanism was (i) the isolation of 1-oxo-3-sodium sulfonate[295] and (ii) the demonstration that for β-naphthol treated with ammonia and HSO_3^-, the rate of the reaction depends only on the substrate and on HSO_3^-, indicating that ammonia is not involved in the rate-determining step.[296] If the starting compound is a β-naphthol, the intermediate is a 2-keto-4-sulfonic acid compound, so the sulfur of the bisulfite in either case attacks *meta* to the OH or NH_2.[297]

Hydroxy groups on benzene rings can be replaced by NH_2 groups if they are first converted to aryl diethyl phosphates. Treatment of these with KNH_2 and potassium metal in

[286] Gelpke, A.E.S.; Kooijman, H.; Spek, A.L.; Hiemstra, H. *Chem. Eur. J.* ***1999***, *5*, 2472; Ding, K.; Wang, Y.; Yun, H.; Liu, J.; Wu, Y.; Terada, M.; Okubo, Y.; Mikami, K. *Chem. Eur. J.* ***1999***, *5*, 1734; Lipshutz, B.H.; Buzard, D.H.; Yun, C.S. *Tetrahedron Lett.* ***1999***, *40*, 201.
[287] Van Allen, D.; Venkataraman, D. *J. Org. Chem.* ***2003***, *68*, 4590.
[288] Tunney, B.H.; Stille, J.K. *J. Org. Chem.* ***1987***, *52*, 748.
[289] Bloomfield, A.J.; Herzon, S.B. *Org. Lett.* ***2012***, *14*, 4370.
[290] Montel, S.; Jia, T.; Walsh, P.J. *Org. Lett.* ***2014***, *16*, 130.
[291] Chan, L.-Y.; Cheong, L.; Kim, S. *Org. Lett.* ***2013***, *15*, 2186.
[292] Zhuang, R.; Xu, J.; Cai, Z.; Tang, G.; Fang, M.; Zhao, Y. *Org. Lett.* ***2011***, *13*, 2110.
[293] Li, L.; Wang, J.-J.; Wang, G.-W. *J. Org. Chem.* ***2016***, *81*, 5433.
[294] Rieche, A.; Seeboth, H. *Liebigs Ann. Chem.* ***1960***, *638*, 66.
[295] Rieche, A.; Seeboth, H. *Liebigs Ann. Chem.* ***1960***, *638*, 43, 57.
[296] Kozlov, V.V.; Veselovskaia, I.K. *J. Gen. Chem. USSR* ***1958***, *28*, 3359.
[297] Rieche, A.; Seeboth, H. *Liebigs Ann. Chem.* ***1960***, *638*, 76.

liquid ammonia gives the corresponding primary aromatic amines.[298] The mechanism of the second step is $S_{RN}1$.[299]

OS **III**, 78.

D. Halogen Nucleophiles

13-6 The Introduction of Halogens

$$Ar{-}X + X'^{-} \rightleftharpoons Ar{-}X' + X^{-}$$

It is possible to replace a halogen on an aromatic ring by another halogen,[300] if the ring is activated. In such cases there is equilibrium, which is usually shifted in the desired direction by the use of an excess of added halide ion.[301] A phenolic hydroxy group can be replaced by chloro with PCl_5 or $POCl_3$, but only if the ring is activated. Unactivated phenols give phosphates when treated with $POCl_3$

$$3\ ArOH + POCl_3 \rightarrow (ArO)_3PO$$

Phenols, even unactivated ones, can be converted to aryl bromides by treatment with Ph_3PBr_2[302] (see **10-46**) and to aryl chlorides by treatment with $PhPCl_4$.[303] *meta*-Chlorophenols were formed by the reaction of phenol derivatives with iodonium salts followed by treatment with HCl in dioxane.[304]

Halide exchange can also be accomplished with copper halides. Since the leaving-group order in this case is $I > Br > Cl \gg F$ (which means that iodides cannot normally be made by this method), the S_NAr mechanism is probably not operating.[305] However, aryl iodides have been prepared from bromides, (i) with an excess of NaI and a Cu catalyst,[306] and (ii) by treatment with excess KI and a Ni catalyst.[307] Interestingly, aryl chlorides have been prepared from aryl iodides using 2 molar equivalents of $NiCl_2$ in DMF, with microwave irradiation.[308] Aryl and vinyl triflates can be converted to the corresponding bromide or chloride using a Pd catalyst.[309] The Rh-catalyzed selective bromination and iodination of electron-rich heterocycles with NIS or *N*-bromophthalimide (NBP) gave the corresponding halogenated heterocycle.[310]

Treatment of $PhB(OH)_2$ with *N*-iodosuccinimide gives iodobenzene.[311] Arylboronic acids (**12-27**) can be converted to the corresponding aryl bromides by reaction with

[298] Rossi, R.A.; Bunnett, J.F. *J. Org. Chem.* ***1972***, *37*, 3570.
[299] See Scherrer, R.A.; Beatty, H.R. *J. Org. Chem.* ***1972***, *37*, 1681.
[300] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 671–672.
[301] Sauer, J.; Huisgen, R. *Angew. Chem.* ***1960***, *72*, 294 (p. 297).
[302] Schaefer, J.P.; Higgins, J. *J. Org. Chem.* ***1967***, *32*, 1607.
[303] Bay, E.; Bak, D.A.; Timony, P.E.; Leone-Bay, A. *J. Org. Chem.* ***1990***, *55*, 3415.
[304] Chittimalla, S.K.; Bandi, C. *Tetrahedron Lett.* ***2016***, *57*, 15.
[305] Bacon, R.G.R.; Hill, H.A.O. *J. Chem. Soc.* ***1964***, 1097, 1108. See also, Clark, J.H.; Jones, C.W.; Duke, C.V.A.; Miller, J.M. *J. Chem. Res. (S)* ***1989***, 238.
[306] Klapars, A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 14844.
[307] Yang, S.H.; Li, C.S.; Cheng, C.H. *J. Org. Chem.* ***1987***, *52*, 691.
[308] Arvela, R.K.; Leadbeater, N.E. *Synlett* ***2003***, 1145.
[309] Shen, X.; Hyde, A.M.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2010***, *132*, 14076.
[310] Schröder, N.; Lied, F.; Glorius, F. *J. Am. Chem. Soc.* ***2015***, *137*, 1448.
[311] Thiebes, C.; Prakash, G.K.S.; Petasis, N.A.; Olah, G.A. *Synlett* ***1998***, 141.

1,3-dibromo-5,5-dimethylhydantoin and 5 mol % NaOMe.[312] Other aryl halides can be prepared using 1,3-dihalo-5,5-dimethylhydantoins.

Halide exchange is particularly useful for putting fluorine into a ring, since there are fewer alternate ways of doing this than for the other halogens. Activated aryl chlorides give fluorides when treated with KF in DMF, DMSO, or dimethyl sulfone.[313] Reaction of aryl halides with Bu_4PF/HF is also effective for exchanging a halogen with fluorine.[314] Aryl alcohols (phenol derivatives) reacted with CsF and aryl nonafluorobutylsulfonates, and subsequent treatment with a Pd catalyst and heating with microwave irradiation gave the corresponding aryl fluoride.[315] The S_NAr fluorination used anhydrous tetraalkylammonium fluoride salts, generated by several approaches.[316]

OS **III**, 194, 272, 475; **V**, 142, 478; **VIII**, 57; **81**, 98.

13-7 Replacement by Boron

Arylboronic acids and aryl boronates have become important synthetic targets due to their extensive application in organic syntheses, especially for the transition metal-catalyzed C—C, C—O, and C—N bond-forming reactions. Aryl halides and also arenes[317] have been converted to arylboranes, aryl boronates and other arylboron compounds.[318] Aryl halides reacted with $B_2(OR)_4$ in the presence of 4-phenylpyridine and KOMe to give the borate, $ArB(OR)_2$.[319] The reaction of aryl aldehydes with B_2Pin_2 (Pin = pinacolato) gave *ortho* borylation using *tert*-butylamine with 8-aminoquinoine whereas *meta* borylation proceeds by using a 1,10-phenanthroline.[320] Aryl boronates have been prepared from aryllithium halides or arylmagnesium halides using flow techniques (Sec. 7.D).[321] Heteroarylboronic acids have also been prepared.[322]

Transition metal-catalyzed reactions are an important area of research. The Ir-catalyzed reaction of B_2Pin_2 and aromatic compounds gave the *ortho* borylation product.[323] The Ru catalyst is known.[324] The BPin product was formed by reaction of sterically congested arenes with B_2Pin_2 and a Pt *N*-heterocyclic carbene catalyst.[325] The borylation of arenes has used an Fe catalyst,[326] and the Mn-catalyzed reaction of aryl chlorides.[327] A Zn/NHC

[312] Szumigala Jr., R.H.; Devine, P.N.; Gauthier Jr., D.R.; Volante, R.P. *J. Org. Chem.* ***2004***, *69*, 566.
[313] Kimura, Y.; Suzuki, H. *Tetrahedron Lett.* ***1989***, *30*, 1271. See Dolby-Glover, L. *Chem. Ind. (London)* ***1986***, 518.
[314] Uchibori, Y.; Umeno, M.; Seto, H.; Qian, Z.; Yoshioka, H. *Synlett* ***1992***, 345.
[315] Wannberg, J.; Wallinder, C.; Ünlüsoy, M.; Sköld, C.; Larhed, M. *J. Org. Chem.* ***2013***, *78*, 4184.
[316] Cismesia, M.A.; Ryan, S.J.; Bland, D.C.; Sanford, M.S. *J. Org. Chem.* ***2017***, *82*, 5020.
[317] See Ingleson, M.J. *Synlett* ***2012***, *23*, 1411.
[318] Preshlock, S.M.; Ghaffari, B.; Maligres, P.E.; Krska, S.W.; Maleczka Jr, R.E.; Smith III, M.R. *J. Am. Chem. Soc.* ***2013***, *135*, 7572.
[319] Zhang, L.; Jiao, L. *J. Am. Chem. Soc.* ***2017***, *139*, 607.
[320] Bisht, R.; Chattopadhyay, B. *J. Am. Chem. Soc.* ***2016***, *138*, 84.
[321] Desai, A.A. *Angew. Chem. Int. Ed.* ***2012***, *51*, 9223. Also see Newby, J.A.; Huck, L.; Blaylock, D.W.; Witt, P.M.; Ley, S.V.; Browne, D.L. *Chem. Eur. J.* ***2014***, *20*, 263.
[322] Erb, W.; Hellal, A.; Albini, M.; Rouden, J.; Blanchet, J. *Chem. Eur. J.* ***2014***, *20*, 6608.
[323] Ghaffari, B.; Preshlock, S.M.; Plattner, D.L.; Staples. R.J.; Maligres, P.E.; Krska, S.W.; Maleczka Jr., R.E.; Smith III, M.R. *J. Am. Chem. Soc.* ***2014***, *136*, 14345. See Ohmura, T.; Torigoe, T.; Suginome, M. *Chem. Commun.* ***2014***, *50*, 6333.
[324] Fernández-Salas, J.A.; Manzini, S.; Piola, L.; Slawin, A.M.Z.; Nolan, S.P. *Chem. Commun.* ***2014***, *50*, 6782.
[325] Furukawa, T.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* ***2015***, *137*, 12211.
[326] Dombray, T.; Werncke, C.G.; Jiang, S.; Grellier, M.; Vendier, L.; Bontemps, S.; Sortais, J.-B.; Sabo-Etienne, S.; Darcel, C. *J. Am. Chem. Soc.* ***2015***, *137*, 4062.
[327] Atack, T.C.; Cook, S.P. *J. Am. Chem. Soc.* ***2016***, *138*, 6139.

system catalyzed the borylation of aryl halides with diboron reagents in the presence of KOMe.[328] The Ni-catalyzed aromatic borylation is known,[329] and the Ni-catalyzed reaction of aryl fluorides and $B_2(nep)_2$ (nep = 5,5-dimethyl-1,3,2-dioxaborolane) gave ArB(nep).[330] Aryl ethers and benzylic ethers were converted to the *ipso*-substituted borylation product by reaction with $B_2(nep)_2$ or B_2Pin_2 and a Ni catalyst.[331] Aryl bromides reacted with pinacolborane using an Fe/Cu co-catalyst system to give the aryl boronate.[332] Aryl thioethers reacted with B_2Pin_2 and a Rh catalyst to give *ipso* substitution and formation of the aryl boronate.[333] Aryl halides reacted with $B_2(NMe_2)_4$ in the presence of a diol and a Pd catalyst to give the aryl boronate.[334]

Aryl nitriles reacted with B_2Pin_2 with a Rh catalyst and with DABCO at 100 °C to give the corresponding aryl boronate via replacement of the cyano group.[335] *N*-Heterocyclic carbenes were used to convert aryl halides and B_2Pin_2 to the corresponding arylboron compound.[336] Arylboronic acids were prepared by the treatment of aryl halides with Mg and LiCl, followed by the *in situ* reaction with $B(OMe)_3$.[337]

Organotrifluoroborates have been prepared and used in many reactions described for organoboronic acids and esters.[338] Potassium aryltrifluoroborates have been prepared using electrochemical synthesis.[339] Aryl halides or triflates reacted with bis(boronic acid) $[(OH)_2B{-}B(OH)_2]$ in the presence of a Pd catalyst, and subsequent treatment with KHF_2 gave the potassium aryltrifluoroborate.[340] Aryl diazonium tetrafluoroborates reacted with diisopropylaminoborane with either a Ti or a Zr catalyst to give aryl boronates, arylboronic acids, or potassium aryltrifluoroborates.[341]

E. Carbon Nucleophiles[342]

Some formations of new aryl–carbon bonds from aryl substrates have been considered in **10-57**, **10-68**, **10-77**, and **10-78**.

13-8 Cyanation of Aromatic Rings: Aryl Nitriles

$$\text{Ar-X} \longrightarrow \text{Ar-CN}$$

Aryl halides react with metal cyanides, often with another transition metal catalyst, to give aryl nitriles (aryl cyanides). The reaction between aryl halides and cuprous cyanide is called the *Rosenmund-von Braun reaction*.[343] Reactivity of the aryl halide is in the order

[328] Bose, S.K.; Marder, T.B. *Org. Lett.* ***2014***, *16*, 4562.
[329] Zhang, H.; Hagihara, S.; Itami, K. *Chem. Lett.* ***2015***, *44*, 779.
[330] Liu, X.-W.; Echavarren, J.; Zarate, C.; Martin, R. *J. Am. Chem. Soc.* ***2015***, *137*, 12470.
[331] Zarate, C.; Manzano, R.; Martin, R. *J. Am. Chem. Soc.* ***2015***, *137*, 6754.
[332] Labre, F.; Gimbert, Y.; Bannwarth, P.; Olivero, S.; Duñach, E.; Chavant, P.Y. *Org. Lett.* ***2014***, *16*, 2366.
[333] Uetake, Y.; Niwa, T.; Hosoya, T. *Org. Lett.* ***2016***, *18*, 2758. For borylation reactions that used a Pd catalyst, see Bhanuchandra, M.; Baralle, A.; Otsuka, S.; Nogi, K.; Yorimitsu, H.; Osuka, A. *Org. Lett.* ***2016***, *18*, 2966.
[334] Bello, C.S.; Schmidt-Leithoff, J. *Tetrahedron Lett.* ***2012***, *53*, 6230.
[335] Kinuta, H.; Kita, Y.; Rémond, E.; Tobisu, M.; Chatani, N. *Synthesis* ***2012***, *44*, 2999.
[336] Ando, S.; Matsunaga, H.; Ishizuka, T. *J. Org. Chem.* ***2015***, *80*, 9671.
[337] Leermann, T.; Leroux, F.R.; Colobert, F. *Org. Lett.* ***2011***, *13*, 4479.
[338] Molander, G.A. *J. Org. Chem.* ***2015***, *80*, 7837.
[339] Nascimento, W.S.; Oliveira, J.L.; Freitas, J.C.R.; Navarro, M.; Menezes, P.H. *Synthesis* ***2014***, *46*, 2579.
[340] Molander, G.A.; Trice, S.L.J.; Kennedy, S.M.; Dreher, S.D.; Tudge, M.T. *J. Am. Chem. Soc.* ***2012***, *134*, 11667.
[341] Marciasini, L.D.; Vaultier, M.; Pucheault, M. *Tetrahedron Lett.* ***2014***, *55*, 1702.
[342] See Artamkina, G.A.; Kovalenko, S.V.; Beletskaya, I.P.; Reutov, O.A. *Russ. Chem. Rev.* ***1990***, *59*, 750.
[343] See Ellis, G.P.; Romney-Alexander, T.M. *Chem. Rev.* ***1987***, *87*, 779. Pradal, A.; Evano, G. *Chem. Commun.* ***2014***, *50*, 11907.

I > Br > Cl > F, indicating that the S_NAr mechanism does not apply.[344] Cyanides alone such as KCN and NaCN do not react with aryl halides, even activated ones, but CuCN catalyzed the reaction in ionic liquids.[345] The reaction has also been done in water using CuCN, a phase-transfer catalyst, and microwave irradiation.[346] L-Proline has been used to promote the reaction.[347] Metal-free methods include conversion of an aromatic compound to the corresponding iminium salt using $POCl_3$ and DMF, and subsequent reaction with I_2 in aqueous ammonia gave the nitrile.[348]

Aryl nitriles were formed by initial formation of a Grignard reagent from aryl halides, followed by reaction with *N*,*N*-dimethyl formamide adducts, and then treatment with molecular iodine (I_2) in aqueous NH_3 at room temperature.[349] Aryl bromides and other aromatic compounds have been converted to aryl nitriles via the corresponding aryllithium and the DMF adduct.[350] The reaction of an aromatic ring with *tert*-butyllithium, followed by reaction with PhOCN (phenyl cyanate) gave the aryl nitrile.[351] Aromatic ethers (ArOR)[352] have been photochemically converted to ArCN.

Alkali cyanides convert aryl halides to nitriles[353] in dipolar aprotic solvents in the presence of Pd,[354] Cu,[355] or Ni[356] complexes. Several different sources of cyanide may be used with the Pd-catalyzed reaction, including $Zn(CN)_2$,[357] CuCN,[358] potassium ferricyanide,[359] and KCN.[360] Microwave irradiation has been used to facilitate Pd-catalyzed cyanation.[361] Aryl triflates may be used in aryl cyanation reactions as well as aryl halides.[362] Benzylthiocyanate reacts with boronic acids to give aryl cyanides in a "cyanide-free" reaction, catalyzed by a Pd complex and mediated by Cu(I).[363] The reaction of aryl halides with CuSCN and a Pd catalyst gave the aryl nitrile.[364] Ethyl cyanoacetate has been used for the Pd-catalyzed conversion of aryl halides to aryl nitriles.[365] Aryl halides have been converted to aryl nitriles using $K_4[Fe(CN)_6]$ and ZnO-supported Pd nanoparticles as a

[344] See Connor, J.A.; Leeming, S.W.; Price, R. *J. Chem. Soc., Perkin Trans. 1* ***1990***, 1127.
[345] Wu, J.X.; Beck, B.; Ren, R.X. *Tetrahedron Lett.* ***2002***, *43*, 387.
[346] Arvela, R.K.; Leadbeater, N.W.; Torenius, H.M.; Tye, H. *Org. Biomol. Chem.* ***2003***, *1*, 1119.
[347] Wang, D.; Kuang, L.; Li, Z.; Ding, K. *Synlett* ***2008***, 69.
[348] Ushijima, S.; Togo, H. *Synlett* ***2010***, 1067; Ushijima, S.; Togo, H. *Synlett* ***2010***, 1562.
[349] Ishii, G.; Moriyama, K.; Togo, H. *Tetrahedron Lett.* ***2011***, *52*, 2404.
[350] Ushijima, S.; Moriyama, K.; Togo, H. *Tetrahedron* ***2011***, *67*, 958.
[351] Sato, N. *Tetrahedron Lett.* ***2002***, *43*, 6403.
[352] Letsinger, R.L.; Colb, A.L. *J. Am. Chem. Soc.* ***1972***, *94*, 3665.
[353] For a list of reagents that convert aryl halides to cyanides, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1705–1709.
[354] Takagi, K.; Sasaki, K.; Sakakibara, Y. *Bull. Chem. Soc. Jpn.* ***1991***, *64*, 1118. See Zhu, Y.-Z.; Cai, C. *Eur. J. Org. Chem.* ***2007***, 2401.
[355] Connor, J.A.; Gibson, D.; Price, R. *J. Chem. Soc., Perkin Trans. 1* ***1987***, 619.
[356] Sakakibara, Y.; Okuda, F.; Shimobayashi, A.; Kirino, K.; Sakai, M.; Uchino, N.; Takagi, K. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 1985.
[357] See Cohen, D.T.; Buchwald, S.L. *Org. Lett.* ***2015***, *17*, 202. For a reaction with $Zn(CHO_2)_2$, see Yu, H.; Richey, R.N; Miller W.D.; Xu, J.; May, S.A. *J. Org. Chem.* ***2011***, *76*, 665. Also see Zhang, X.; Xia, A.; Chen, H.; Liu, Y. *Org. Lett.* ***2017***, *19*, 2118.
[358] Sakamoto, T.; Ohsawa, K. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2323.
[359] See Velmathi, S.; Leadbeater, N.E. *Tetrahedron Lett.* ***2008***, *49*, 4693.
[360] Yang, C.; Williams, J.M. *Org. Lett.* ***2004***, *6*, 2837.
[361] Chobanian, H.R.; Fors, B.P.; Lin, L.S. *Tetrahedron Lett.* ***2006***, *47*, 3303.
[362] Yeung, P.Y.; So, C.M.; Lau. C.-P.; Kwong, F.Y. *Angew. Chem. Int. Ed.* ***2010***, *49*, 8918.
[363] Zhang, Z.; Liebeskind, L.S. *Org. Lett.* ***2006***, *8*, 4331.
[364] Zhang, G.-Y.; Yu, J.-.T.; Hu, M.-L.; Cheng, J. *J. Org. Chem.* ***2013***, *78*, 2710.
[365] Zheng, S.; Yu, C.; Shen, Z. *Org. Lett.* ***2012***, *14*, 3644.

catalyst.[366] Heteroaryl halides or triflates reacted with $Zn(CN)_2$ and a Pd catalyst in aqueous THF to give the heteroaryl nitrile.[367] Aryl halides were converted to aryl nitriles using a Pd catalyst and ethyl 2-nitroaceatate and an alkene.[368] The decarbonylative Pd-catalyzed reaction of benzamide derivatives with $Zn(CN)_2$ gave the aryl nitrile.[369] Aryl iodides reacted with *t*-butyl isocyanides to form the corresponding aryl nitrile using a Pd catalyst.[370]

Cyanation reactions catalyzed by Cu salts are common.[371] Aryl halides reacted with DMF, ammonium salts, and $Cu(Ac)_2$ to give the aryl nitrile.[372] The Cu-catalyzed reaction of arylboronic acids and DDQ gave the aryl nitrile.[373] The synthesis of 3-cyanoindole derivatives has been reported using benzyl cyanide and mediated by CuI.[374] Heating aryl iodides with nitromethane and a CuBr catalyst with DMAP/*N*-methylpiperidide gave the aryl nitrile.[375]

Aryl bromides react with $Ni(CN)_2$ with microwave irradiation to give ArCN.[376] A Ni complex also catalyzes the reaction between aryl triflates and KCN to give aryl nitriles.[377] Iridium-catalyzed borylation of arenes also leads to aryl nitriles.[378] Arylboronic acids reacted with methylbenzenesulfonamide and a Rh catalyst to give the aryl nitrile.[379]

OS **III**, 212, 631.

13-9 Coupling of Aryl Organometallic Compounds with Aryl Halides or Aryl Sulfonates

$$\mathrm{Ar{-}X + Ar'{-}M \longrightarrow Ar{-}Ar'}$$

Organometallic compounds, sometimes with a transition metal catalyst, react with aryl halides to give the corresponding biaryl. Aryl Grignard reagents react with aryltrimethylammonium triflates in the presence of a Pd catalyst to give the corresponding biaryl.[380] Arylmagnesium halides couple with aryl tosylates in the presence of a Pd catalyst to give

[366] Chatterjee, T.; Dey, R.; Ranu, B.C. *J. Org. Chem.* ***2014***, *79*, 5875; Hajipour, A.R.; Rafiee, F.; Ruoho, A.E. *Tetrahedron Lett.* ***2012***, *53*, 526. Also see Yeung, P.Y.; Liu, L.; Li, J.; Xu, J.; Sun, J.-t. *Tetrahedron Lett.* ***2012***, *53*, 6954.

[367] Cohen, D.T.; Buchwald, S.L. *Org. Lett.* ***2015***, *17*, 202; Senecal, T.D.; Shu, W.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***2013***, *52*, 10035.

[368] Maestri, G.; Cañeque, T.; Ca', N.D.; Derat, E.; Catellani, M.; Chiusoli, G.P.; Malacria, M. *Org. Lett.* ***2016***, *18*, 6108.

[369] Shi, S.; Szostak, M. *Org. Lett.* ***2017***, *19*, 3095.

[370] Jiang, X.; Wang, J.-M.; Zhang, Y.; Chen, Z.; Zhu, Y.-M.; Ji, S.-J. *Tetrahedron* ***2015***, *71*, 4883.

[371] Cristau, H.-J.; Ouali, A.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* ***2005***, *11*, 2483.

[372] Zhang, G.; Ren, X.; Chen, J.; Hu, M.; Cheng, J. *Org. Lett.* ***2011***, *13*, 5004. Copper-mediated cyanation reactions have been reviewed, see Wen, Q.; Jin, J.; Zhang, L.; Luo, Y.; Lu, P.; Wang, Y. *Tetrahedron Lett.* ***2014***, *55*, 1271.

[373] Zhang, G.; Chen, S.; Fei, H.; Cheng, J.; Chen, F. *Synlett* ***2012***, *23*, 2247. Also see Qi, C.; Hu, X.; He, H. *Synlett* ***2016***, *27*, 1979.

[374] Yuen, O.Y.; Choy, P.Y.; Chow, W.K.; Wong, W.T.; Kwong, F.Y. *J. Org. Chem.* ***2013***, *78*, 3374.

[375] Ogiwara, Y.; Morishita, H.; Sasaki, M.; Imai, H.; Sakai, N. *Chem. Lett.* ***2017***, *46*, 1736.

[376] Arvela, R.K.; Leadbeater, N.E. *J. Org. Chem.* ***2003***, *68*, 9122.

[377] Chambers, M.R.I.; Widdowson, D.A. *J. Chem. Soc., Perkin Trans. 1* ***1989***, 1365; Takagi, K.; Sakakibara, Y. *Chem. Lett.* ***1989***, 1957.

[378] Liskey, C.W.; Liao, X.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2010***, *132*, 11389.

[379] Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* ***2011***, *50*, 519.

[380] Reeves, J.T.; Fandrick, D.R.; Tan, Z.; Song, J.J.; Lee, H.; Yee, N.K.; Senanayake, C.H. *Org. Lett.* ***2010***, *12*, 4388.

unsymmetrical biaryls,[381] and couple to halopyridines to give the arylated pyridine.[382] Aryl Grignard reagents are coupled to aryliodonium salts, with $ZnCl_2$ and a Pd catalyst, to give the biaryl.[383]

A number of methods involving transition metals have been used to prepare unsymmetrical biaryls[384] (see also, **13-10**). The uncatalyzed coupling of aryl halides and metalated aryls (particularly aryllithium reagents) is also known, including cyclization of organolithium reagents to aromatic rings.[385] Noncatalyzed coupling reactions of aryllithium reagents and haloarenes can proceed via the well-known aryne route, but a novel addition–elimination pathway is possible when substituents facilitate a chelation-driven nucleophilic substitution pathway.[386] Such noncatalyzed coupling reactions often proceed with high regioselectivity and high yield.[386] 2-Bromopyridine reacts with pyrrolidine, at 130 °C with microwave irradiation, to give 2-(2-pyrrolidino)pyridine.[387] Aryl iodides undergo homocoupling to give the biaryl by heating with triethylamine in an ionic liquid.[388] The arylation of anilines has been reported using flow conditions (Sec. 7.D).[389]

Transition metal catalysts have been used to effect the aryl coupling. Aryl halides undergo homocoupling to give the biaryl with a Pd catalyst[390] or a Ni catalyst.[391] Homocoupling occurs with aryl triflates under electrolysis conditions with a Pd catalyst.[392] A recyclable Pd catalyst for use in ionic liquids has been developed.[393] Thiophene derivatives,[394] pyrrole,[395] azoles,[396] quinoline,[397] and indolizine[398] have been coupled to aryl halides using a Pd catalyst. A related reaction is the Pd-catalyzed decarboxylative coupling of arylcarboxylic acids with aryl iodides.[399]

Palladium catalysts are often used in conjunction with another metal compound or complex. Arylgermanium compounds are coupled with aryl iodides using tetrabutylammonium fluoride and a Pd catalyst.[400] Homocoupling of triphenylbismuth is known,[401] as is the coupling of arylbismuth reagents to aryliodonium salts[402] and to aryltin compounds[403] with Pd compounds or complexes. Aryl triflates were coupled to triphenylbismuth using

[381] Roy, A.H.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2003***, *125*, 8704.
[382] Bonnet, V.; Mongin, F.; Trècourt, F.; Quèguiner, G.; Knochel, P. *Tetrahedron Lett.* ***2001***, *42*, 5717.
[383] Wang, L.; Chen, Z.-C. *Synth. Commun.* ***2000***, *30*, 3607.
[384] Alberico, D.; Scott, M.E.; Lautens, M. *Chem. Rev.* ***2007***, *107*, 174.
[385] See Clayden, J.; Kenworthy, M.N. *Synthesis* ***2004***, 1721.
[386] See Becht, J.-M.; Gissot, A.; Wagner, A.; Mioskowski, C. *Chem. Eur. J.* ***2003***, *9*, 3209.
[387] Narayan, S.; Seelhammer, T.; Gawley, R.E. *Tetrahedron Lett.* ***2004***, *45*, 757.
[388] Park, S.B.; Alper, H. *Tetrahedron Lett.* ***2004***, *45*, 5515.
[389] Gemoets, H.P.L.; Laudadio, G.; Verstraete, K.; Hessel, V.; Noël, T. *Angew. Chem. Int. Ed.* ***2017***, *56*, 7161.
[390] Silveira, P.B.; Lando, V.R.; Dupont, J.; Monteiro, A.L. *Tetrahedron Lett.* ***2002***, *43*, 2327; Kuroboshi, M.; Waki, Y.; Tanaka, H. *Synlett* ***2002***, 637. See also, Venkatraman, S.; Li, C.-J. *Org. Lett.* ***1999***, *1*, 1133.
[391] Leadbeater, N.E.; Resouly, S.M. *Tetrahedron Lett.* ***1999***, *40*, 4243.
[392] de Franca, K.W.R.; Navarro, M.; Léonel, É; Durandetti, M.; Nédélec, J.-Y. *J. Org. Chem.* ***2002***, *67*, 1838.
[393] Wang, R.; Twamley, B.; Shreeve, J.M. *J. Org. Chem.* ***2006***, *71*, 426.
[394] Glover, B.; Harvey, K.A.; Liu, B.; Sharp, M.J.; Tymoschenko, M.F. *Org. Lett.* ***2003***, *5*, 301.
[395] See Rieth, R.D.; Mankad, N.P.; Calimano, E.; Sadighi, J.P. *Org. Lett.* ***2004***, *6*, 3981.
[396] Sezen, B.; Sames, D. *Org. Lett.* ***2003***, *5*, 3607.
[397] Quintin, J.; Franck, X.; Hocquemiller, R.; Figadère, B. *Tetrahedron Lett.* ***2002***, *43*, 3547.
[398] Park, C.-H.; Ryabova, V.; Seregin, I.V.; Sromek, A.W.; Gevorgyan, V. *Org. Lett.* ***2004***, *6*, 1159.
[399] Wang, Z.; Ding, Q.; He, X.; Wu, J. *Tetrahedron* ***2009***, *65*, 4635.
[400] Nakamura, T.; Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* ***2002***, *4*, 3165.
[401] Ohe, T.; Tanaka, T.; Kuroda, M.; Cho, C.S.; Ohe, K.; Uemura, S. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 1851.
[402] Kang, S.-K.; Ryu, H.-C.; Kim, J.-W. *Synth. Commun.* ***2001***, *31*, 1021.
[403] See Kim, Y.M.; Yu, S. *J. Am. Chem. Soc.* ***2003***, *125*, 1696.

a Pd catalyst.[404] Specialized arylbismuth compounds have been used with a Pd catalyst to convert aryl chlorides to biaryls.[405] An aryltin–aryl halide coupling has been done in ionic liquids.[406]

The homocoupling of arylzinc iodides, with a Pd catalyst, has been reported.[407] In a related reaction, arylsulfonyl chlorides also react with $ArSnBu_3$, with Pd and Cu catalysts, to give the biaryl.[408] Biaryls were prepared by heating thiophenol and ArZnCl with MeZnCl, Mg^{2+}, and Li^+.[409] Aryl halides were cross coupled with arylmagnesium bromides to give the biaryl, catalyzed by *N*-heterocyclic carbene nickel complexes.[410]

OS **VI**, 916; **VIII**, 430, 586; **X**, 9, 448.

13-10 Homo-coupling of Aryl Halides: The Ullmann Reaction

$$2\ ArI \xrightarrow[\Delta]{\text{Slow}} Ar{-}Ar$$

The homocoupling of aryl halides with copper is called the *Ullmann reaction*.[411] The reaction is clearly related to **13-9**, but involves aryl Cu intermediates. The reaction is of broad scope and has been used to prepare many symmetrical and unsymmetrical biaryls.[412] There are three possible products when a mixture of two different aryl halides is used, but often only one is obtained. The best leaving group is iodo, and the reaction is most often done on aryl iodides, but bromides, chlorides, and even thiocyanates have been used. New ligands have been developed to promote the reaction, including an air-stable diazaphospholane ligand.[413] Intramolecular reactions are known.[414] The coupling reaction can be applied to heterocyclic compounds.[415] Ullmann-type couplings have been promoted by potassium *tert*-butoxide.[416]

The effects of other groups on the ring are not easily predicted. The nitro group is strongly activating, but only in the *ortho* (not *meta* or *para*) position.[417] Both R and OR groups activate in all positions. Not only do OH, NH_2, NHR, and NHCOR inhibit the reaction, as would be expected for aromatic nucleophilic substitution. However, so do CO_2H (but not CO_2R), SO_2NH_2, and similar groups, for which the reaction fails completely by causing side reactions.

[404] Rao, M.L.N.; Yamazaki, O.; Shimada, S.; Tanaka, T.; Suzuki, Y.; Tanaka, M. *Org. Lett.* ***2001***, *3*, 4103.
[405] Yamazaki, O.; Tanaka, T.; Shimada, S.; Suzuki, Y.; Tanaka, M. *Synlett* ***2004***, 1921.
[406] Grasa, G.A.; Nolan, S.P. *Org. Lett.* ***2001***, *3*, 119.
[407] With NCS: Hossain, K.M.; Kameyama, T.; Shibata, T.; Takagi, K. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 2415. See also, Venkatraman, S.; Li, C.-J. *Tetrahedron Lett.* ***2000***, *41*, 4831.
[408] Dubbaka, S.R.; Vogel, P. *J. Am. Chem. Soc.* ***2003***, *125*, 15292.
[409] Yang, B.; Wang, Z.-X. *Org. Lett.* ***2017***, *19*, 6220.
[410] Guo, W.-J.; Wang, Z.-X. *J. Org. Chem.* ***2013***, *78*, 1054.
[411] Lin, H.; Sun, D. *Org. Prep. Proceed. Int.* ***2013***, *45*, 341. See Fanta, P.E. *Synthesis* ***1974***, 9; Goshaev, M.; Otroshchenko, O.S.; Sadykov, A.S. *Russ. Chem. Rev.* ***1972***, *41*, 1046. For a continuous flow reaction, see Zhang, Y.; Jamison, T.F.; Patel, S.; Mainolfi, N. *Org. Lett.* ***2011***, *13*, 280.
[412] See Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem. Int. Ed.* ***1990***, *29*, 977. Also see, Meyers, A.I.; Price, A. *J. Org. Chem.* ***1998***, *63*, 412.
[413] Yang, M.; Liu, F. *J. Org. Chem.* ***2007***, *72*, 8969.
[414] See for example, Karimipour, M.; Semones, A.M.; Asleson, G.L.; Heldrich, F.J. *Synlett*, ***1990***, 525.
[415] D'Angelo, N.D.; Peterson, J.J.; Booker, S.K.; Fellows, I.; Dominguez, C.; Hungate, R.; Reider, P.J.; Kim, T.-S. *Tetrahedron Lett.* ***2006***, *47*, 5045.
[416] Yang, S.; Wu, C.; Ruan, M.; Yang, Y.; Zhao, Y.; Niu, J.; Yang, W.; Xu, J. *Tetrahedron Lett.* ***2012***, *53*, 4288.
[417] Forrest, J. *J. Chem. Soc.* ***1960***, 592.

The mechanism is not known with certainty. It seems likely that it is basically a two-step process, similar to that of the *Wurtz reaction* (**10-56**), and which can be represented schematically by:

$$\mathrm{ArI + Cu} \longrightarrow \mathrm{ArCu} \xrightarrow{\mathrm{Ar{-}I}} \mathrm{Ar{-}Ar}$$

Organocopper compounds have been trapped by coordination with organic bases.[418] In addition, aryl copper compounds (ArCu) have been independently prepared and shown to give biaryls (Ar—Ar′) when treated with aryl iodides Ar′I.[419] A similar reaction has been used for ring closure:[420]

A modified Cu(0)–Cu(I) mediated reaction that gave biaryls was reported.[421] *N*-phenylpicolinamide (NPPA) was shown to be an effective ligand for Ullmann-type homocoupling reactions of aryl iodides and bromides to give the biaryl derivative.[422] A green procedure using a reusable Pd/ZrO_2 catalyst has been reported.[423] A microwave-assisted reaction has been reported in alkaline water.[424]

An alternative to the Ullmann method is the use of Ni complexes.[425] Aryl halides, ArX, can also be converted to Ar—Ar[426] by treatment with activated Ni metal,[427] with Zn and Ni complexes,[428] and in an electrochemical process catalyzed by a Ni complex.[429] An asymmetric Ullmann reaction has been reported.[430]

OS **III**, 339; **V**, 1120.

13-11 Coupling of Aryl Compounds and Alkenyl Compounds With Arylboronic acid Derivatives

$$\mathrm{Ar{-}Br + Ar'B(OH)_2} \xrightarrow{\mathrm{PdL_4}} \mathrm{Ar{-}Ar'}$$

Arylboronic acids, $ArB(OH)_2$ (**12-27**),[431] are coupled to aryl halides using a Pd catalyst to give the biaryl[432] in what is called *Suzuki coupling* (or *Suzuki-Miyaura coupling*).[433]

[418] Lewin, A.H.; Cohen, T. *Tetrahedron Lett.* ***1965***, 4531.
[419] See Mack, A.G.; Suschitzky, H.; Wakefield, B.J. *J. Chem. Soc., Perkin Trans. 1* ***1980***, 1682.
[420] See Salfeld, J.C.; Baume, E. *Tetrahedron Lett.* ***1966***, 3365.
[421] Yasamut, K.; Jongcharoenkamol, J.; Ruchirawat, S.; Ploypradith, P. *Tetrahedron* ***2016***, *72*, 5994.
[422] Damkaci, F.; Altay, E.; Waldron, M.;. Knopp, M.A.; Snow, D.; Massaro, N. *Tetrahedron Lett.* ***2014***, *55*, 690.
[423] Dumbre, D.K.; Wakharkar, R.D.; Choudhary, V.R. *Synth. Commun.* ***2010–2011***, *41*, 164.
[424] Gädda, T.M.; Kawanshi, Y.; Miyazawa, A. *Synth. Commun.* ***2012***, *42*, 1259.
[425] See Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 80. For a review of the mechanism, see Amatore, C.; Jutand, A. *Acta Chem. Scand.* ***1990***, *44*, 755.
[426] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp.82–84.
[427] Matsumoto, H.; Inaba, S.; Rieke, R.D. *J. Org. Chem.* ***1983***, *48*, 840; Chao, C.S.; Cheng, C.H.; Chang, C.T. *J. Org. Chem.* ***1983***, *48*, 4904.
[428] Takagi, K.; Hayama, N.; Sasaki, K. *Bull. Chem. Soc. Jpn.* ***1984***, *57*, 1887.
[429] Meyer, G.; Rollin, Y.; Perichon, J. *J. Organomet. Chem.* ***1987***, *333*, 263.
[430] Nelson, T.D.; Meyers, A.I. *J. Org. Chem.* ***1994***, *59*, 2655; Nelson, T.D.; Meyers, A.I. *Tetrahedron Lett.* ***1994***, *35*, 3259.
[431] For a synthesis of arylboranes, see Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* ***2012***, *134*, 134.
[432] See Davies, H.M.L.; Morton, D. *J. Org. Chem.* ***2016***, *81*, 343. See Segawa, Y.; Maekawa, T.; Itami, K. *Angew. Chem. Int. Ed.* ***2015***, *54*, 66.
[433] Suzuki, A. *Angew. Chem. Int. Ed.* ***2011***, *50*, 6722. Miyaura, N.; Suzuki, A. *Chem. Rev.* ***1995***, *95*, 2457; Rossi, R.; Bellina, F.; Lessi, M. *Tetrahedron* ***2011***, *67*, 6969; Heravi, M.M.; Hashemi, E. *Tetrahedron* ***2012***, *68*, 9145.

Aryl triflates react with arylboronic acids,[434,435] or with organoboranes,[436] in the presence of a Pd catalyst.[437] Even hindered boronic acids give good yields of the coupled product.[438] Homocoupling of arylboronic acids has been reported.[439] Some aromatic compounds are so reactive that a catalyst may not be required. Arylation of heterocycles with unreactive and hindered aryl chlorides[440] or aryl bromides[441] have been reported; these reactions use a Pd catalyst. Biocatalysis has been used to prepare biaryls.[442] Decarboxylative oxidative cross coupling has been applied to biaryl synthesis.[443] The intramolecular reaction is well known.[444] Radical arylation reactions are known.[445] Aryl boronates also react with π-allyl palladium complexes to form the alkylated aromatic compound.[446] Transition metal-free cross-coupling reactions have been reported.[447] Chemoselective cross-coupling strategies have been explored.[448]

Different conditions (including additives and solvent) for the reaction have been reported,[449] often focusing on the catalyst[450] or the ligand.[451] Phosphine-free conditions[452] and ligand-free conditions[453] have been developed. A ligand-free In-catalyzed

See Suzuki, A.; Yamamoto, Y. *Chem. Lett.* ***2011***, *40*, 894; Shirakawa, E.; Hayashi, T. *Chem. Lett.* ***2012***, *41*, 130; Kündig, E.P.; Jia, Y.; Katayev, D.; Nakanishi, M. *Pure Appl. Chem.* ***2012***, *84*, 1741.

[434] For the use of boronic acid surrogates, see Bonin, H.; Leuma-Yona, R.; Marchiori, B.; Demonchaux, P.; Gras, E. *Tetrahedron Lett.* ***2011***, *52*, 1132.

[435] Badone, D.; Baroni, M.; Cardomone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* ***1997***, *62*, 7170. See Torrell, E.; Brookes, P. *Synthesis* ***2003***, 469.

[436] Fürstner, A.; Seidel, G. *Synlett* ***1998***, 161.

[437] For a review, see Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* ***2004***, 2419.

[438] Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* ***1992***, 207.

[439] Lei, A.; Zhang, X. *Tetrahedron Lett.* ***2002***, *43*, 2525; Parrish, J.P.; Jung, Y.C.; Floyd, R.J.; Jung, K.W. *Tetrahedron Lett.* ***2002***, *43*, 7899.

[440] Ghosh, D.; Lee, H.M. *Org. Lett.* ***2012***, *14*, 5534.

[441] Roy, D.; Mom, S.; Lucas, D.; Cattey, H.; Hierso, J.-C.; Doucet, H. *Chem. Eur. J.* ***2011***, *17*, 6453.

[442] Aldemir, H.; Richarz, R.; Gulder, T.A.M. *Angew. Chem. Int. Ed.* ***2014***, *53*, 8286.

[443] Perry, G.J.P.; Larrosa, I. *Eur. J. Org. Chem.* ***2017***, 3517.

[444] Heravi, M.M.; Hashemi, E. *Monatsh. Chem.* ***2012***, *143*, 861.

[445] Hofmann, J.; Heinrich, M.R. *Tetrahedron Lett.* ***2016***, *57*, 4334; Yong, G.-P.; She, W.-L.; Zhang, Y.-M.; Li, Y.-Z. *Chem. Commun.* ***2011***, *47*, 11766.

[446] Ortar, G. *Tetrahedron Lett.* ***2003***, *44*, 4311.

[447] Gray, V.J.; Wilden, J.D. *Chem. Commun.* ***2014***, *50*, 2575; Jadhav, S.; Rashinkar, G.; Salunkhe, R.; Kumbhar, A. *Tetrahedron. Lett.* ***2017***, *58*, 3201. For electrochemical couplings, see Schäfer, H.J. *Angew. Chem. Int. Ed.* ***2017***, *56*, 1552.

[448] Fyfe, J.W.B.; Watson, A.J.B. *Synlett* ***2015***, *26*, 1139.

[449] Fairlamb, I.J.S.; Kapdi, A.R.; Lee, A.F. *Org. Lett.* ***2004***, *6*, 4435; Artok, L.; Bulat, H. *Tetrahedron Lett.* ***2004***, *45*, 3881.

[450] For a discussion of catalysts in this reaction, see Bhayana, B.; Fors, B.P.; Buchwald, S.L. *Org. Lett.* ***2009***, *11*, 3954; Nishikata, T.; Abela, A.R.; Huang, S.; Lipshutz, B.H. *J. Am. Chem. Soc.* ***2010***, *132*, 4978;. Moseley, J.D.; Murray, P.M.; Turp, E.R.; Tyler, S.N.G.; Burn, R.T. *Tetrahedron* ***2012***, *68*, 6010; Feng, Y.-S.; Lin, X.-Y.; Hao, J.; Xu, H.-J. *Tetrahedron* ***2014***, *70*, 5249; Fang, Y.; Wang, S.-Y.; Ji, S.-J. *Tetrahedron* ***2015***, *71*, 9679; Wang, L.; Cui, X.; Li, J.; Wu, Y.; Zhu, Z.; Wu, Y. *Eur. J. Org. Chem.* ***2012***, 595; Diebold, C.; Becht, J.-M.; Lu, J.; Toy, P.H.; Le Drian, C. *Eur. J. Org. Chem.* ***2012***, 893.

[451] Tang, W.; Keshipeddy, S.; Zhang, Y.; Wei, X.; Savoie, S.; Patel, N.D.; Yee, N.K.; Senanayake, C.H. *Org. Lett.* ***2011***, *13*, 1366; Qiu, Y.; Liu, Y.; Yang, K.; Hong, W.; Li, Z.; Wang, Z.; Yao, Z.; Jiang, S. *Org. Lett.* ***2011***, *13*, 3556; Mastalir, M.; Stöger, B.; Pittenauer, E.; Allmaier, G.; Kirchner, K. *Org. Lett.* ***2016***, *18*, 3186; Mondal, M.; Bora, U. *Tetrahedron Lett.* ***2014***, *55*, 3038; Mešková, M.; Putala, M. *Tetrahedron: Asymmetry* ***2013***, *24*, 894.

[452] See Mino, T.; Kajiwara, K.; Shirae, Y.; Sakamoto, M.; Fujita, T. *Synlett* ***2008***, 2711.

[453] See Zhou, W.-J.; Wang, K.-H.; Wang, J.-X.; Gao, Z.-R. *Tetrahedron* ***2010***, *66*, 7633; Qiu, J.; Wang, L.; Liu, M.; Shen, Q.; Tang, J. *Tetrahedron Lett.* ***2011***, *52*, 6489.

reaction has been reported.[454] Magnetically recoverable[455] or otherwise recyclable[456] catalysts have been developed. Catalysts have been developed for deactivated aryl chlorides.[457] Suzuki coupling has also been done in ionic liquids,[458] in supercritical CO_2,[459] (Sec. 9.D.ii), in three-phase microemulsions,[460] and there are solvent-free procedures.[461] Several procedures for coupling in aqueous media have been reported.[462] The reaction has been done neat on alumina,[463] and on alumina with microwave irradiation.[464] Several procedures have been reported using microwave irradiation.[465] Flow conditions[466] (Sec. 7.D) have been used, as have ball-milling techniques (Sec. 7.E).[467] Modifications to the basic procedure include tethering the aryl triflate[468] or the boronic acid[469] to a polymer.

A variety of functional groups are compatible with Suzuki coupling, including CHO,[470] C═O of a ketone,[471] CO_2R,[472] cyclopropyl,[473] NO_2,[474] CN, and halogen substituents.[475] In a variation, vinylboronic acids coupled to aryl halides to give the vinyl-coupling

[454] Liu, P.; Pan, Y.-m.; Hu, K.; Huang, X.-c.; Liang, Y.; Wang, H.-s. *Tetrahedron* ***2013***, *69*, 7925.

[455] Pd catalysts: Guerra, R.R.G.; Martins, F.C.P.; Lima, C.G.S.; Gonçalves, R.H.; Leite, E.R.; Pereira-Filho, E.R.; Schwab, R.S. *Tetrahedron Lett.* ***2017***, *58*, 903. Fe catalysts: Du, Q.; Zhang, W.; Ma, H.; Zheng, J.; Zhou, B.; Li, Y. *Tetrahedron* ***2012***, *68*, 3577.

[456] Ethernet cable

[457] Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem. Int. Ed.* ***2000***, *39*, 4153. See Saha, D.; Ghosh, R.; Sarkar, A. *Tetrahedron* ***2013***, *69*, 3951; Sau, S.C.; Santra, S.; Sen, T.K.; Mandal, S.K.; Koley, D. *Chem. Commun.* ***2012***, *48*, 555.

[458] See dos Santos Castro, K.L.; de Lima, P.G.; Miranda, L.S.M.; de Souza, R.O.M.A. *Tetrahedron Lett.* ***2011***, *52*, 4168; Boruah, P.R.; Koiri, M.J.; Bora, U.; Sarma, D. *Tetrahedron Lett.* ***2014***, *55*, 2423; Lin, L.; Li, Y.; Zhang, S.; Li, S. *Synlett* ***2011***, *22*, 1779; Leadbeater, N.E. *Chem. Commun.* ***2014***, *50*, 1515.

[459] Early, T.R.; Gordon, R.S.; Carroll, M.A.; Holmes, A.B.; Shute, R.E.; McConvey, I.F. *Chem. Commun.* ***2001***, 1966.

[460] Nowothnick, H.; Blum, J.; Schomäcker, R. *Angew. Chem. Int. Ed.* ***2011***, *50*, 1918.

[461] Li, J.-H.; Deng, C.-L.; Xie, Y.-X. *Synth. Commun.* ***2007***, *37*, 2433.

[462] For a review, see Franzén, R.; Xu, Y. *Can. J. Chem.* ***2005***, *83*, 266. See. Babu, G.N.; Pal, S. *Tetrahedron Lett.* ***2017***, *58*, 1000; Rathod, P.V.; Jadhav, V.H. *Tetrahedron Lett.* ***2017***, *58*, 1006; Du, Z.; Zhou, W.; Wang, F.; Wang, J.-X. *Tetrahedron* ***2011***, *67*, 4914; Liu, Y.-s.; Gu, N.-n.; Liu, P.; Ma, X.-w.; Liu, Y.; Xie, J.-w.; Dai, B. *Tetrahedron* ***2015***, *71*, 7985; Qiu, P.; Zhao, J.Y.; Shi, X.; Duan, X.H. *New J. Chem.* ***2016***, 6568.

[463] Kabalka, G.W.; Pagni, R.M.; Hair, C.M. *Org. Lett.* ***1999***, *1*, 1423. See Basu, B.; Das, P.; Bhuiyan, Md.M.H.; Jha, S. *Tetrahedron Lett.* ***2003***, *44*, 3817.

[464] Villemin, D.; Caillot, F. *Tetrahdron Lett.* ***2001***, *42*, 639.

[465] Chanthavong, F.; Leadbeater, N.E. *Tetrahedron Lett.* ***2006***, *47*, 1909; Baxendale, I.R.; Griffiths-Jones, C.M.; Ley, S.V.; Tranmer, G.K. *Chem. Eur. J.* ***2006***, *12*, 4407. See da Silva, J.F.M.; Perez, A.F.Y.; de Almeida, N.P. *Synth. Commun.* ***2015***, *45*, 1995.

[466] Noël, T.; Musacchio, A.J. *Org. Lett.* ***2011***, *13*, 5180; Mateos, C.; Rincón, J.A.; Martín-Hidalgo, B.; Villanueva, J. *Tetrahedron Lett.* ***2014***, *55*, 3701; Bao, J.; Tranmer, G.K. *Tetrahedron Lett.* ***2016***, *57*, 654; Noël, T.; Kuhn, S.; Musacchio, A.J.; Jensen, K.F.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***2011***, *50*, 5943; Shu, W.; Pellegatti, L.; Oberli, M.A.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***2011***, *50*, 10665; Lange, P.P.; Gooßen, L.J.; Podore, P.; Underwood, T.; Sciammetta, H. *Chem. Commun.* ***2011***, *47*, 3618.

[467] Jiang, Z.-J.; Li, Z.-H.; Yu, J.-B.; Su, W.-K. *J. Org. Chem.* ***2016***, *81*, 10049.

[468] Blettner, C.G.; König, W.A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* ***1999***, *64*, 3885. For other reactions on solid support, see Franzén, R. *Can. J. Chem.* ***2000***, *78*, 957.

[469] See Islam, M.; Mondal, P.; Tuhina, K.; Hossain, D.; Roy, A.S. *Chem. Lett.* ***2010***, *39*, 1200.

[470] Phan, N.T.S.; Brown, D.H.; Styring, P. *Tetrahedron Lett.* ***2004***, *45*, 7915.

[471] Baillie, C.; Zhang, L.; Xiao, J. *J. Org. Chem.* ***2004***, *69*, 7779.

[472] Mutele, I.; Suna, E. *Tetrahedron Lett.* ***2004***, *45*, 3909.

[473] Ma, H.-r.; Wang, X.-L.; Deng, M.-z. *Synth. Commun.* ***1999***, *29*, 2477.

[474] Tao, B.; Boykin, D.W. *J. Org. Chem.* ***2004***, *69*, 4330; Li, J.-H.; Liu, W.-J. *Org. Lett.* ***2004***, *6*, 2809.

[475] Colacot, T.J.; Shea, H.A. *Org. Lett.* ***2004***, *6*, 3731; DeVasher, R.B.; Moore, L.R.; Shaughnessy, K.H. *J. Org. Chem.* ***2004***, *69*, 7919.

product.[476] Vinylboronic acids have been coupled to aryldiazonium salts (see **13-25**) without added base, using a Pd catalyst with an imidazolium ligand.[477] The Pd-catalyzed oxidative coupling of vinylboronic acids and alkenes in the presence of O_2 gave 1,3-disubstituted conjugated dienes.[478]

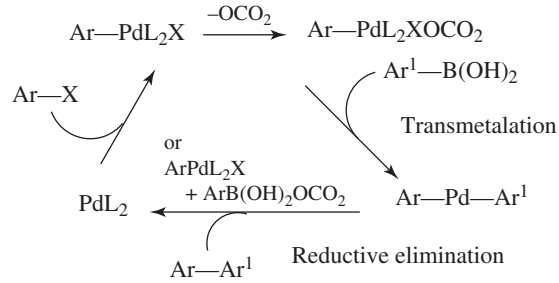
Arylboronic acids have been coupled to vinyl halides[479] or vinyl tosylates,[480] using a Pd catalyst. Aryl fluorides have been used, using a Ni catalyst.[481] Aryl sulfonates have been used[482] and arylboronic acids couple with aryl sulfonate esters.[483] Alkenyl tosylates and mesylates have been used.[484] Halogenated heteroaromatic compounds react, as do aryl carbamates,[485] carbonates, sulfamates,[486] and aryl phosphoramides.[487] Myriad heterocycles have been arylated.[488] Electron-deficient bipyridines have been prepared using a Ni catalyst.[489] The Pd-catalyzed C3-selective arylation of pyridine with heteroarenes has been reported.[490] The Fe-catalyzed cross coupling of *N*-heterocyclic halides and aryl Grignard reagents has been reported.[491]

The reaction of α-halocarbonyl compounds with alkenes gave conjugated alkenes when catalyzed by Cu catalysts.[492] The Ir-catalyzed oxidative coupling of furans with unactivated alkenes gave branched vinylfuran products.[493] The Ni-catalyzed reaction of aryl halides and vinyl halides is known.[494]

[476] Peyroux, E.; Berthiol, F.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* ***2004***, 1075.
[477] Andrus, M.B.; Song, C.; Zhang, J. *Org. Lett.* ***2002***, *4*, 2079.
[478] Zheng, C.; Wang, D.; Stahl, S.S. *J. Am. Chem. Soc.* ***2012***, *134*, 16496.
[479] See Clarisse, D.; Peltier, B.; Piva, O.; Fache, F. *Chem. Commun.* ***2012***, *48*, 203.
[480] Wu, J.; Zhu, Q.; Wang, L.; Fathi, R.; Yang, Z. *J. Org. Chem.* ***2003***, *68*, 670.
[481] Tobisu, M.; Xu, T.; Shimasaki, T.; Chatani, N. *J. Am. Chem. Soc.* ***2011***, *133*, 19505.
[482] Zhang, W.; Chen, C.H.-T.; Lu, Y.; Nagashima, T. *Org. Lett.* ***2004***, *6*, 1473; Riggleman, S.; DeShong, P. *J. Org. Chem.* ***2003***, *68*, 8106.
[483] So, C.M.; Lau, C.P.; Chan, A.S.C.; Kwong, F.Y. *J. Org. Chem.* ***2008***, *73*, 7731; So, C.M.; Lau, C.P.; Kwong, F.Y. *Angew. Chem. Int. Ed.* ***2008***, *47*, 8059.
[484] Wong, P.Y.; Chow, W.K.; Chung, K.H.; So, C.M.; Lau, C.P.; Kwong, F.Y. *Chem. Commun.* ***2011***, *47*, 8328.
[485] Baghbanzadeh, M.; Pilger, C.; Kappe, C.O. *J. Org. Chem.* ***2011***, *76*, 1507; Ohtsuki, A.; Yanagisawa, K.; Furukawa, T.; Tobisu, M.; Chatani, N. *J. Org. Chem.* ***2016***, *81*, 9409; Wang, X.-X.; Luo, M.-J.; Lu, J.-M. *Org. Biomol. Chem.* ***2015***, *13*, 11438. For a stereospecific reaction, see Harris, M.R.; Hanna, L.E.; Greene, M.A.; Moore, C.E.; Jarvo, E.R. *J. Am. Chem. Soc.* ***2013***, *135*, 3303.
[486] Quasdorf, K.W.; Riener, M.; Petrova, K.V.; Garg, N.K. *J. Am. Chem. Soc.* ***2009***, *131*, 17748. See Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* ***2009***, *131*, 17750.
[487] Zhao, Y.-L.; Li, Y.; Li, Y.; Gao, L.-X.; Han, F.-S. *Chem. Eur. J.* ***2010***, *16*, 4991.
[488] For a few examples from a vast number, see Düfert, M.A.; Billingsley, K.L.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2013***, *135*, 12877; Tollefson, E.J.; Dawson, D.D.; Osborne, C.A.; Jarvo, E.R. *J. Am. Chem. Soc.* ***2014***, *136*, 14951; Yang, Y.; Li, R.; Zhao, Y.; Zhao, D.; Shi, Z. *J. Am. Chem. Soc.* ***2016***, *138*, 8734; Leowanawat, P.; Zhang, N.; Resmerita, A.-M.; Rosen, B.M.; Percec, V. *J. Org. Chem.* ***2011***, *76*, 9946; Yan, T.; Chen, L.; Bruneau, C.; Dixneuf, P.H.; Doucet, H. *J. Org. Chem.* ***2012***, *77*, 7659; Hovey, M.T.; Check, C.T.; Sipher, A.F.; Scheidt, K.A. *Angew. Chem. Int. Ed.* ***2014***, *53*, 9603; Liu, X.; Meng, Z.; Li, C.; Lou, H.; Liu, L. *Angew. Chem. Int. Ed.* ***2015***, *54*, 6012; Chen, J.; Wu, J. *Angew. Chem. Int. Ed.* ***2017***, *56*, 3951; Murru, S.; Gallo, A.A.; Srivastava, R.S. *Eur. J. Org. Chem.* ***2011***, 2035; Deb, A.; Manna, S.; Maji, A.; Dutta, U.; Maiti, D. *Eur. J. Org. Chem.* ***2013***, 5251; Jakab, A.; Dalicsek, Z.; Soós, T. *Eur. J. Org. Chem.* ***2015***, 56.
[489] Li, H.; Oppenheimer, J.; Smith III, M.R.; Maleczka Jr., R.E. *Tetrahedron Lett.* ***2016***, *57*, 2231.
[490] Gao, G.-L.; Xia, W.; Jain, P.; Yu, J.-Q. *Org. Lett.* ***2016***, *18*, 744.
[491] Kuzmina, O.M.;. Steib, A.K.; Flubacher, D.; Knochel, P. *Org. Lett.* ***2012***, *14*, 4818.
[492] Nishikata, T.; Noda, Y.; Fujimoto, R.; Sakashita, T. *J. Am. Chem. Soc.* ***2013***, *135*, 16372.
[493] Sevov, C.S.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2014***, *136*, 10625.
[494] Liu, J.; Ren, Q.; Zhang, X.; Gong, H. *Angew. Chem. Int. Ed.* ***2016***, *55*, 15544. Also see Desrosiers, J.-N.; Hie, L.; Biswas, S.; Zatolochnaya, O.V.; Rodriguez, S.; Lee, H.; Grinberg, N; Haddad, N.; Yee, N.K.; Garg, N.K.; Senanayake, C.H. *Angew. Chem. Int. Ed.* ***2016***, *55*, 11921. Gu, J.; Qiu, C.; Lu, W.; Qian, Q.; Lin, K.; Gong, H. *Synthesis* ***2017***, *49*, 1867.

Alkyl groups may be coupled to aryls, as in the Pd-catalyzed reaction of arylboronic acids with benzylic carbonates.[495] Alkyl/alkyl Suzuki reactions using alkyl chlorides are known, using a Ni catalyst,[496] and asymmetric reactions are known.[497] Arylboronic acids also couple with alkyl halides using either a Pd[498] or a Ni catalyst.[499] Conversely, arylboronic acids can be coupled to aliphatic halides.[500] Arylboronic acids can be coupled to allylic alcohols as well.[501] Benzylic phosphonates have also been used.[502] Double Suzuki coupling reactions are known.[503]

Since many biaryls are chiral due to atropisomerism (Sec. 4.C, category 5), the use of a chiral catalyst, and/or a chiral ligand can lead to enantioselectivity in the Suzuki coupling.[504] The asymmetric synthesis of axially chiral heterobiaryls in known.[505] The choice of ligand has important effects on the stereochemistry.[506] The chemoselective and enantioselective cross coupling of benzylic organoboronic esters has been reported.[507]



For a mechanistic viewpoint,[508] the Suzuki coupling proceeds via oxidative addition of areneboronic acids to give a Pd species, followed by 1,2-arene migration to an electron-deficient Pd atom, eventually leading to very fast reductive elimination to afford biaryls.[509] This mechanism is discussed in detail.[510] Several intermediates of the oxidative coupling

[495] Kuwano, R.; Yokogi, M. *Org. Lett.* ***2005***, *7*, 945. Di Franco, T.; Boutin, N.; Hu, X. *Synthesis* ***2013***, *45*, 2949.
[496] See Zultanski, S.L.; Fu, G.C. *J. Am. Chem. Soc.* ***2013***, *135*, 624.
[497] Wilsily, A.; Tramutola, F.; Owston, N.A.; Fu, G.C. *J. Am. Chem. Soc.* ***2012***, *134*, 5794.
[498] Kirchhoff, J.H.; Netherton, M.R.; Hills, I.D.; Fu, G.C. *J. Am. Chem. Soc.* ***2002***, *124*, 13662.
[499] Zhou, J.; Fu, G.C. *J. Am. Chem. Soc.* ***2004***, *126*, 1340.
[500] Bandgar, B.P.; Bettigeri, S.V.; Phopase, J. *Tetrahedron Lett.* ***2004***, *45*, 6959.
[501] Tsukamoto, H.; Sato, M.; Kondo, Y. *Chem. Commun.* ***2004***, 1200; Kayaki, Y.; Koda, T.; Ikariya, T. *Eur. J. Org. Chem.* ***2004***, 4989.
[502] McLaughlin, M. *Org. Lett.* ***2005***, *7*, 4875.
[503] Habashneh, A.Y.; Dakhil, O.O.; Zein, A.; Georghiou, P.E. *Synth. Commun.* ***2009***, *39*, 4221.
[504] See Baudoin, O. *Eur. J. Org. Chem.* ***2005***, 4223. Lu, G.-P.; Voigtritter, K.R.; Cai, C.; Lipshutz, B.H. *J. Org. Chem.* ***2012***, *77*, 3700.
[505] Ros, A.; Estepa, B.; Ramírez-López, P.; Álvarez, E.; Fernández, R.; Lassaletta, J.M. *J. Am. Chem. Soc.* ***2013***, *135*, 15730.
[506] Lu, G.-P.; Voigtritter, K.R.; Cai, C.; Lipshutz, B.H. *J. Org. Chem.* ***2012***, *77*, 3700; Ros, A.; Estepa, B.; Bermejo, A.; Álvarez, E.; Fernández, R.; Lassaletta, J.M. *J. Org. Chem.* ***2012***, *77*, 4740.
[507] Glasspoole, B.W.; Oderinde, M.S.; Moore, B.D.; Antoft-Finch, A.; Crudden, C.M. *Synthesis* ***2013***, *45*, 1759.
[508] Amatore, C.; Le Duc, G.; Jutand, A. *Chem. Eur. J.* ***2013***, *19*, 10082. For a $S_{RN}1$ reaction, see Haines, B.E.; Wiest, O. *J. Org. Chem.* ***2014***, *79*, 2771. See Esponet, P.; Echavarren, A.M. *Angew. Chem. Int. Ed.* ***2004***, *43*, 4704.
[509] Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* ***1996***, *61*, 2346. See Audran, G.; Brémond, P.; Marque, S.R.A.; Siri, D.; Santelli, M. *Tetrahedron* ***2014***, *70*, 2272. See Malecea, R.; Saffon, N.; Gómez, M.; Bourissou, D. *Chem. Commun.* ***2011***, *47*, 8163.
[510] *Metal-Catalyzed Cross-Coupling Reactions*, Diederich, F.; Stang, P.J. Wiley-VCH, Weinheim, ***1998***, p. 212. See Maestri, G.; Motti, E.; Ca', N.D.; Malacria, M.; Derat, E.; Catellani, M. *J. Am. Chem. Soc.* ***2011***, *133*, 8574.

process have been identified by electrospray ionization mass spectrometry.[511] Palladium peroxo complexes have been shown to be key intermediates.[512] Benzyne intermediates have been observed as intermediates in aniline *ortho*-arylation reactions.[513]

Diaryliodonium salts[514] have been coupled to arenes,[515] indoles, and pyrroles using metal-free conditions.[516] The Na_2PtCl_4-catalyzed C—H arylation of naphthalene and the reaction of other arenes with diaryliodonium salts has been reported.[517] The Cu-catalyzed preparation of biaryls using diaryliodonium salts has been reported.[518]

Other transition metals have been employed in these coupling reactions, sometimes as co-catalysts.[519] Arylboronic acids have been coupled to conjugated alkenes to give the aryl/alkene coupling product using Grignard reagents,[520] aryl Zn reagents,[521] or Pd,[522] Ni,[523] Ir,[524] Co,[525] Cu,[526] Ce,[527] Fe,[528] Mn,[529] Au,[530] or Rh catalysts.[531] Arylboronic acids are coupled with aryl ammonium salts to give the biaryl, with a Ni

[511] Aramendia, M.A.; Lafont, F.; Moreno-Mañas, M.; Pleixats, R.; Roglans, A. *J. Org. Chem.* ***1999***, *64*, 3592; Kozuch, S.; Martin, J.M.L. *Chem. Commun.* ***2011***, *47*, 4935.

[512] Adamo, C.; Amatore, C.; Ciofini, I.; Jutand, A.; Lakmini, H. *J. Am. Chem. Soc.* ***2006***, *128*, 6829.

[513] Truong, T.; Daugulis, O. *Org. Lett.* ***2012***, *14*, 5964.

[514] Aradi, K.; Tóth, B.L.; Tolnai, G.L.; Novák, Z. *Synlett* ***2016***, *27*, 1456.

[515] Liu, Y.-X.; Xue, D.; Wang, J.-D.; Zhao, C.-J.; Zou, Q.-Z.; Wang, C.; Xiao, J. *Synlett* ***2013***, *24*, 517.

[516] Ackermann, L.; Dell'Acqua, M.; Fenner, S.; Vicente, R.; Sandmann, R. *Org. Lett.* ***2011***, *13*, 2358; Storr, T.E.; Greaney, M.F. *Org. Lett.* ***2013***, *15*, 1410.

[517] Wagner, A.M.; Hickman, A.J.; Sanford, M.S. *J. Am. Chem. Soc.* ***2013***, *135*, 15710.

[518] Fañanás-Mastral, M. *Synthesis* ***2017***, *49*, 1905. Wang, X.; Huang, D.; Wang, X.; Zeng, X.; Wang, X.; Hu, Y. *Tetrahedron Lett.* ***2016***, *57*, 4235.

[519] Lee, D.-H.; Jin, M.-J. *Org. Lett.* ***2011***, *13*, 252; Zeng, J.; Liu, K.M.; Duan, X.F. *Org. Lett.* ***2013***, *15*, 5342; Wang, D.; Stahl, S.S. *J. Am. Chem. Soc.* ***2017***, *139*, 5704. Distinguishing pathways for transmetalation has been discussed, see Carrow, B.P.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2011***, *133*, 2116.

[520] Shirakawa, E.; Hayashi, Y.; Itoh, K.-i.; Watabe, R.; Uchiyama, N.; Konagaya, W.; Masui, S.; Hayashi, T. *Angew. Chem. Int. Ed.* ***2012***, *51*, 218. See Zhou, F.; Simon, M.-O.; Li, C.-J. *Chem. Eur. J.* ***2013***, *19*, 7151.

[521] Zhang, X.-Q.; Wang, Z.-X. *J. Org. Chem.* ***2012***, *77*, 3658; Liu, N.; Wang, L.; Wang, Z.-X. *Chem. Commun.* ***2011***, *47*, 1598.

[522] Jung, Y.C.; Mishra, R.K.; Yoon, C.H.; Jung, K.W. *Org. Lett.* ***2003***, *5*, 2231.

[523] Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* ***2013***, 19. See Ramgren, S.D.; Hie, L.; Ye, Y.; Garg, N.K. *Org. Lett.* ***2013***, *15*, 3950. See Sontag, S.K.; Bilbrey, J.A.; Huddleston, N.E.; Sheppard, G.R.; Allen, W.D.; Locklin, J. *J. Org. Chem.* ***2014***, *79*, 1836; Hu, F.; Kumpati, B.N.; Lei, X. *Tetrahedron Lett.* ***2014***, *55*, 7215; Hu, F.; Lei, X. *Tetrahedron* ***2014***, *70*, 3854; Abe, T.; Mino, T.; Watanabe, K.; Sakamoto, M. *Eur. J. Org. Chem.* ***2014***, 6983.

[524] García-Melchor, M.; Gorelsky, S.I.; Woo, T.K. *Chem. Eur. J.* ***2011***, *17*, 13847.

[525] Tan, G.; He, S.; Huang, X.; Liao, X.; Cheng, Y.; You, J. *Angew. Chem. Int. Ed.* ***2016***, *55*, 10414; Liu, L.; Cao, H.; Xin, J.; Jin, L.; Lei, A. *Chem. Eur. J.* ***2011***, *17*, 3586; Asghar, S.; Tailor, S.B.; Elorriaga, D.; Bedford, R.B. *Angew. Chem. Int. Ed.* ***2017***, *56*, 16367.

[526] Crowley, B.M.; Potteiger, C.M.; Deng, J.Z.; Prier, C.K.; Paone, D.V.; Burgey, C.S. *Tetrahedron Lett.* ***2011***, *52*, 5055; Hirano, K.; Miura, M. *Chem. Lett.* ***2015***, *44*, 868. See Zou, L.-H.; Johansson, A.J.; Zuidema, E.; Bolm, C. *Chem. Eur. J.* ***2013***, *19*, 8144.

[527] Mayer, M.G.; Nador, F.; Volpe, M.A.; Radivoy, G. *Synlett* ***2013***, *24*, 338.

[528] Chandrasekharam, M.; Chiranjeevi, B.; Gupta, K.S.V.; Sridhar, B. *J. Org. Chem.* ***2011***, *76*, 10229; Sirois, J.J.; Davis, R.; DeBoef, B. *Org. Lett.* ***2014***, *16*, 868. However, see Bedford, R.B.; Nakamura, M.; Gower, N.J.; Haddow, M.F.; Hall, M.A.; Huwe, M.; Hashimoto, T.; Okopie, R.A. *Tetrahedron Lett.* ***2009***, *50*, 6110.

[529] Yang, J.; Sun, S.; Zeng, Z.; Zheng, H.; Li, W.; Lou, H.; Li, L. *Org. Biomol. Chem.* ***2014***, *12*, 7774; Ghaleshahi, H.G.; Antonacci, G.; Madsen, R. *Eur. J. Org. Chem.* ***2017***, 1331.

[530] Hofer, M.; Nevado, C. *Tetrahedron* ***2013***, *69*, 5751; Wang, L.; Zhang, W.; Su, D.S.; Meng, X.; Xiao, F.-S. *Chem. Commun.* ***2012***, *48*, 5476; Gauchot, V.; Lee, A.-L. *Chem. Commun.* ***2016***, *52*, 10163.

[531] See Baars, H.; Unoh, Y.; Okada, T.; Hirano, K.; Satoh, T.; Tanaka, K.; Bolm, C.; Miura, M. *Chem. Lett.* ***2014***, *43*, 1782.

catalyst.[532] Merging Pd catalysts with organic photoredox catalysts allowed visible light-promoted reactions.[533] Aryltrimethylammonium iodides have been cross coupled with organozinc reagents, using a Ni catalyst.[534] The carbonylative cross coupling of triarylbismuths with aryl iodides to give biaryl ketones has been reported.[535]

Suzuki-type coupling reactions have been reported involving acyl halides. When arylboronic acids were reacted with benzoyl chloride and $PdCl_2$, the product was the diaryl ketone,[536] and a Pd(0)) catalyst has been used.[537] Cyclopropylboronic acids couple with benzoyl chloride, in the presence of Ag_2O and a Pd catalyst, to give the cyclopropyl ketone.[538] A Ni catalyst has been used.[539] Arylboronic acids have also been coupled to anhydrides,[540] and the methoxy group of anisole derivatives has been replaced with phenyl using phenylboronic acid and a Ru catalyst.[541]

Arylboronic esters (see **12-27**), $ArB(OR)_2$, can be used in place of the boronic acid.[542] Base-free conditions, using nitrogen ligands, have been reported.[543] Aryl and heteroarylboroxines can be coupled to aryl halides using a Pd catalyst.[544] Vinylboranes have been coupled to aryl iodides to give the aryl alkene, in the presence of a Pd catalyst.[545] Organoboranes are coupled to aryl halides with a Pd catalyst.[546] Boronic esters have been coupled with *N*-heteroaromatic compounds.[547]

In a useful variation, aryltrifluoroborates $ArBF_3^+ X^-$ (**12-27**), are coupled to aryl halides with a Pd catalyst to give the biaryl.[548] Potassium phenyltrifluoroborates can be coupled to aromatics using a combination of Pd and Cu catalysts.[549] Alkyltrifluoroborates[550] (RBF_3K, see **12-27**) react with aryl triflates,[551] aryl halides,[552] or aryliodonium salts,[553] with a Pd catalyst, to give the arene. Vinyltrifluoroborates ($C{=}C{-}BF_3^+ X^-$, see **12-27**), are coupled to aryl halides with a Pd catalyst to give the styrene derivative.[554] Alkyl

[532] Blakey, S.B.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2003***, *125*, 6046.
[533] Jiang, J.; Zhang, W.-M.; Dai, J.-J.; Xu, J.; Xu, H.-J. *J. Org. Chem.* ***2017***, *82*, 3622. Also see Cheng, Y.; Gu, X.; Li, P. *Org. Lett.* ***2013***, *15*, 2664.
[534] Xie, L.-G.; Wang, Z.-X. *Angew. Chem. Int. Ed.* ***2011***, *50*, 4901.
[535] Hao, W.; Liu, H.; Yin, L.; Cai, M. *J. Org. Chem.* ***2016***, *81*, 4244.
[536] Bumagin, N.A.; Korolev, D.N. *Tetrahedron Lett.* ***1999***, *40*, 3057.
[537] Haddach, M.; McCarthy, J.R. *Tetrahedron Lett.* ***1999***, *40*, 3109.
[538] Chen, H.; Deng, M.-Z. *Org. Lett.* ***2000***, *2*, 1649.
[539] Leadbeater, N.E.; Resouly, S.M. *Tetrahedron* ***1999***, *55*, 11889.
[540] Gooßen, L.J.; Ghosh, K. *Angew. Chem. Int. Ed.* ***2001***, *40*, 3458.
[541] Kakiuchi, F.; Usai, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* ***2004***, *126*, 2706.
[542] See Odachowski, M.; Bonet, A.; Essafi, S.; Conti-Ramsden, P.; Harvey, J.N.; Leonori, D.; Aggarwal, V.K. *J. Am. Chem. Soc.* ***2016***, *138*, 9521.
[543] Yoo, K.S.; Yoon, C.H.; Jung, K.W. *J. Am. Chem. Soc.* ***2006***, *128*, 16384.
[544] Cioffi, C.L.; Spencer, W.T.; Richards, J.J.; Herr, R.J. *J. Org. Chem.* ***2004***, *69*, 2210.
[545] Nishihara, Y.; Miyasaka, M.; Okamoto, M.; Takahashi, H.; Inoue, E.; Tanemura, K.; Takagi, K. *J. Am. Chem. Soc.* ***2007***, *129*, 12634.
[546] Iglesias, B.; Alvarez, R.; de Lera, A.R. *Tetrahedron* ***2001***, *57*, 3125.
[547] Llaveria, J.; Leonori, D.; Aggarwal, V.K. *J. Am. Chem. Soc.* ***2015***, *137*, 10958.
[548] See Raushel, J.; Sandrock, D.L.; Josyula, K.V.; Pakyz, D.; Molander, G.A. *J. Org. Chem.* ***2011***, *76*, 2762. With a Mn oxidant, see Seigerman, C.K.; Micyus, T.M.; Neufeldt, S.R.; Sanford, M.S. *Tetrahedron* ***2013***, *69*, 5580.
[549] Zhao, J.; Zhang, Y.; Cheng, K. *J. Org. Chem.* ***2008***, *73*, 7428.
[550] Darses, S.; Genet, J.-P. *Chem. Rev.* ***2008***, *108*, 288.
[551] Molander, G.A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* ***2003***, *68*, 5534.
[552] Dreher, S.D.; Lim, S.-E.; Sandrock, D.L.; Molander, G.A. *J. Org. Chem.* ***2009***, *74*, 3626.
[553] Xia, M.; Chen, Z.-C. *Synth. Commun.* ***1999***, *29*, 2457.
[554] Molander, G.A.; Bernardi, C.R. *J. Org. Chem.* ***2002***, *67*, 8424; Math, S.K.; Mokri, H.H.; LaMunyon, J.B.; Cefalo, D.R.; Testa, C.A. *Tetrahedron Lett.* ***2012***, *53*, 2847.

and alkoxymethyltrifluoroborates have been coupled to heteroaryls.[555] Potassium Boc-protected aminomethyltrifluoroborate has been coupled to aryl and heteroaryl halides.[556] Photoredox coupling of trifluoroborates and aryl bromides has been reported using flow conditions (Sec. 7.D).[557] Trifluoro(*N*-methylheteroaryl)borates[558] and potassium 2-pyridyl trifluoroborates[559] have also been used. Suzuki coupling with trifluoroborates has also been done using microwave irradiation[560] and in water.[561] Aryl tellurides have been used in this reaction.[562] A Pd-catalyzed reaction with enamino ketones, mediated by Cu(II) salts, led to coupling to give the aryl derivative.[563] Ruthenium catalysts have also been used.[564]

OS **75**, 53, 61.

The coupling reactions of alkylboronic acids are covered in **13-17**.

13-12 Alkylation of Aryl Compounds

$$\text{Ar—X} \longrightarrow \text{Ar—R}$$

Alkyl halides or alkyl sulfonate esters react with aryl organometallics to give the corresponding arene, sometimes directly but often using a transition metal catalyst. *Grignard reagents* couple with aryl halides without a catalyst, by the benzyne mechanism,[565] but metal-catalyzed reactions are known. Typical catalysts include Fe,[566] Ni,[567] Co,[568] Ti,[569] and Pd.[570] Benzene, naphthalene, and phenanthrene have been alkylated with alkyllithium reagents, although the usual reaction with these reagents is **12-22**,[571] and *Grignard reagents* have been used to alkylate naphthalene.[572] The addition–elimination mechanism apparently applies in these cases. Formation of the *ortho* arylmagnesium compound has been accomplished with bases of the form $(R_2N)_2Mg$.[573] It is noted that the transition metal-free alkylation of pyridines has been reported.[574] The transition metal-free cross coupling of allylic bromides with aryl- and vinylboronic acids has been reported.[575]

[555] Molander, G.A.; Colombel, V.; Braz, V.A. *Org. Lett.* ***2011***, *13*, 1852.
[556] See Molander, G.A.; Shin, I. *Org. Lett.* ***2012***, *14*, 4458.
[557] DeLano, T.J.; Bandarage, U.K.; Palaychuk, N.; Green, J.; Boyd, M.J. *J. Org. Chem.* ***2016***, *81*, 12525.
[558] Molander, G.A.; Ryu, D.; Hosseini-Sarvari, M.; Devulapally, R.; Seapy, D.G. *J. Org. Chem.* ***2013***, *78*, 6648.
[559] Ren, W.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *Tetrahedron* ***2012***, *68*, 1351.
[560] Harker, R.L.; Crouch, R.D. *Synthesis* ***2007***, 25; Kabalka, G.W.; Naravane, A.; Zhao, L.L. *Tetrahedron Lett.* ***2007***, *48*, 709.
[561] Liu, L.; Dong, Y.; Pang, B.; Ma, J. *J. Org. Chem.* ***2014***, *79*, 7193.
[562] Cella, R.; Cunha, R.L.O.R.; Reis, A.E.S.; Pimenta, D.C.; Klitzke, C.F.; Stefani, H.A. *J. Org. Chem.* ***2006***, *71*, 244.
[563] Ge, H.; Niphakis, M.J.; Georg, G.I. *J. Am. Chem. Soc.* ***2008***, *130*, 3708.
[564] Wu, J.; Zhang, L.; Gao, K. *Eur. J. Org. Chem.* ***2006***, 5260.
[565] Du, C.F.; Hart, H.; Ng, K.D. *J. Org. Chem.* ***1986***, *51*, 3162.
[566] Yamaguchi, Y.; Ando, H.; Nagaya, M.; Hinago, H.; Ito, T.; Asami, M. *Chem. Lett.* ***2011***, *40*, 983; Guo, W.-J.; Wang, Z.-W. *Tetrahedron* ***2013***, *69*, 9580.
[567] Yoshikai, N.; Mashima, H.; Nakamura, E. *J. Am. Chem. Soc.* ***2005***, *127*, 17978.
[568] Korn, T.J.; Cahiez, G.; Knochel, P. *Synlett* ***2003***, 1892.
[569] Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *Tetrahedron* ***2000***, *56*, 9601.
[570] Manabe, K.; Ishikawa, S. *Synthesis* ***2008***, 2645.
[571] Eppley, R.L.; Dixon, J.A. *J. Am. Chem. Soc.* ***1968***, *90*, 1606.
[572] Bryce-Smith, D.; Wakefield, B.J. *Tetrahedron Lett.* ***1964***, 3295.
[573] Eaton, P.E.; Lee, C.; Xiong, Y. *J. Am. Chem. Soc.* ***1989***, *111*, 8016. Also see Kronenburg, C.M.P.; Rijnberg, E.; Jastrzebski, J.T.B.H.; Kooijman, H.; Lutz, M.; Spek, A.L.; Gossage, R.A.; van Koten, G. *Chem. Eur. J.* ***2005***, *11*, 253.
[574] Li, X.; Wang, H.-Y.; Shi, Z.-J. *New J. Chem.* ***2013***, 1704.
[575] Ueda, M.; Nishimura, K.; Kashima, R.; Ryu, I. *Synlett* ***2012***, *23*, 1085.

The reaction of an aromatic ring with an organolithium reagent can give H–Li exchange to form an aryllithium.[576] This reaction tends to be slow if there are activating substituents on the aryl halide or in the absence of diamine additives.[577] When heteroatom substituents are present on the aromatic ring, however, the reaction is facile and the Li goes into the 2 position.[578] This regioselectivity can be quite valuable synthetically, and is now known as *directed ortho metalation*[579] (see **10-57**). The reaction occurs by an addition–elimination mechanism and the adduct can be isolated.[580] Upon heating of the adduct, elimination of LiH occurs and an alkylated product is obtained. The alkylation of heterocyclic nitrogen compounds[581] with alkyllithium reagents is called *Ziegler alkylation*. Note that H–Li exchange can be faster than Cl–Li exchange. The reaction of *N*-triisopropylsilyl indole with *tert*-butyllithium and then iodomethane gave the 3-methyl derivative.[582] Heteroaromatic compounds can be alkylated. Pyrrole, for example, reacts with an allylic halide and zinc to give primarily the 3-substituted pyrrole.[583]

With TMEDA/*n*-butyllithium-mediated arene lithiation reactions, the viability of directive effects (complex-induced proximate effects) has been questioned,[584] although it is not clear if this extends to other systems (particularly when there is a strong coordinating group such as carbamate).[585] The 2 position is much more acidic than the 3 position (see Table 8.1), but a negative charge at C-3 is in a more favorable position to be stabilized by the Li^+. Lithiation reactions do not necessarily rely on a complex-induced proximity effect.[586]

The metal-catalyzed reaction of aryl derivatives leads to alkylated aromatic compounds.[587] The coupling of alkyl substrates and alkene substrates using transition metal catalysis is also known. The transition metal-catalyzed α-arylation reaction is known.[588] The trifluoromethylation of aryl and heteroaryl halides has been reviewed.[589]

The development of transition metal-catalyzed reactions is a very active area of research, and a sampling of current work follows. The Ni-catalyzed cross-coupling reaction of Grignard reagents such as butylmagnesium bromide and an alkyl or aryl halide such as

[576] See Erb, W.; Mongin, F. *Tetrahedron* ***2016***, *72*, 4973.

[577] See Becht, J.-M.; Gissot, A.; Wagner, A.; Misokowski, C. *Tetrahedron Lett.* ***2004***, *45*, 9331.

[578] Slocum, D.W.; Jennings, C.A. *J. Org. Chem.* ***1976***, *41*, 3653. However, the regioselectivity can depend on reaction conditions: see Meyers, A.I.; Avila, W.B. *Tetrahedron Lett.* ***1980***, 3335.

[579] See Snieckus, V. *Chem. Rev.* ***1990***, *90*, 879; Gschwend, H.W.; Rodriguez, H.R. *Org. React.* ***1979***, *26*, 1; Green, L.; Chauder, B.; Snieckus, V. *J. Heterocylic Chem.* ***1999***, *36*, 1453. Also see, Green, L.; Chauder, B.; Snieckus, V. *J. Heterocycl. Chem.* ***1999***, *36*, 1453.

[580] Armstrong, D.R.; Mulvey, R.E.; Barr, D.; Snaith, R.; Reed, D. *J. Organomet. Chem.* ***1988***, *350*, 191.

[581] See Vorbrüggen, H.; Maas, M. *Heterocycles* ***1988***, *27*, 2659. Also see Comins, D.L.; O'Connor, S. *Adv. Heterocycl. Chem.* ***1988***, *44*, 199.

[582] Matsuzono, M.; Fukuda, T.; Iwao, M. *Tetrahedron Lett.* ***2001***, *42*, 7621.

[583] Yadav, J.S.; Reddy, B.V.S.; Reddy, P.M.; Srinivas, Ch. *Tetrahedron Lett.* ***2002***, *43*, 5185.

[584] Chadwick, S.T.; Rennels, R.A.; Rutherford, J.L.; Collum, D.B. *J. Am. Chem. Soc.* ***2000***, *122*, 8640.

[585] Hay, D.R.; Song, Z.; Smith, S.G.; Beak, P. *J. Am. Chem. Soc.* ***1988***, *110*, 8145.

[586] Chadwick, S.T.; Rennels, R.A.; Rutherford, J.L.; Collum, D.B. *J. Am. Chem. Soc.* ***2000***, *122*, 8640; Collum, D.B. *Acc. Chem. Res.* ***1992***, *25*, 448. For a discusison of mechanistic possibilities, see Nguyen, T.-H.; Chau, N.T.T.; Castanet, A.-S.; Nguyen, K.P.P.; Mortier, J. *Org. Lett.* ***2005***, *7*, 2445.

[587] For a review, see Terao, J.; Kambe, N. *Acc. Chem. Res.* ***2008***, *41*, 1545. Dong, J.; Wu, Q.; You, J. *Tetrahedron Lett.* ***2015***, *56*, 1591; Weix, D.J. *Acc. Chem. Res.* ***2015***, *48*, 1767. See Jana, R.; Pathak, T.P.; Sigman, M.S. *Chem. Rev.* ***2011***, *111*, 1417.

[588] Mazet, C. *Synlett* ***2012***, *23*, 1999.

[589] Weng, Z.; He, W.; Chen, C.; Lee, R.; Tan, D.; Lai, Z.; Kong, D.; Yuan, Y.; Huang, K.-W. *Angew. Chem. Int. Ed.* ***2013***, *52*, 1548; Chen, P.; Liu, G. *Synthesis* ***2013***, *45*, 2919; Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Asian J.* ***2012***, *7*, 1744; Roy, S.; Gregg, B.T.; Gribble, G.W.; Le, V.-D.; Roy, S. *Tetrahedron* ***2011***, *67*, 2161.

chlorobenzene to give butylbenzene,[590] is called *Kumada coupling*.[591] Pd catalysts have also been used.

$$\text{Ph–Cl} + \text{BuMgBr} \xrightarrow[\substack{\text{Reflux, 20 h}\\ \text{2. } H_3O^+}]{\substack{\text{1. cat. } NiCl_2(dpp)\\ m\text{-Dichlorobenzene}}} \text{Ph–Bu}$$

The Ni-catalyzed reaction of alkyl Grignard reagents with aryl bromides or triflates has also been reported.[592] The Ni-catalyzed reaction of aryl, heteroaryl, or vinyl chlorides gave the coupling product.[593] Alkenyl halides were coupled to Grignard reagents using a Pd catalyst.[594] Both the intermolecular and the intramolecular Fe-mediated cross coupling of alkyl chlorides and aryl bromides has been reported.[595] An Fe-catalyzed Kumada cross-coupling reaction has been reported using flow conditions (Sec. 7.D).[596] An asymmetric Kumada cross-coupling reaction for the enantioselective arylation of α-bromo esters catalyzed by a Co–bis(oxazoline) complex gave chiral α-aryl alkanoic esters with excellent enantioselectivity.[597]

There are many current examples of Pd-catalyzed reactions. The lithium enolate anion of an ester was coupled to an aryl halide using a Pd catalyst.[598] Ketones can be coupled to aryl triflates, in the presence of a Pd catalyst, and with good enantioselectivity.[599] Aryl halides reacted with acetone to give α-aryl acetone in the presence of a Pd catalyst.[600] Aryl halides led to β-arylation of simple ketones using a Pd catalyst, in the presence of AgTFA.[601] The Pd-catalyzed α-arylation of α-fluoro ketones has been reported, with high enantioselectivity.[602] α-Allyl acetoxy cyclic ketones reacted with α-aryl derivatives, and subsequent treatment with Meldrum's acid and a Pd catalyst gave the tertiary α-aryl ketones.[603] Indium homoenolates[604] reacted with aryl halides to give β-aryl ketones in the presence of a Pd

[590] Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* ***1972***, *94*, 4374.

[591] Kambe, N. *Acc. Chem. Res.* ***2008***, *41*, 1545; Hua, X.Y.; Masson-Makdissi, J.; Sullivan, R.J.; Newman, S.G. *Org. Lett.* ***2016***, *18*, 5312; Xu, S.; Kim, E.H.; Wei, A.; Negishi, E.-i. *Sci. Technol. Adv. Mater.* ***2014***, *15*, 044201; Zhang, X.-Q.; Wang, Z.-X. *Synlett* ***2013***, *24*, 2081. See Gauthier, D.; Beckendorf, S.; Gøgsig, T.M.; Lindhardt, A.T.; Skrydstrup, T. *J. Org. Chem.* ***2009***, ***74***, 3536.

[592] Joshi-Pangu, A.; Wang, C.-Y.; Biscoe, M.R. *J. Am. Chem. Soc.* ***2011***, *133*, 8478.

[593] Liu, N.; Wang, Z.-X. *J. Org. Chem.* ***2011***, *76*, 10031. See Soler-Yanes, R.; Guisán-Ceinos, M.; Buñuel, E.; Cárdenas, D.J. *Eur. J. Org. Chem.* ***2014***, 6625.

[594] Krasovskiy, A.L.; Haley, S.; Voigtritter, K.; Lipshutz, B.H. *Org. Lett.* ***2014***, *16*, 4066.

[595] Li, Z.; Sun, H.-M.; Shen, Q. *Org. Biomol. Chem.* ***2016***, *14*, 3314.

[596] Buono, F.G.; Zhang, Y.; Tan, Z.; Brusoe, A.; Yang, B.-S.; Lorenz, J.C.; Giovannini, R.; Song, J.J.; Yee, N.K.; Senanayake, C.H. *Eur. J. Org. Chem.* ***2016***, 2599.

[597] Mao, J.; Liu, F.; Wang, M.; Wu, L.; Zheng, B.; Liu, S.; Zhong, J.; Bian, Q.; Walsh, P.J. *J. Am. Chem. Soc.* ***2014***, *136*, 17662.

[598] Moradi, W.A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2001***, *123*, 7996.

[599] Liao, X.; Weng, Z.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2008***, *130*, 195.

[600] Ge, S.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2011***, *133*, 16330. Xu, Q.-L.; Gao, H.; Yousufuddin, M.; Ess, D.H.; Kürti, L. *J. Am. Chem. Soc.* ***2013***, *135*, 14048. See MacQueen, P.M.; Chisholm, A.J.; Hargreaves, B.K.V.; Stradiotto, M. *Chem. Eur. J.* ***2015***, *21*, 11006.

[601] Huang, Z.; Dong, G. *J. Am. Chem. Soc.* ***2013***, *135*, 17747.

[602] Jiao, Z.; Beiger, J.J.; Jin, Y.; Ge, S.; Zhou, J.S.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2016***, *138*, 15980.

[603] Doran, R.; Guiry, P.J. *J. Org. Chem.* ***2014***, *79*, 9112.

[604] For a review of C—C bond formation via Pd homoenolates, see Nithiy, N.; Rosa, D.; Orellana, A. *Synthesis* ***2013***, *45*, 3199.

catalyst.[605] The direct reaction of a ketone, a vinyl halide, sodium *tert*-butoxide, and a Pd catalyst also gave the α-vinyl ketone.[606]

Organolithium reagents are coupled to aryl bromides in the presence of a Ni catalyst,[607] as are arylzinc compounds.[608] The mechanism of the Ni-catalyzed cross-coupling reaction of aryl halides and alkyl halides has been examined.[609] The Ni-catalyzed cross coupling of heteroaryl iodides and α-chloronitriles is known.[610] Aryl halides reacted with secondary alkyl bromides or with allylic acetates, in the presence of Zn and a Ni catalyst, to give the alkylated aryl compound.[611] Alkyl halides are coupled to aryl halides using a Ni-catalyzed reductive cross coupling.[612] The Ni-catalyzed coupling of aryl bromides and tertiary alkyl halides has been reported.[613] Aryl halides reacted with methyl tosylate using a Ni catalyst.[614] The Ni-catalyzed α-arylation of ketones has been reported using phenol derivatives.[615] The Ni-catalyzed trifluoromethylation of arylboronic acids has been reported.[616]

The decarboxylative coupling of simple alkyl carboxylic acids with aryl zinc reagents, using a Ni catalyst, has been reported.[617] An electrochemical method for reducing catalytic Ni complexes allowed the coupling of aryl bromides with alkyl bromides to give the arene.[618] Aryl halides and alkyl halides gave the photo-coupled product in the presence of a Ni catalyst, an Ir photosensitizer, and an amine electron donor.[619] The Ni-catalyzed synthesis of α-aryl nitriles was reported by the cross coupling of α-bromonitriles and arylboronic acids.[620] Vinylic and aryl halides can be used to vinylate or arylate carboxylic esters (but not ketones) by the use of $NiBr_2$ as a catalyst.[621]

The Pd-catalyzed coupling of arylboronic acids with alkyl α-bromoacetates gave aryl acetic acid esters.[622] The Pd-catalyzed 2-alkylation reaction of N—H indoles relies on a norbornene-mediated cascade activation of the indole C—H.[623] The Zn-mediated, Pd-catalyzed coupling of benzylic halides with heteroaryl halides gave arylheteroarylmethanes in aqueous media.[624] The Pd-catalyzed reaction of aryl halides and cyclic alkyl halides has

[605] Shen, Z.-L.; Lai, Y.-C.; Wong, C.H.A.; Goh, K.K.K.; Yang, Y.-S.; Cheong, H.-L.; Loh, T.-P. *Org. Lett.* ***2011***, *13*, 422.

[606] Chieffi, A.; Kamikawa, K.; Åhman, J.; Fox, J.M.; Buchwald, S.L *Org. Lett.* ***2001***, *3*, 1897.

[607] Jhaveri, S.B.; Carter, K.R. *Chem. Eur. J.* ***2008***, *14*, 685.

[608] Wang, L.; Wang, Z.-X. *Org. Lett.* ***2007***, *9*, 4335.

[609] Biswas, S.; Weix, D.J. *J. Am. Chem. Soc.* ***2013***, *135*, 16192. For a similar reaction with aniline derivatives, see Li, J.; Warratz, S.; Zell, D.; Sarkar, S.D.; Ishikawa, E.E.; Ackermann, L. *J. Am. Chem. Soc.* ***2015***, *137*, 13894; Duan, Z.; Li, W.; Lei, A. *Org. Lett.* ***2016***, *18*, 4012.

[610] Kadunce, N.T.; Reisman, S.E. *J. Am. Chem. Soc.* ***2015***, *137*, 10480.

[611] Wang, S.; Qian, Q.; Gong, H. *Org. Lett.* ***2012***, *14*, 3352.

[612] Everson, D.A.; Jones, B.A.; Weix, D.J. *J. Am. Chem. Soc.* ***2012***, *134*, 6146.

[613] Wang, X.; Wang, S.; Xue, W.; Gong, H. *J. Am. Chem. Soc.* ***2015***, *137*, 11562. Also see Qureshi, Z.; Toker, C.; Lautens, M. *Synthesis* ***2017***, *49*, 1.

[614] Wang, J.; Zhao, J.; Gong, H. *Chem. Commun.* ***2017***, *53*, 10180.

[615] Takise, R.; Muto, K.; Yamaguchi, J.; Itami, K. *Angew. Chem. Int. Ed.* ***2014***, *53*, 6791.

[616] Su, Y.-M.; Feng, G.-S.; Wang, Z.-Y.; Lan, Q.; Wang, X.-S. *Angew. Chem. Int. Ed.* ***2015***, *54*, 6003.

[617] Cornella, J.; Edwards, J.T.; Qin, T.; Kawamura, S.; Wang, J.; Pan, C.-M.; Gianatassio, R.; Schmidt, M.; Eastgate, M.D.; Baran, P.S. *J. Am. Chem. Soc.* ***2016***, *138*, 2174.

[618] Perkins, R.J.; Pedro, D.J.; Hansen, E.C. *Org. Lett.* ***2017***, *19*, 3755.

[619] Paul, A.; Smith, M.D.; Vannucci, A.K. *J. Org. Chem.* ***2017***, *82*, 1996.

[620] Yang, Y.; Tang, S.; Liu, C.; Zhang, H.; Sun, Z.; Lei, A. *Org. Biomol. Chem.* ***2011***, *9*, 5343.

[621] Millard, A.A.; Rathke, M.W. *J. Am. Chem. Soc.* ***1977***, *99*, 4833.

[622] Zimmermann, B.; Dzik, W.I.; Himmler, T.; Goossen, L.J. *J. Org. Chem.* ***2011***, *76*, 8107.

[623] Jiao, L.; Bach, T. *J. Am. Chem. Soc.* ***2011***, *133*, 12990.

[624] Krasovskiy, A.; Thomé, I.; Graff, J.; Krasovskaya, V.; Konopelski, P.; Duplais, C.; Lipshutz, B.H. *Tetrahedron Lett.* ***2011***, *52*, 2203; Krasovskaya, V.; Krasovskiy, A.; Lipshutz, B.H. *Chem. Asian J.* ***2011***, *6*, 1974.

been reported using a zinc mediator and octanoic acid as a surfactant.[625] Alkylzinc reagents were coupled to heteroaryl halides using a Pd catalyst.[626] Organozinc compounds, available by reaction of an alkyl halide and zinc metal, are coupled to aryl halides using a Pd catalyst.[627] Specialized alkyl In complexes have been used with a Pd catalyst to give arenes.[628] The intramolecular alkylation of aryl and heteroaryl amine derivatives using a Pd catalyst gave the corresponding carbocycle and/or heterocycle.[629]

Copper compounds are important in these coupling reactions. The cross coupling of organoboron compounds with primary alkyl halides was catalyzed by Cu catalysts. Arylmagnesium bromide with $Cu(acac)_2$ reacts in an S_N2' reaction, displacing a pyridyl ester unit to give an allylic aryl compound.[630] The Cu–*N*-heterocyclic carbene-catalyzed allylation and alkenylation of heteroarenes has been reported.[631] The enantioselective α-arylation of aldehydes has been reported using diaryliodonium salts and a combination of Cu and organic catalysts.[632] The Cu-mediated trifluoromethylation of aryl and heteroaryl boronic acids with F_3C^- has been reported, in the presence of oxygen.[633] Silyl enol ethers react with diaryliodonium triflates in the presence of a Cu(I)-bisoxazoline catalyst, to give the α-aryl ester or amide.[634]

Cobalt compounds[635] and Fe compounds[636] have been used to catalyze aryl/alkyl coupling. Alkyl halides are coupled to alkenes to form substituted alkenes using a Co catalyst, promoted by Me_3SiCH_2MgCl.[637] Alkylation requires that the alkyl group lacks a β-hydrogen, and the reaction is successful for the introduction of methyl, benzyl, and neopentyl groups.[638] Cobalt has been used to catalyze aryl/allyl cross-coupling reactions.[639] The Co-catalyzed intramolecular cross coupling of alkyl iodides with alkenes upon irradiation with visible light in the presence of a tertiary amine base gave alkylated alkenes.[640] Cycloalkyl iodides were coupled to alkynyl or aryl or heteroaryl Grignard reagents with a Co catalyst.[641] The C4 alkylation of pyridines was reported using a Co catalyst.[642] Alkyl Grignard reagents were coupled to aryl sulfamates or tosylates using an Fe catalyst.[643] The Fe-catalyzed reaction of alkyl, benzyl, or allyl halides led to coupling with arylboronic esters.[644] Potassium vinyltrifluoroborates were trifluoromethylated using an Fe catalyst.[645]

[625] Bhonde, V.R.; O'Neill, B.T.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***2016***, *55*, 1849.
[626] Yang, Y.; Niedermann, K.; Han, C.; Buchwald, S.L. *Org. Lett.* ***2014***, *16*, 4638.
[627] Hama, T.; Culkin, D.A.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2006***, *128*, 4976.
[628] Shenglof, M.; Gelman, D.; Heymer, B.; Schumann, H.; Molander, G.A.; Blum, J. *Synthesis* ***2003***, 302.
[629] Venning, A.R.O.; Bohan, P.T.; Alexanian, E.J. *J. Am. Chem. Soc.* ***2015***, *137*, 3731.
[630] Feng, C.; Kobayashi, Y. *J. Org. Chem.* ***2013***, *78*, 3755.
[631] Xie, W.; Chang, S. *Angew. Chem. Int. Ed.* ***2016***, *55*, 1876.
[632] Allen, A.E.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2011***, *133*, 260.
[633] Senecal, T.D.; Parsons, A.T.; Buchwald, S.L. *J. Org. Chem.* ***2011***, *76*, 1174.
[634] Harvey, J.S.; Simonovich, S.P.; Jamison, C.R.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2011***, *133*, 13782.
[635] Ackermann, L. *J. Org. Chem.* ***2014***, *79*, 8948.
[636] Sherry, B.D.; Fürstner, A. *Acc. Chem. Res.* ***2008***, *41*, 1500. Hatakeyama, T.; Fujiwara, Y.-i.; Okada, Y.; Itoh, T.; Hashimoto, T.; Kawamura, S.; Ogata, K.; Takaya, H.; Nakamura, M. *Chem. Lett.* ***2011***, *40*, 1030.
[637] Affo, W.; Ohmiya, H.; Fujioka T.; Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K.; Imamura, Y.; Mizuta, T.; Miyoshi, K. *J. Am. Chem. Soc.* ***2006***, *128*, 8068.
[638] See Heck, R.F.; Nolley Jr., J.P. *J. Org. Chem.* ***1972***, 3720.
[639] Hammann, J.M.; Hofmayer, M.S.; Lutter, F.H.; Thomas, L.; Knochel, P. *Synthesis* ***2017***, *49*, 3887.
[640] Weiss, M.E.; Kreis, L.M.; Lauber, A.; Carreira, E.M. *Angew. Chem. Int. Ed.* ***2011***, *50*, 11125.
[641] Hammann, J.M.; Haas, D.; Tüllmann, C.-P.; Karaghiosoff, K.; Knochel, P. *Org. Lett.* ***2016***, *18*, 4778.
[642] Andou, T.; Saga, Y.; Komai, H.; Matsunaga, S.; Kanai, M. *Angew. Chem. Int. Ed.* ***2013***, *52*, 3213.
[643] Agrawal, T.; Cook, S.P. *Org. Lett.* ***2013***, *15*, 96.
[644] Bedford, R.B.; Brenner, P.B.; Carter, E.; Carvell, T.W.; Cogswell, P.M.; Gallagher, T.; Harvey, J.N.; Murphy, D.M.; Neeve, E.C.; Nunn, J.; Pye, D.R. *Chem. Eur. J.* ***2014***, *20*, 7935.
[645] Parsons, A.T.; Senecal, T.D.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***2012***, *51*, 2947.

A Rh catalyst has also been used for the coupling of allylic carbonates and arenes.[646] The Ru complex-catalyzed reaction of benzaldehyde imines and secondary alkyl halides gave the *meta* alkylated product.[647] Rhodium/Au catalysis of aryldiazonium salts with trialkylallylsilanes gave the 3-arylpropene.[648] The Au-catalyzed allylation of arylboronic acids has been reported.[649] A Au-photoredox catalyst was used for the coupling of iodoarenes and bromoalkanes.[650] Indium catalysts have been used for aromatic alkylation reactions.[651] The coupling of alkylzinc reagents with aryl iodides gave alkylated aromatic compounds.[652] Mercuration of aromatic compounds[653] can be accomplished with mercuric salts, most often $Hg(OAc)_2$,[654] to give ArHgOAc. This is ordinary electrophilic aromatic substitution and takes place by the arenium ion mechanism (Sec. 11.A.i).[655]

OSCV **X**, 102, 467; OS **81**, 89, OS **II**, 517.

13-13 Aryl-Alkene Coupling: The Heck Reaction

$$R_2C{=}CH_2 + Ar\text{-}X \xrightarrow{Pd(0)} R_2C{=}CH{-}Ar$$

Arylation of alkenes,[656] catalyzed by an *in situ*-generated Pd complex, has become an important reaction in organic chemistry.[657] The Pd-catalyzed aryl-alkene coupling reaction is known as *the Heck reaction*.[658] Mizoroki had earlier described the coupling between iodobenzene and styrene to form stilbene in methanol at 120 °C in the presence

[646] Wang, H.; Schröder, N.; Glorius, F. *Angew. Chem. Int. Ed.* ***2013***, *52*, 5386.
[647] Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* ***2013***, *135*, 5877.
[648] Akram, M.O.; Mali, P.S.; Patil, N.T. *Org. Lett.* ***2017***, *19*, 3075.
[649] Levin, M.D.; Toste, F.D. *Angew. Chem. Int. Ed.* ***2014***, *53*, 6211. See Yang, C.-T.; Zhang, Z.-Q.; Liu, Y.-C.; Liu, L. *Angew. Chem. Int. Ed.* ***2011***, *50*, 3904.
[650] Tran, H.; McCallum, T.; Morin, M.; Barriault, L. *Org. Lett.* ***2016***, *18*, 4308.
[651] Mack, R.; Askins, G.; Lowry, J.; Hurley, N.; Reeves, P.C. *Can. J. Chem.* ***2013***, *91*, 1262.
[652] Okura, K.; Shirakawa, E. *Eur. J. Org. Chem.* ***2016***, 3043.
[653] See Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 60–97; Wardell, J.L. in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 308–318.
[654] See Butler, R.N. in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, ***1981***, pp. 1–145.
[655] See Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 186–194. An alternative mechanism, involving radical cations, has been reported: Courtneidge, J.L.; Davies, A.G.; McGuchan, D.C.; Yazdi, S.N. *J. Organomet. Chem.* ***1988***, *341*, 63.
[656] See Heck, R.F. *Palladium Reagents in Organic Syntheses*, Academic Press, NY, ***1985***, pp. 179–321; Ryabov, A.D. *Synthesis* ***1985***, 233; Heck, R.F. *Org. React.* ***1982***, *27*, 345; Moritani, I.; Fujiwara, Y. *Synthesis* ***1973***, 524. See Cabri, W.; Candiani, I. *Acc. Chem. Res.* ***1995***, *28*, 2; Boyarskiy, V.P.; Ryabukhin, D.S.; Bokach, N.A.; Vasilyev, A.V. *Chem. Rev.* ***2016***, *116*, 5894.
[657] See Heck, R.F. *Acc. Chem. Res.* ***1979***, *12*, 146; Kozhevnikov, I.V. *Russ. Chem. Rev.* ***1983***, *52*, 138. See also, Spencer, A. *J. Organomet. Chem.* ***1983***, *258*, 101; Andersson, C.; Karabelas, K.; Hallberg, A.; Andersson, C. *J. Org. Chem.* ***1985***, *50*, 3891; Larock, R.C.; Johnson, P.L. *J. Chem. Soc., Chem. Commun.* ***1989***, 1368. See Li, T.H.; Wang, C.M.; Xie, X.G. *J. Phys. Org. Chem.* ***2011***, *24*, 292.
[658] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 994–996. Johansson Seechurn, C.C.C.; Kitching, M.O.; Colacot, T.J.; Snieckus, V. *Angew. Chem. Int. Ed.* ***2012***, *51*, 5062. Molander, G.A.; Wolfe, J.P.; Larhed, M. (Eds.) *Cross Coupling and Heck-Type Reactions. Workbench Three-Volume Set*, Thieme, Stuttgart, ***2013***; Le Bras, J.; Muzart, J. *Chem. Rev.* ***2011***, *111*, 1170; de Meijere, A.; Bräse, S.; Oestreich, M. (Eds.) *Metal-Catalyzed Cross-Coupling Reactions and More*, 3 Volume Set, Wiley-VCH, Weinheim, ***2014***; Molnár, Á. (Ed.) *Palladium-Catalyzed Coupling Reactions: Practical Aspects and Future Developments*, Wiley-VCH, ***2013***; Colacot, T.J. (Ed.) *New Trends in Cross-Coupling: Theory and Applications*, RSC Publishing, Cambridge, ***2015***. See Yus, M.; Pastor, I.M. *Chem. Lett.* ***2013***, *42*, 94; Sun, P.; Zhu, Y.; Yang, H.; Yan, H.; Lu, L.; Zhang, X.; Mao, J. *Org. Biomol. Chem.* ***2012***, *10*, 4512.

of potassium acetate and a $PdCl_2$ catalyst,[659] leading many to call this the *Mizoroki-Heck reaction*. The reaction works best with aryl iodides, but conditions are available for aryl bromides and aryl chlorides.[660] Aryldiazonium salts (see **13-25** and **13-27**) have also been used.[661] Activated aromatic compounds couple readily[662] but unactivated aromatic compounds often require special reaction conditions. The Heck reaction can be done with heterocyclic compounds,[663] and heteroaryl halides can be used in the coupling reaction.[664]

Phosphine-free catalysts,[665] halogen-free reactions,[666] and base-free reactions[667] have been developed for the Heck reaction. Ligand-free and base-free Heck reactions with heteroaryl halides have been reported.[668] Improvements to the Pd catalyst system are constantly being reported,[669] including polymer-supported catalysts,[670] silica-supported catalysts,[671] and recoverable catalysts.[672]

The Heck reaction can be done in aqueous media,[673] in polyethylene glycol,[674] in supercritical CO_2 (Sec. 9.D.ii),[675] and in ionic liquids.[676] Heck reactions have been reported using flow conditions (Sec. 7.D)[677] and ball-milling techniques have been used

[659] Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* ***1971***, *4*, 581.

[660] See Littke, A.F.; Fu, G.C. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4176. See Xu, H.-J.; Zhao, Y.-Q.; Zhou, X.-F. *J. Org. Chem.* ***2011***, *76*, 8036.

[661] Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. C*hem. Rev.* ***2006***, *106*, 4622.

[662] Myers, A.G.; Tanaka, D.; Mannion, M.R. *J. Am. Chem. Soc.* ***2002***, *124*, 11250.

[663] Felpin, F.-X.; Hardy, L.N.; Le Callonnec, F.; Fouquet, E. *Tetrahedron* ***2011***, *67*, 2815; Yang, Y.; Lan, J.; You, J. *Chem. Rev.* ***2017***, *117*, 8787.

[664] See Park, S.B.; Alper, H. *Org. Lett.* ***2003***, *5*, 3209. See also, Zeni, G.; Larock, R.C. *Chem. Rev.* ***2004***, *104*, 2285.

[665] Senra, J.D.; Malta, L.F.B.; de Souza, A.L.F.; Medeiros, M.E.; Aguiar, L.C.S.; Antunes, O.A.C. *Tetrahedron Lett.* ***2007***, *48*, 8153; Allam, B.K; Singh, K.N. *Synthesis* ***2011***, *43*, 1125.

[666] Hirabayashi, K.; Nishihara, Y.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* ***1998***, *39*, 7893. Nowrouzi, N.; Zarei, M. *Tetrahedron* ***2015***, *71*, 7847.

[667] Gottumukkala, A.L.; Teichert, J.F.; Heijnen, D.; Eisink, N.; van Dijk, S.; Ferrer, C.; van den Hoogenband, A.; Minnaard, A.J. *J. Org. Chem.* ***2011***, *76*, 3298; Mi, X.; Huang, M.; Guo, H.; Wu, Y. *Tetrahedron* ***2013***, *69*, 5123.

[668] Kantam, M.L.; Reddy, P.V.; Srinivas, P.; Bhargava, S. *Tetrahedron Lett.* ***2011***, *52*, 4490; An, G.; Li, X.; Han, J.; Pan, Y. *Synth. Commun.* ***2010–2011***, *41*, 1464.

[669] Sabounchei, S.J.; Ahmadi, M.; Azizi, T.; Panahimehr, M. *Synlett* ***2014***, *25*, 336; Zou, Y.; Zhou, J. *Chem. Commun.* ***2014***, *50*, 3725; Hu, J.; Lu, Y.; Li, Y.; Zhou, J. *Chem. Commun.* ***2013***, *49*, 9425; Rossy, C.; Fouquet, E.; Felpin, F.-X. *Synthesis* ***2012***, *44*, 37; Hajipour, A.R.; Rafiee, F.; Rouho, A.E. *Tetrahedron Lett.* ***2011***, *52*, 4782; Raja, M.U.; Ramesh, R.; Liu, Y. *Tetrahedron Lett.* ***2011***, *52*, 5427; Petrović, V.P.; Marković, S. *Monatsh. Chem.* ***2011***, *142*, 141.

[670] Kim, J.-H.; Kim, J.W.; Shokouhimehr, M.; Lee, Y.-S. *J. Org. Chem.* ***2005***, *70*, 6714.

[671] Polshettiwar, V.; Molnár, Á. *Tetrahedron* ***2007***, *63*, 6949.

[672] Karimi, B.; Enders, D. *Org. Lett.* ***2006***, *8*, 1237; Li, H.; Wang, L.; Li, P. *Synthesis* ***2007***, 1635; Chung, J.; Kim, J.; Jang, Y.; Byun, S.; Hyeon, T.; Kim, B.M. *Tetrahedron Lett.* ***2013***, *54*, 5192; Sun, P.; Qu, X.; Li, T.; Zhu, Y.; Yang, H.; Xing, Z.; Mao, J. *Synlett* ***2012***, *23*, 150.

[673] Wang, Y.; Yang, Q.; Yang, L.; Shi, J.; Zhang, M. *Tetrahedron Lett.* ***2013***, *54*, 5314. See Stouten, S.C.; Wang, Q.; Noël, T.; Hessel, V. *Tetrahedron Lett.* ***2013***, *54*, 2194; Samarasimhareddy, B.M.; Prabhu, G.; Sureshbabu, V.V. *Tetrahedron Lett.* ***2014***, *55*, 2256; Roberts, G.M.; Zhang, S.; Zhao, Y.; Woo, L.K. *Tetrahedron* ***2015***, *71*, 8263; Tang, Y.-Q.; Chu, C.-Y.; Zhu, L.; Qian, B.; Shao, L.-X. *Tetrahedron* ***2011***, *67*, 9479; Gaikwad, D.S.; Pore, D.M. *Synlett* ***2012***, *23*, 2631; Zayas, H.A.; Valade, D.; Jia, Z.; Monteiro, M.J. *Aust. J. Chem.* ***2012***, *65*, 1090.

[674] Chandrasekhar, S.; Narsihmulu, Ch.; Sultana, S.S.; Reddy, N.R. *Org.Lett.* ***2002***, *4*, 4399.

[675] Early, T.R.; Gordon, R.S.; Carroll, M.A.; Holmes, A.B.; Shute, R.E.; McConvey, I.F. *Chem. Commun.* ***2001***, 1966. See Kayaki, Y.; Noguchi, Y.; Ikariya, T. *Chem. Commun.* ***2000***, 2240.

[676] See Gaikwad, D.S.; Park, Y.; Pore, D.M. *Tetrahedron Lett.* ***2012***, *53*, 3077; Gyton, M.R.; Cole, M.L.; Harper, J.B. *Chem. Commun.* ***2011***, *47*, 9200.

[677] Cyr, P.; Deng, S.T.; Hawkins, J.M.; Price, K.E. *Org. Lett.* ***2013***, *15*, 4342; Bourne, S.L.; Koos, P.; O'Brien, M.; Martin, B.; Schenkel, B.; Baxendale, I.R.; Ley, S.V. *Synlett* ***2011***, *22*, 2643; Oger, N.; Le Grognec, E.; Felpin, F.-X. *J. Org. Chem.* ***2014***, *79*, 8255.

(Sec.7.E).[678] The reaction has been done on solid support,[679] on a reverse-phase silica support,[680] and using microwave irradiation.[681] A noncatalytic reaction was reported using supercritical water.[682] The effects of high pressure have been studied.[683] Aryl halides were coupled photochemically with styrene derivatives, in the presence of 18-crown-6, to give the aryl alkene. This reaction was transition metal-free and solvent-free.[684]

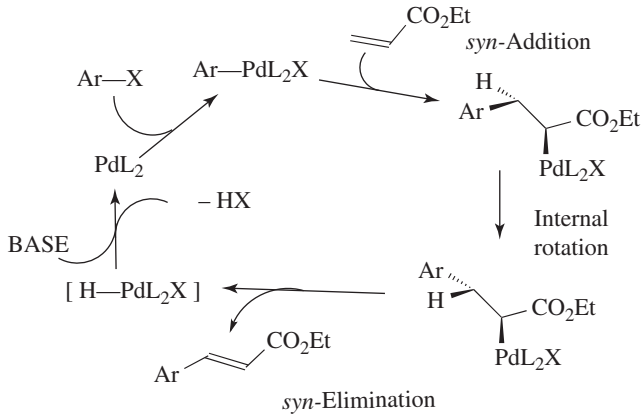
Control of regiochemistry is a serious problem in the coupling to unsymmetrical alkenes.[685] The presence of an auxiliary coordinating group,[686] or the use of special ligands and acrylate or styrene as substrates,[687] leads to improved regioselectivity. Steric effects are thought to control regioselectivity,[688] but electronic influences have also been proposed.[689] Steric effects generally improve 1,2-selectivity, and electronic effects can be used to favor 1,2- or 2,1-selectivity.[690] Neighboring group effects play a role in the Heck reaction.[691] Migration of the double bond is a problem in some cases, and reaction conditions play a significant role in such migrations.[692] Because the product is formed by an elimination step, double bond migration can occur with suitable substrates, resulting in allylic rearrangement, as in the reaction of cyclopentene and iodobenzene to give 3-phenylcyclopentene.[693] It has been reported that double bond isomerization can be suppressed in intramolecular Heck reactions done in supercritical CO_2 (Sec. 9.D.ii).[694] Intramolecular Heck reactions are increasingly important.[695] A silane-tethered, intramolecular Heck reaction is known.[696]

The Pd-catalyzed reactions are usually stereospecific,[697] yielding products expected from *syn* addition followed by *syn* elimination.[698] Asymmetric Heck reactions are

[678] Declerck, V.; Colacino, E.; Bantreil, X.; Martinez, J.; Lamaty, F. *Chem. Commun.* ***2012***, *48*, 11778.
[679] Franzén, R. *Can. J. Chem.* ***2000***, *78*, 457.
[680] Anson, M.S.; Mirza, A.R.; Tonks, L.; Williams, J.M.J. *Tetrahedron Lett.* ***1999***, *40*, 7147.
[681] Leadbeater, N.E.; Williams, V.A.; Barnard, T.M.; Collins Jr., M.J. *Synlett* ***2006***, 2953; Zhu, M.; Song, Y.; Cao, Y. *Synthesis* ***2007***, 853; Du, L.-H.; Wang, Y.-G. *Synth. Commun.* ***2007***, *37*, 217. See Nilsson, P.; Gold, H.; Larhed, M.; Hallberg, A. *Synthesis* ***2002***, 1611.
[682] Zhang, R.; Sato, O.; Zhao, F.; Sato, M.; Ikushima, Y. *Chem. Eur. J.* ***2004***, *10*, 1501.
[683] Buback, M.; Perkovic, T.; Redlich, S.; de Meijere, A. *Eur. J. Org. Chem.* ***2003***, 2375; Handy, S.T.; Okello, M. *Tetrahedron Lett.* ***2003***, *44*, 8395.
[684] Guastavino, J.F.; Budén, M.E.; Rossi, R.A. *J. Org. Chem.* ***2014***, *79*, 9104.
[685] See Qi, L.; Hirao, H.; Zhou, J. *Chem. Commun.* ***2013***, *49*, 10236.
[686] Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* ***2001***, *123*, 8217 and earlier references.
[687] Ludwig, M.; Strömberg, S.; Svensson, M.; Åkermark, B. *Organometallics* ***1999***, *18*, 970.
[688] Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA, ***1987***; Cornils, B.; Herrmann, A.W., Eds. *Applied Homogeneous Catalysis with Organometallic Compounds*, Wiley, NY, ***1996***, Vol. 2; Heck, R.F. *Acc. Chem. Res.* ***1979***, *12*, 146.
[689] Cabri, W.; Candiani, I. *Acc. Chem. Res.* ***1995***, *28*, 2.
[690] von Schenck, H.; Akermark, B.; Svensson, M. *J. Am. Chem. Soc.* ***2003***, *125*, 3503.
[691] Oestreich, M. *Eur. J. Org. Chem.* ***2005***, 783.
[692] Fall, Y.; Berthiol, F.; Doucet, H.; Santelli, M. *Synthesis* ***2007***, 1683. See Lauer, M.G.; Thompson, M.K.; Shaughnessy, K.H. *J. Org. Chem.* ***2014***, *79*, 10837.
[693] Larock, R.C.; Gong, W.H.; Baker, B.E. *Tetrahedron Lett.* ***1989***, *30*, 2603.
[694] Shezad, N.; Clifford, A.A.; Rayner, C.M. *Tetrahedron Lett.* ***2001***, *42*, 323.
[695] See Firmansjah, L.; Fu, G.C. *J. Am. Chem. Soc.* ***2007***, *129*, 11340, for example.
[696] Mayasundari, A.; Young, D.G.J. *Tetrahedron Lett.* ***2001***, *42*, 203.
[697] Su, Y.; Jiao, N. *Org. Lett.* ***2009***, *11*, 2980.
[698] Heck, R.F. *J. Am. Chem. Soc.* ***1969***, *91*, 6707; See Masllorens, J.; Moreno-Mañas, M.; Pla-Quintana, A.; Pleixats, R.; Roglans, A. *Synthesis* ***2002***, 1903. See Tan, Z.; Negishi, E. *Angew. Chem. Int. Ed.* ***2006***, *45*, 762.

known,[699] including asymmetric intramolecular Heck reactions.[700] The intermolecular dehydrogenative Heck arylation of trisubstituted alkenes used a Pd catalyst and was used to construct quaternary stereocenters.[701]

In the conventionally accepted reaction mechanism,[702] which is shown,[703] a four-coordinate aryl–Pd(II) intermediate (a palladacycle)[704] is formed by oxidative addition of the aryl halide to a Pd(0) complex prior to alkene addition.[705]



This description suggests that cleavage of the dimeric precursor complex, reduction of Pd^{2+}, and ligand dissociation combine to give a viable catalytic species.[706] σ-Alkyl Pd(II) intermediates are thought to be involved.[707] An analysis of reaction kinetics under dry conditions was reported.[700] In this study, the mechanism requires a first-order dependence on alkene concentration, and anomalous kinetics may be observed when the rate-limiting step is not directly on the catalytic cycle.[700] The mechanism requires a proton abstraction step, and there are substituent effects for this step.[708] A mechanistic study has been reported for the Pd-catalyzed decarboxylative reaction of alkenes and arylcarboxylic acids.[709] The

[699] Diéguez, M.; Pàmies, O. *Isr. J. Chem.* ***2012***, *52*, 572. Oestreich, M. *Angew. Chem. Int. Ed.* ***2014***, *53*, 2282; Yue, G.; Lei, K.; Hirao, H.; Zhou, J. *Angew. Chem. Int. Ed.* ***2015***, *54*, 6531; Mazuela, J.; Tolstoy, P.; Pàmies, O.; Andersson, P.G.; Diéguez, M. *Org. Biomol. Chem.* ***2011***, *9*, 941; Oestreich, M. *Angew. Chem. Int. Ed.* ***2014***, *53*, 2282; Wu, C.; Zhou, J. *J. Am. Chem. Soc.* ***2014***, *136*, 650.

[700] Lapierre, A.J.B.; Geib, S.J.; Curran, D.P. *J. Am. Chem. Soc.* ***2007***, *129*, 494. See Dounay, A.B.; Overman, L.E. *Chem. Rev.* ***2002***, *102*, 2945.

[701] Zhang, C.; Santiago, C.B.; Crawford, J.M.; Sigman, M.S. *J. Am. Chem. Soc.* ***2015***, *137*, 15668.

[702] Heck, R.F. *Comprehensive Organic Synthesis*, Vol. 4, Trost, B.M.; Fleming, I., Eds., Pergamon Press, Oxford, ***1991***, p. 833; de Meijere, A.; Meyer, F.E. *Angew. Chem. Int. Ed.* ***1994***, *33*, 2379; Cabri, W.; Candiani, I. *Acc. Chem. Res.* ***1995***, *28*, 2; Crisp, G.T. *Chem. Soc. Rev.* ***1998***, *27*, 427. See Heck, R.F.; Nolley Jr., J.P. *J. Org. Chem.* ***1972***, 3720; Henriksen, S.T.; Norrby, P.-O.; Kaukoranta, P.; Andersson, P.G. *J. Am. Chem. Soc.* ***2008***, *130*, 10414.

[703] See Diederich, F.; Stang, P.J., Eds. *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, ***1998***; Heck, R.F. *Palladium Reagents in Organic Syntheses*, Academic Press, NY, ***1985***.

[704] Masselot, D.; Charmant, J.P.H.; Gallagher, T. *J. Am. Chem. Soc.* ***2006***, *128*, 694.

[705] See Amatore, C.; Godin, B.; Jutand, A.; Lemaître, F. *Chem. Eur. J.* ***2007***, *13*, 2002; Baxter, R.D.; Sale, D.; Engle, K.M.; Yu, J.-Q.; Blackmond, D.G. *J. Am. Chem. Soc.* ***2012***, *134*, 4600.

[706] Rosner, T.; Pfaltz, A.; Blackmond, D.G. *J. Am. Chem. Soc.* ***2001***, *123*, 4621.

[707] For related work, see Kalyani, D.; Sanford, M.S. *J. Am. Chem. Soc.* ***2008***, *130*, 2150.

[708] García-Cuadrado, D.; de Mendoza, P.; Braga, A.C.; Maseras, F.; Echavarren, A.M. *J. Am. Chem. Soc.* ***2007***, *129*, 6880.

[709] Tanaka, D.; Romeril, S.P.; Myers, A.G. *J. Am. Chem. Soc.* ***2005***, *127*, 10323.

kinetics and mechanism of the Heck reaction promoted by a C—N palladacycle have been studied.[710] The mechanistic implications of asymmetric Heck reactions have been examined.[711] Mechanistic studies of the Ru-catalyzed[712] and the Pd-catalyzed[713] reactions of arenes and alkenes to give styryl derivatives have been reported.

Ethylene is the most reactive alkene, and increasing substitution lowers the reactivity. Coupling generally takes place at the less highly substituted side of the double bond.[714] Both electron-deficient alkenes, such as acrylates,[715] and electron-rich alkenes[716] undergo the Heck reaction. The substrate can be an unactivated alkene,[717] and the alkene can contain a variety of functional groups, such as esters, ether,[718] enol ethers,[719] enamides,[720] and carboxyl, phenolic, or cyano groups.[721] Silyl-Heck reactions are known.[722] The aryl halide or aryl triflate can be coupled to dienes,[723] allenes,[724] allylic acetates,[725] allylic silanes,[726] allylic amines,[727] and vinyl phosphonate esters.[728] Aryliodonium salts can be coupled to conjugated alkenes in a Heck-like manner using a Pd catalyst.[729] Heck-type reactions have been reported with imines.[730] The *para*-selective alkenylation of anilines has been reported.[731] The ligand acridine promoted a biomimetic aerobic oxidative cross coupling between arenes and alkenes under ambient oxygen pressure; this reaction gave alkenylarenes.[732] Heck reactions have been an important part of domino reactions.[733] The Pd-catalyzed arylation of α,β-unsaturated Weinreb amides with arenes or aryl iodides gave β-aryl-α,β-unsaturated Weinreb amides.[734] Aryl triflates were coupled to alkenes at the

[710] Consorti, C.S.; Flores, F.R.; Dupont, J. *J. Am. Chem. Soc.* ***2005***, *127*, 12054.
[711] Hii, K.K.; Claridge, T.D.W.; Brown, J.M.; Smith, A.; Deeth, R.J. *Helv. Chim. Acta* ***2001***, *84*, 3043.
[712] Brasse, M.; Cámpora, J.; Ellman, J.A.; Bergman, R.G. *J. Am. Chem. Soc.* ***2013***, *135*, 6427.
[713] Xu, L.; Hilton, M.J.; Zhang, X.; Norrby, P.-O.; Wu, Y.-D.; Sigman, M.S.; Wiest, O. *J. Am. Chem. Soc.* ***2014***, *136*, 1960; Deb, A.; Hazra, A.; Peng, Q.; Paton, R.S.; Maiti, D. *J. Am. Chem. Soc.* ***2017***, *139*, 763; Yahiaoui, S.; Fardost, A.; Trejos, A.; Larhed, M. *J. Org. Chem.* ***2011***, *76*, 2433; Allolio, C.; Strassner, T. *J. Org. Chem.* ***2014***, *79*, 12096; Huang, L.; Qi, J.; Wu, X.; Huang, K.; Jiang, H. *Org. Lett.* ***2013***, *15*, 2330.
[714] Heck, R.F. *J. Am. Chem. Soc.* ***1969***, *91*, 6707; ***1971***, *93*, 6896.
[715] Xu, Y.-H.; Lu, J.; Loh, T.-P. *J. Am. Chem. Soc.* ***2009***, *131*, 1372.
[716] Mo, J.; Xiao, J. *Angew. Chem. Int. Ed.* ***2006***, *45*, 4152.
[717] Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* ***2003***, *125*, 1476.
[718] Larhed, M.; Hallberg, A. *J. Org. Chem.* ***1996***, *61*, 9582.
[719] Battace, A.; Zair, T.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* ***2006***, *47*, 459. For a review pertaining to enol ethers, see Daves Jr., G.D. *Adv. Met. Org. Chem.* ***1991***, *2*, 59.
[720] Liu, Z.; Xu, D.; Tang, W.; Xu, L.; Mo, J.; Xiao, J. *Tetrahedron Lett.* ***2008***, *49*, 2756.
[721] See Daves Jr., G.D.; Hallberg, A. *Chem. Rev.* ***1989***, *89*, 1433.
[722] McAtee, J.R.; Martin, S.E.S.; Cinderella, A.P.; Reid, W.B.; Johnson, K.A.; Watson, D.A. *Tetrahedron* ***2014***, *70*, 4250.
[723] Jeffery, T. *Tetrahedron Lett.* ***1992***, *33*, 1989.
[724] Chang, H.-M.; Cheng, C.-H. *J. Org. Chem.* ***2000***, *65*, 1767.
[725] Mariampillai, B.; Herse, C.; Lautens, M. *Org. Lett.* ***2005***, *7*, 4745.
[726] Jeffery, T. *Tetrahedron Lett.* ***2000***, *41*, 8445.
[727] Olofsson, K.; Larhed, M.; Hallberg, A. *J. Org. Chem.* ***2000***, *65*, 7235; Wu, J.; Marcoux, J.-F.; Davies, I.W.; Reider, P.J. *Tetrahedron Lett.* ***2001***, *42*, 159.
[728] Kabalka, G.W.; Guchhait, S.K.; Naravane, A. *Tetrahedron Lett.* ***2004***, *45*, 4685.
[729] Xia, M.; Chen, Z.C. *Synth. Commun.* ***2000***, *30*, 1281.
[730] Li, Z.; Fu, Y.; Zhang, S.-L.; Guo, Q.-X.; Liu, L. *Chem. Asian J.* ***2010***, *5*, 1475.
[731] Moghaddam, F.M.; Pourkaveh, R.; Karimi, A. *J. Org. Chem.* ***2017***, *82*, 10635.
[732] Gigant, N.; Bäckvall, J.E. *Org. Lett.* ***2014***, *16*, 4432.
[733] Muzart, J. *Tetrahedron* ***2013***, *69*, 6735. Zhu, Z.-Q.; He, J.-S.; Wang, H.-J.; Huang, Z.-Z. *J. Org. Chem.* ***2015***, *80*, 9354; Prakash, G.K.S.;. Krishnan, H.S.; Jog, P.V.; Iyer, A.P.; Olah, G.A. *Org. Lett.* ***2012***, *14*, 1146.
[734] Kim, K.H.; Lee, S.; Kim, S.H.; Lim, C.H.; Kim, J.N. *Tetrahedron Lett.* ***2012***, *53*, 5088.

internal position using a Pd catalyst and a ferrocenyl ligand.[735] The cross coupling of indoles and conjugated alkenes using a Pd catalyst has been reported using flow conditions (Sec. 7.D).[736] There are a number of variations of this reaction, including the use of transition metal catalysts other than Pd. Catalysts used in this reaction include complexes with Rh,[737] Co,[738] Ru,[739] Ni,[740] and Fe.[741] Aryl halides have been coupled to allenyltin compounds ($C{=}C{=}C{-}SnR_3$).[742]

Very many reactions catalyzed by various transition metals have been reported. The Ni-catalyzed reaction of alkenes with aryl sulfonates or chlorides is known.[743] Aryl halides reacted with Mn and a Co catalyst; subsequent treatment with vinyl halides gave the stilbene derivative.[744] Aryl pivalates were coupled to alkenes using a Ni(dppf) catalyst generated *in situ*.[745] Catalytic cationic Ru complexes with $Cu(OAc)_2$ facilitated the coupling of benzoate derivatives and conjugated esters to give the *ortho* aryl-alkene coupling product.[746] The Rh-catalyzed coupling of phenols and alkenes to give the *ortho*-alkenyl product has been reported.[747] Arylaluminum reagents reacted with alkyl alkenes, in the presence of a ketone and a Rh catalyst, and gave give stilbene-type derivatives.[748] Aromatic compounds reacted with styrene-type derivatives in the presence of $Cu(OAc)_2$ and a Rh catalyst to give diaryl alkenes.[749] The Rh-catalyzed reaction of anthracene-9-carboxylic acid derivatives and electron-deficient alkenes in the presence of $Cu(OAc)_2$ has been reported.[750] 2-Alkenylfurans were prepared using a Bi catalyst.[751] The influence of trace metals on Mn-catalyzed cross-coupling reactions has been reported.[752]

Potassium vinyltrifluoroborates can be coupled to aryl halides in Heck-like coupling reactions.[753] Likewise, the reaction of aryltrifluoroborates with vinyl halides, in the presence of a Pd catalyst, leads to the aryl alkene.[754] In a related reaction, alkyltrifluoroborates react with aryl halides in the presence of a Pd catalyst and a Rh catalyst.[755]

OS **VI**, 815; **VII**, 361; **81**, 42, 54, 63, 263.

[735] Qin, L.; Ren, X.; Lu, Y.; Li, Y.; Zhou, J. *Angew. Chem. Int. Ed.* ***2012***, *51*, 5915.
[736] Gemoets, H.P.L.; Hessel, V.; Noël, T. *Org. Lett.* ***2014***, *16*, 5800.
[737] Kurahashi, T.; Shinokubo, H.; Osuka, A. *Angew. Chem. Int. Ed.* ***2006***, *45*, 6336.
[738] Zhou, P.; Li, Y.; Sun, P.; Zhou, J.; Bao, J. *Chem. Commun.* ***2007***, 1418.
[739] Matsuura, Y.; Tamura, M.; Kochi, T.; Sato, M.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* ***2007***, *129*, 9858.
[740] Denmark, S.E.; Butler, C.R. *Chem. Commun.* ***2009***, 20.
[741] Liu, W.; Cao, H.; Lei, A. *Angew. Chem. Int. Ed.* ***2010***, *49*, 2004.
[742] Huang, C.-W.; Shanmugasundaram, M.; Chang, H.-M.; Cheng, C.-H. *Tetrahedron* ***2003***, *59*, 3635.
[743] See Tasker, S.Z.; Gutierrez, A.C.; Jamison, T.F. *Angew. Chem. Int. Ed.* ***2014***, *53*, 1858. See Gøgsig, T.M.; Kleimark, J.; Nilsson Lill, S.O.; Korsager, S.; Lindhardt, A.T.; Norrby, P.-O.; Skrydstrup, T. *J. Am. Chem. Soc.* ***2012***, *134*, 443.
[744] Moncomble, A.; Le Floch, P.; Lledos, A.; Gosmini, C. *J. Org. Chem.* ***2012***, *77*, 5056.
[745] Ehle, A.R.; Zhou, Q.; Watson, M.P. *Org. Lett.* ***2012***, *14*, 1202.
[746] Graczyk, K.; Ma, W.; Ackermann, L. *Org. Lett.* ***2012***, *14*, 4110.
[747] Shen, Y.; Liu, G.; Zhou, Z.; Lu, X. *Org. Lett.* ***2013***, *15*, 3366.
[748] Tanaka, S.; Mori, A. *Eur. J. Org. Chem.* ***2014***, 1167.
[749] Patureau, F.W.; Nimphius, C.; Glorius, F. *Org. Lett.* ***2011***, *13*, 6346.
[750] Karthikeyan, J.; Yoshikai, N. *Org. Lett.* ***2014***, *16*, 4224.
[751] Nitsch, D.; Bach, T. *J. Org. Chem.* ***2014***, *79*, 6372.
[752] Santilli, C.; Beigbaghlou, S.S.; Ahlburg, A.; Antonacci, G.; Fristrup, P.; Norrby, P.-O.; Madsen, R. *Eur. J. Org. Chem.* ***2017***, 5269.
[753] Molander, G.A.; Brown, A.R. *J. Org. Chem.* ***2006***, *71*, 9681. Also see Alacid, E.; Njera, C. *J. Org. Chem.* ***2009***, *74*, 2321.
[754] Molander, G.A.; Fumagalli, T. *J. Org. Chem.* ***2006***, *71*, 5743.
[755] Molander, G.A.; Jean-Gérard, L. *J. Org. Chem.* ***2007***, *72*, 8422.

13-14 Aryl-Alkyne Coupling Reactions

$$ArI + RC{\equiv}CCu \longrightarrow ArC{\equiv}CR$$

When aryl halides react with copper acetylides to give 1-aryl alkynes, the reaction is known as *Stephens-Castro coupling*.[756] Both aliphatic and aromatic substituents can be attached to the alkyne unit, and a variety of aryl iodides have been used. Coupling of the alkynes to form a diyne (see **14-16**) can be a problem is some cases, although the aryl-alkyne coupling usually predominates.[757]

A Pd-catalyzed reaction of aryl halides with a terminal alkyne to give 1-aryl alkynes is called *Sonogashira coupling*.[758] Terminal aryl alkynes react with aryl iodides and Pd(0)[759] to give the corresponding diaryl alkyne,[760] but monoalkynes are easily prepared.[761] Aryl iodides are more reactive than aryl fluorides.[762] Alkynes can be coupled to heteroaromatic compounds.[763] As with all of the metal-catalyzed reactions in this chapter, work has been done to vary reaction conditions, including the catalyst,[764] the ligand,[765] the solvent, and additives.[766] The reaction has been done using flow conditions (Sec. 7.D).[767] Copper catalysts have been used in water media,[768] and the reaction has been done in water

[756] Castro, C.E.; Stephens, R.D. *J. Org. Chem.* ***1963***, *28*, 2163; Stephens, R.D.; Castro, C.E. *J. Org. Chem.* ***1963***, *28*, 3313. See Sladkov, A.M.; Gol'ding, I.R. *Russ. Chem. Rev.* ***1979***, *48*, 868. See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 985–986.

[757] See Chow, H.-F.; Wan, C.-W.; Low, K.-H.; Yeung, Y.-Y. *J. Org. Chem.* ***2001***, *66*, 1910.

[758] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* ***1975***, 4467; Chinchilla, R.; Nájera, C. *Chem. Rev.* ***2007***, *107*, 874; Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proced. Int.* ***1995***, *27*, 127; Sonogashira, K. in Diederich, F.; Stang, P.J. *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, NY, ***1998***, Chapter 5. Park, J.; Park, E.; Kim, A.; Park, S.-A.; Lee, Y.; Chi, K.-W.; Jung, Y.H.; Kim, I.S. *J. Org. Chem.* ***2011***, *76*, 2214; Schilz, M.; Plenio, H. *J. Org. Chem.* ***2012***, *77*, 2798. See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 985–986.

[759] See Novák, Z.; Szabó, A.; Répási, J.; Kotschy, A. *J. Org. Chem.* ***2003***, *68*, 3327.

[760] Böhm, V.P.W.; Herrmann, W.A. *Eur. J. Org. Chem.* ***2000***, 3679. See Mori, A.; Shimada, T.; Kondo, T.; Sekiguchi, A. *Synlett* ***2001***, 649.

[761] Liang, B.; Dai, M.; Chen, J.; Yang, Z. *J. Org. Chem.* ***2005***, *70*, 391.

[762] See Mio, M.J.; Kopel, L.C.; Braun, J.B.; Gadzikwa, T.L.; Hull, K.; Brisbois, R.G.; Markworth, C.J.; Grieco, P.A. *Org. Lett.* ***2002***, *4*, 3199.

[763] Chen, Y.; Markina, N.A.; Larock, R.C. *Tetrahedron* ***2009***, *65*, 8908; R'kyek, O.; Halland, N.; Lindenschmidt, A.; Alonso, J.; Lindemann, P.; Urmann, M.; Nazaré, M. *Chem. Eur. J.* ***2010***, *16*, 9986; Kim, S.H.; Yoon, J.; Chang, S. *Org. Lett.* ***2011***, *13*, 1474.

[764] Sabounchei, S.J.; Ahmadi, M.; Nasri, Z.; Shams, E.; Panahimehr, M. *Tetrahedron Lett.* ***2013***, *54*, 4656; Khairnar, B.J.; Dey, S.; Jain, V.K.; Bhanage, B.M. *Tetrahedron Lett.* ***2014***, *55*, 716; Hajipour, A.R.; Mohammadsaleh, F. *Tetrahedron Lett.* ***2014***, *55*, 3459; Li, X.; Li, D.; Bai, Y.; Zhang, C.; Chang, H.; Gao, W.; Wei, W. *Tetrahedron* ***2016***, *72*, 6996; Panda, B.; Sarkar, T.K. *Synthesis* ***2013***, *45*, 817.

[765] Sarmah, M.; Dewan, A.; Thakur, A.J.; Bora, U. *Tetrahedron Lett.* ***2016***, *57*, 914; Borude, V.S.; Shah, R.V.; Shukla, S.R. *Monatsh. Chem.* ***2013***, *144*, 1663.

[766] See Sakai, N.; Annaka, K.; Konakahara, T. *Org. Lett.* ***2004***, *6*, 1527; Djakovitch, L.; Rollet, P. *Tetrahedron Lett.* ***2004***, *45*, 1367; Hierso, J.-C.; Fihri, A.; Amardeil, R.; Meunier, P.; Doucet, H.; Santelli, M.; Ivanov, V.V. *Org. Lett.* ***2004***, *6*, 3473.

[767] Tan, L.-M.; Sem, Z.-Y.; Chong, W.-Y.; Hendra, X.L.; Kwan, W.L.; Lee, C.-L.K. *Org. Lett.* ***2013***, *15*, 65; Lee, H.J.; Park, K.; Bae, G.; Choe, J.; Song, K.H.; Lee, S. *Tetrahedron Lett.* ***2011***, *52*, 5064; Battilocchio, C.; Bhawal, B.N.; Chorghade, R.; Deadman, B.J.; Hawkins, J.M.; Ley, S.V. *Isr. J. Chem.* ***2014***, *54*, 371.

[768] Yang, D.; Li, B.; Yang, H.; Fu, H.; Hu, L. *Synlett* ***2011***, *22*, 702; Li, T.; Qu, X.; Xie, G.; Mao, J. *Chem. Asian J.* ***2011***, *6*, 1325; Marziale, A.N.; Schlüter, J.; Eppinger, J. *Tetrahedron Lett.* ***2011***, *52*, 6355. Also see Chen, G.; Zhu, X.; Cai, J.; Wan, Y. *Synth. Commun.* ***2007***, *37*, 1355.

without Cu.[769] The coupling has been done in ionic liquids.[770] There are copper-free[771] and ligand-free variations.[772] Transition metal-free coupling[773] has been reported using 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical as an oxidant.[774] Microwave irradiation is an important tool in this reaction.[775] Sonogashira coupling was reported on microbeads,[776] with nanoparticulate Ni powder,[777] and the aryl iodide was tethered to a polymer for a solid-state reaction.[778] The *N*-heterocyclic carbene Cu and Pd complex-catalyzed reactions have been reported.[779] Arylsulfonium salts have been used.[780]

There are variations of the Sonogashira reaction that use other metals as catalysts or co-catalysts. A Pd-free reaction is known, using Cu complexes as the catalyst.[781] Other metals used as catalysts include Zn,[782] Mn,[783] In,[784] Ag,[785] Au,[786] Rh,[787] Ni,[788] Fe,[789] alkynyl tin,[790] and alkynyl Au compounds.[791]

Lithium alkynyl trimethylborates are coupled to aryl chlorides as well.[792] Terminal alkynes are coupled to acylpyridinium salts in the presence of a Cu catalyst, giving a product

[769] Lipshutz, B.L.; Chung, D.W.; Rich, B. *Org. Lett.* ***2008***, *10*, 3793.

[770] See de Lima, P.G.; Antunes, O.A.C. *Tetrahedron Lett.* ***2008***, *49*, 2506; Fukuyama, T.; Rahman, Md.T.; Maetani, S.; Ryu, I. *Chem. Lett.* ***2011***, *40*, 1027.

[771] Teratani, T.; Ohtaka, A.; Kawashima, T.; Shimomura, O.; Nomura, R. *Synlett* ***2010***, 2271; Li, J.-H.; Bakherad, M.; Keivanloo, A.; Bahramian, B.; Hashemi, M. *Tetrahedron Lett.* ***2009***, *50*, 1557.

[772] Gholap, A.R.; Venkatesan, K.; Pasricha, R.; Daniel, T.; Lahoti, R.J.; Srinivasan, K.V. *J. Org. Chem.* ***2005***, *70*, 4869; Pan, C.; Luo, F.; Wang, W.; Ye, Z.; Cheng, J. *Tetrahedron Lett.* ***2009***, *50*, 5044.

[773] Jin, G.; Zhang, X.; Cao, S. *Org. Lett.* ***2013***, *15*, 3114.

[774] Maji, M.S.; Murarka, S.; Studer, A. *Org. Lett.* ***2010***, *12*, 3878.

[775] Appukkuttan, P.; Dehaen, W.; van der Eyken, E. *Eur. J. Org. Chem.* ***2003***, 4713. See also, Kabalka, G.W.; Wang, L.; Namboodiri, V.; Pagni, R.M. *Tetrahedron Lett.* ***2000***, *41*, 515.

[776] Liao, Y.; Fathi, R.; Reitman, M.; Zhang, Y.; Yang, Z. *Tetrahedron Lett.* ***2001***, *42*, 1815; Gonthier, E.; Breinbauer, R. *Synlett* ***2003***, 1049.

[777] Wang, M.; Li, P.; Wang, L. *Synth. Commun.* ***2004***, *34*, 2803.

[778] Erdélyi, M.; Gogoll, A. *J. Org. Chem.* ***2003***, *68*, 6431. See Bakherad, M.; Amin, A.H.; Keivanloo, A.; Bahramian, B.; Raeissi, M. *Tetrahedron Lett.* ***2010***, *51*, 5653.

[779] Gallop, C.W.D.; Chen, M.-T.; Navarro, O. *Org. Lett.* ***2014***, *16*, 3724.

[780] Tian, Z.-Y.; Wang, S.-M.; Jia, S.-J.; Song, H.-X.; Zhang, C.-P. *Org. Lett.* ***2017***, *19*, 5454.

[781] Monnier, F.; Turtaut, F.; Duroure, L.; Taillefer, M. *Org. Lett.* ***2008***, *10*, 3203; Wang, Z.-L.; Zhao, L.; Wang, M.-X. *Org. Lett.* ***2012***, *14*, 1472; Moegling, J.; Benischke, A.D.; Hammann, J.M.; Vepřek, N.A.; Zoller, F.; Rendenbach, B.; Hoffmann, A.; Sievers, H.; Schuster, M.; Knochel, P.; Herres-Pawlis, S. *Eur. J. Org. Chem.* ***2015***, 7475.

[782] Thankachan, A.P.; Sindhu, K.S.; Krishnan, K.K.; Anilkumar, G. *Tetrahedron Lett.* ***2015***, *56*, 5525. See Nakagawa, N.; Hatakeyama, T.; Nakamura, M. *Chem. Lett.* ***2015***, *44*, 486.

[783] Qi, X.; Jiang, L.-B.; Wu, X.-F. *Tetrahedron Lett.* ***2016***, *57*, 1706.

[784] Borah, H.N.; Prajapati, D.; Boruah, R.C. *Synlett* ***2005***, 2823.

[785] Li, P.; Wang, L. *Synlett* ***2006***, 2261.

[786] Li, P.; Wang, L.; Wang, M.; You, F. *Eur. J. Org. Chem.* ***2008***, 5946; Pankajakshan, S.; Loh, T.-P. *Chem. Asian J.* ***2011***, *6*, 2291. However, see Lauterbach, T.; Livendahl, M.; Roselln, A.; Espinet, P.; Echavarren, A.M. *Org. Lett.* ***2010***, *12*, 3006. See also, Beaumont, S.K.; Kyriakou, G.; Lambert, R.M. *J. Am. Chem. Soc.* ***2010***, *132*, 12246.

[787] Feng, C.; Loh, T.-P. *Angew. Chem. Int. Ed.* ***2014***, *53*, 2722.

[788] Bakherad, M.; Keivanloo, A.; Mihanparast, S. *Synth. Commun.* ***2010***, *40*, 179.

[789] Sawant, D.N.; Tambade, P.J.; Wagh, Y.S.; Bhanage, B.M. *Tetrahedron Lett.* ***2010***, *51*, 2758; Midya, G.C.; Parasar, B.; Dhara, K.; Dash, J. *Org. Biomol. Chem.* ***2014***, *12*, 1812. Panda, N.; Jena, A.K.; Mohapatra, S. *Chem. Lett.* ***2011***, *40*, 956. See Nakagawa, N.; Hatakeyama, T.; Nakamura, M. *Chem. Lett.* ***2015***, *44*, 486.

[790] See Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* ***2004***, *6*, 2821.

[791] Nielsen, M.B. *Synthesis* ***2016***, *48*, 2732. See Corma, A.; Juárez, R.; Boronat, M.; Sánchez, F.; Iglesias, M.; Garcia, H. *Chem. Commun.* ***2011***, *47*, 1446.

[792] Torres, G.H.; Choppin, S.; Colobert, F. *Eur. J. Org. Chem.* ***2006***, 1450.

with high enantioselectivity when a chiral ligand is used.[793] Aryl iodides were also coupled to lithium alkynyl borate complexes, Li[R—C≡C—B(OR′)$_3$], to give the aryl alkyne.[794] A variation of this aryl alkyne coupling reaction reacted methylthioalkynes (R—C≡C—SMe) with arylboronic acids and a Pd catalyst to give the aryl alkyne.[795]

4-Chloroacetophenone reacts with 1-phenylethyne, showing that the carbonyl group is compatible with this reaction.[796] Arenediazonium salts can be used for the coupling reaction.[797] Similar Pd-catalyzed coupling of bromoalkynes with heterocycles also leads to the alkynyl derivative.[798] The coupling of terminal alkynes and aryl chlorides using base-mediated, transition metal-free reactions proceeds via benzyne intermediates and gave aryl alkynes.[799] Alkyl aryl tellurides and a tellurol ester were coupled to alkynes using a Pd catalyst and microwave-assisted reactions in the presence of CuI, and gave alkynyl arenes.[800] The Pd- and Cu-catalyzed decarboxylative cross-coupling reaction of aryl halides and alkynyl carboxylic acids gave aryl alkynes.[801] A green protocol for the coupling of aryl halides and terminal alkynes using an *in situ*-generated catalytic system of Pd(OAc)$_2$ and water extract of banana peel ash was reported.[802] The Cu-catalyzed reaction of diaryldiazomethanes with terminal alkynes in the presence of diisopropylethylamine gave tri-aryl-substituted allenes.[803] The isomerization of internal alkadiynols with lithium 2-aminoethylamide into their terminal isomers followed by Sonogashira cross coupling led to an acetylene-zipper reaction sequence that gave conjugated arylalkydiynols.[804] Macrocycles have been prepared by the intramolecular, Cu/Cs_2CO_3-catalyzed Sonogashira-type cross-coupling reaction.[805] Sonogashira coupling was used for the reaction of 2-bromobenzenesulfonamides and terminal alkynes and cyclization led to substituted benzosultams.[806]

Aryl halides are coupled to alkynyl trifluoroboronates (R—C≡C—BF_3K, **12-27**) using a Pd catalyst.[807]

OS 11, ***2009***, 234.

13-15 Arylation at a Carbon Containing an Active Hydrogen

The arylation of compounds of the form ZCH$_2$Z′ is analogous to **10-67**, where Z is as defined as an electron-withdrawing group (ester, cyano, sulfonyl, etc.). Activated aryl

[793] Sun, Z.; Yu, S.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* ***2007***, *129*, 9300.
[794] Oh, C.H.; Jung, S.H. *Tetrahedron Lett.* ***2000***, *41*, 8513.
[795] Savarin, C.; Srogl, J.; Liebeskind, L.S. *Org. Lett.* ***2001***, *3*, 91.
[796] Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* ***2004***, *45*, 8443.
[797] Fabrizi, G.; Goggiamani, A.; Sferrazza, A.; Cacchi, S. *Angew. Chem. Int. Ed.* ***2010***, *49*, 4067.
[798] Seregin, I.V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* ***2007***, *129*, 7742.
[799] Truong, T.; Daugulis, O. *Org. Lett.* ***2011***, *13*, 4172.
[800] Kawaguchi, S.; Srivastava, P.; Engman, L. *Tetrahedron Lett.* ***2011***, *52*, 4120.
[801] Maaliki, C.; Chevalier, Y.; Thiery, E.; Thibonnet, J. *Tetrahedron Lett.* ***2016***, *57*, 3358.
[802] Dewan, A.; Sarmah, M.; Bora, U.; Thakur, A.J. *Tetrahedron Lett.* ***2016***, *57*, 3760.
[803] Wu, C.; Hu, F.; Liu, Z.; Deng, G.; Ye, F.; Zhang, Y.; Wang, J. *Tetrahedron* ***2015***, *71*, 9196.
[804] Kulyashova, A.E.; Sorokoumov, V.N.; Popik, V.V.; Balova, I.A. *Tetrahedron Lett.* ***2013***, *54*, 2235.
[805] Santandrea, J.; Bédard, A.-C.; Collins, S.K. *Org. Lett.* ***2014***, *16*, 3892.
[806] Debnath, S.; Mondal, S. *J. Org. Chem.* ***2015***, *80*, 3940.
[807] Molander, G.A.; Katona, B.W.; Machrouhi, F. *J. Org. Chem.* ***2002***, *67*, 8416.

halides generally give good results.[808] Treatment of propanone with an aryl halide in liquid ammonia containing Na or K, for example, gave 1-arylpropan-2-one and 1-arylpropan-2-ol.[809] When the solution is irradiated with near-UV light, and the Na or K is omitted, the same products are obtained, but in different proportions.[810] In either case, other leaving groups can be used instead of halogens (e.g., NR_3^+, SAr) and the mechanism is the $S_{RN}1$ mechanism. *N*-Heterocyclic carbene ligands in the presence of alkoxide bases leads to coupling of ketones and aryl halides at the α position of the ketone.[811] The reaction can also take place without an added initiator. β-Keto esters were coupled to aryl fluorides using CsOH and a chiral quaternary ammonium salt, leading to the aryl substitution product with good enantioselectivity.[812]

Even unactivated aryl halides can be employed if the reaction is carried out in the presence of a strong base, such as $NaNH_2$[813] or LDA. Compounds of the form ZCH_2Z', and even simple ketones[814] or carboxylic esters, have been arylated in this manner. The reaction with unactivated halides proceeds by the benzyne mechanism and represents a method for extending the malonic ester (and similar) syntheses to aromatic compounds. The base performs two functions: (i) it removes a proton from ZCH_2Z' and (ii) it catalyzes the benzyne mechanism. The reaction has been used for ring closure to prepare an indole.[815]

Palladium catalysts have been developed for the α-arylation of ketones[816] and the α-arylation of esters.[817] Malonate esters are coupled to unactivated aryl halides using a Pd catalyst.[818] The coupling of active methylene compounds and unactivated aryl halides can also be done with copper halide catalysts[119] (the *Hurtley reaction*).[819] Similar coupling was accomplished with $CH_2(CN)_2$ and a Ni catalyst.[820] Malonic esters and β-keto esters can be arylated at the α carbon in high yields by treatment with Bi reagents.[821] Arylzinc reagents[822] and iron(II) salts have also been used to initiate this reaction.[823] *Bis*-sulfones,

[808] There is evidence for both the SNAr mechanism (see Leffek, K.T.; Matinopoulos-Scordou, A.E. *Can. J. Chem.* ***1977***, *55*, 2656, 2664) and the SRN1 mechanism (see Zhang, X.; Yang, D.; Liu, Y.; Chen, W.; Cheng, J. *Res. Chem. Intermed.* ***1989***, *11*, 281).

[809] Bunnett, J.F.; Gloor, B.F. *J. Org. Chem.* ***1973***, *38*, 4156; ***1974***, *39*, 382.

[810] Rossi, R.A.; Alonso, R.A. *J. Org. Chem.* ***1980***, *45*, 1239; Beugelmans, R. *Bull. Soc. Chim. Belg.* ***1984***, *93*, 547.

[811] Matsubara, K.; Ueno, K.; Koga, Y.; Hara, K. *J. Org. Chem.* ***2007***, *72*, 5069.

[812] Bella, M.; Kobbelgaard, S.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2005***, *127*, 3670.

[813] Leake, W.W.; Levine, R. *J. Am. Chem. Soc.* ***1959***, *81*, 1169, 1627.

[814] See Caubere, P.; Guillaumet, G. *Bull. Soc. Chim. Fr.* ***1972***, 4643, 4649.

[815] See Biehl, E.R.; Khanapure, S.P. *Acc. Chem. Res.* ***1989***, *22*, 275; Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, ***1967***, pp. 150–164. See also, Kessar, S.V. *Acc. Chem. Res.* ***1978***, *11*, 283.

[816] Grasa, G.A.; Colacot, T.J. *Org. Lett.* ***2007***, *9*, 5489. See You, J.; Verkade, J.G. *Angew. Chem. Int. Ed.* ***2003***, *42*, 5051.

[817] Hama, T.; Hartwig, J.F. *Org. Lett.* ***2008***, *10*, 1545, 1549; Biscoe, M.R.; Buchwald, S.L. *Org. Lett.* ***2009***, *11*, 1773.

[818] See Korsager, S.; Nielsen, D.U.; Taaning, R.H.; Skrydstrup, T. *Angew. Chem. Int. Ed.* ***2013***, *52*, 9763.

[819] See Osuka, A.; Kobayashi, T.; Suzuki, H. *Synthesis* ***1983***, 67; Hennessy, E.J.; Buchwald, S.L. *Org. Lett.* ***2002***, *4*, 269.

[820] Cristau, H.J.; Vogel, R.; Taillefer, M.; Gadras, A. *Tetrahedron Lett.* ***2000***, *41*, 8457.

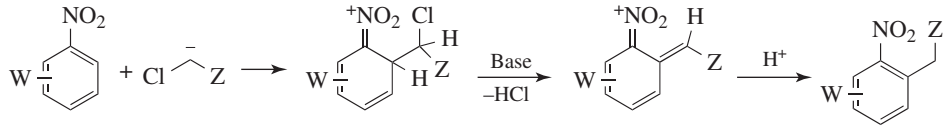
[821] See Elliott, G.I.; Konopelski, J.P. *Tetrahedron* ***2001***, *57*, 5683; Barton, D.H.R.; Blazejewski, J.; Charpiot, B.; Finet, J.; Motherwell, W.B.; Papoula, M.T.B.; Stanforth, S.P. *J. Chem. Soc., Perkin Trans. 1* ***1985***, 2667; O'Donnell, M.J.; Bennett, W.D.; Jacobsen, W.N.; Ma, Y. *Tetrahedron Lett.* ***1989***, *30*, 3913.

[822] Lundin, P.M.; Esquivias, J.; Fu, G.C. *Angew. Chem. Int. Ed.* ***2009***, *48*, 154.

[823] Galli, C.; Bunnett, J.F. *J. Org. Chem.* ***1984***, *49*, 3041.

$CH_2(SO_2Ar)_2$, reacted with aryl halides in the presence of a Pd catalyst.[824] A variation of α-arylation reacts α-halocarbonyl compounds with arylboronic acids in the presence of a Ni catalyst.[825]

The carbanions with a chlorine at the carbanionic carbon react with aromatic nitro compounds uses carbanion nucleophiles to give the *ortho*-substitution product.[826]



This type of process is called *vicarious nucleophilic substitution of hydrogen*.[827] The Z group is electron withdrawing (e.g., SO_2R, SO_2OR, SO_2NR_2, COOR, or CN); it stabilizes the negative charge. The carbanion attacks the activated ring *ortho* or *para* to the nitro group.[828] The presence of the adjacent Cl allows the hydrogen to be replaced, so, Cl is a "vicarious" leaving group. Other leaving groups have been used (e.g., OMe, SPh), but Cl is generally the best. The reaction is also successful for di- and trinitro compounds, for nitronaphthalenes,[829] and for many nitro heterocycles; $^{-}$Z—CR—Cl may also be used.[830]

Enolate ions of ketones react with aryl iodides in the dark.[831] It has been suggested[832] that initiation takes place by formation of an α-keto radical, so this reaction proceeds by an SET mechanism (Sec. 10.B). The photo-stimulated reaction has also been used for ring closure.[833] In certain instances of the intermolecular reaction there is evidence that the leaving group exerts an influence on the product ratios, even when it has already departed at the time that product selection takes place.[834]

The reaction of aryl halides with the enolate anions of ketones and aldehydes, generated *in situ* by addition of a suitable base, can be accomplished by treatment with a Pd catalyst.[835] Nickel-catalyzed α-arylation of ketone enolate anions is also known.[836] The enolate anions of lactams will react with aryl halides in the presence of a Pd catalyst via the 3-aryl lactam.[837] When the enolate anion of a ketone is generated in the presence of a Pd catalyst and a chiral phosphine ligand, the α-aryl ketone is formed with good enantioselectivity.[838]

OS **V**, 12, 263; **VI**, 36, 873, 928; **VII**, 229.

[824] Kashin, A.N.; Mitin, A.V.; Beletskaya, I.P.; Wife, R. *Tetrahedron Lett.* ***2002***, *43*, 2539.
[825] Liu, C.; He, C.; Shi, W.; Chen, M.; Lei, A. *Org. Lett.* ***2007***, *9*, 5601.
[826] See Stahly, G.P.; Stahly, B.C.; Maloney, J.R. *J. Org. Chem.* ***1988***, *53*, 690.
[827] Makosza, M. *Synthesis* ***1991***, 103; Makosza, M.; Winiarski, J. *Acc. Chem. Res.* ***1987***, *20*, 282.
[828] For a discussion of the mechanism of vicarious nucleophilic aromatic substitution, see Makosza, M.; Lemek, T.; Kwast, A.; Terrier, F. *J. Org. Chem.* ***2002***, *67*, 394.
[829] Makosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs Ann. Chem.* ***1987***, 711.
[830] See Mudryk, B.; Makosza, M. *Tetrahedron* ***1988***, *44*, 209.
[831] Scamehorn, R.G.; Hardacre, J.M.; Lukanich, J.M.; Sharpe, L.R. *J. Org. Chem.* ***1984***, *49*, 4881.
[832] Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwjima, I. *J. Am. Chem. Soc.* ***1988***, *110*, 3296.
[833] See Semmelhack, M.F.; Bargar, T. *J. Am. Chem. Soc.* ***1980***, *102*, 7765; Bard, R.R.; Bunnett, J.F. *J. Org. Chem.* ***1980***, *45*, 1546.
[834] See Tremelling, M.J.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1980***, *102*, 7375.
[835] See Culkin, D.A.; Hartwig, J.F. *Acc. Chem. Res.* ***2003***, *36*, 234.
[836] Chen, G.; Kwong, F.Y.; Chan, H.O.; Yu, W.-Y.; Chan, A.S.C. *Chem. Commun.* ***2006***, 1413.
[837] Cossy, J.; de Filippis, A.; Pardo, D.G. *Org. Lett.* ***2003***, *5*, 3037.
[838] Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 1261.

13-16 Conversion of Aryl Substrates to Carboxylic Acids, Their Derivatives, Aldehydes, and Ketones[839]

$$\mathrm{ArX + CO + ROH} \xrightarrow[\text{Pd Complex}]{\text{Base}} \mathrm{ArCOOR}$$

Carbonylation of aryl halides[840] and aryl triflates[841] with carbon monoxide, an alcohol, and a base (which gives an alkoxide), using a Pd catalyst, gives carboxylic esters. Similar carbonylation reactions are possible with alkyl halides. Aryl carboxylic acids were also prepared from aryl iodides by heating in DMF with lithium formate, LiCl, acetic anhydride, and a Pd catalyst.[842] Even very sterically hindered alkoxides can be used to produce the corresponding ester.[843] The use of H_2O, RNH_2, or an alkali metal or calcium carboxylate in reactions with ArX,[844] instead of ROH, gives the carboxylic acid,[845] amide,[846] or mixed anhydride, respectively.[847] Ester formation via carbonylation was carried out in supercritical CO_2 (Sec. 9.D.ii).[848] Microwave-promoted carbonylation reactions have been reported.[849]

Variations include a silica-supported Pd reagent that has been used to convert iodobenzene to butyl benzoate, in the presence of CO and butan-1-ol.[850] 2-Chloropyridine was converted to butyl pyridine 2-carboxylate with this procedure.[851] Heating an aryl iodide and CO, in ethanol and DBU, with a Pd catalyst, gave the ethyl ester of the aryl carboxylic acid.[852] A similar result was obtained when an aryl iodide was heated in ethanol with triethylamine, CO, and Pd/C.[853] Phenols and aryl halides react with a Pd catalyst, and carbonylation leads to the phenyl ester.[854]

Modification of this approach allows the synthesis of ketones and aryl iodides can also be converted to aldehydes.[855] Aryllithium and *Grignard reagents* react with iron pentacarbonyl to give aldehydes, ArCHO.[856] The reaction of CO with aryllithium may occur by electron transfer.[857] Aryl iodides are carbonylated to give the aryl alkyl ketone with CO and R_3In.[858] Aryl iodides are coupled with aryl acid chlorides in the presence of an In complex to form

[839] See Weil, T.A.; Cassar, L.; Foà, M. in Wender, I.; Pino, P. *Organic Synthesis Via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 517–543.
[840] See Shimomaki, K.; Murata, K.; Martin, R.; Iwasawa, N. *J. Am. Chem. Soc.* ***2017***, *139*, 9467.
[841] Garrido, F.; Raeppel, S.; Mann, A.; Lautens, M. *Tetrahedron Lett.* ***2001***, *42*, 265.
[842] Cacchi, S.; Babrizi, G.; Goggiamani, A. *Org. Lett.* ***2003***, *5*, 4269.
[843] Antebi, S.; Arya, P.; Manzer, L.E.; Alper, H. *J. Org. Chem.* ***2002***, *67*, 6623. For an interesting variation that generated a lactone ring, see Cho, C.S.; Baek, D.Y.; Shim, S.C. *J. Heterocycl. Chem.* ***1999***, *36*, 289.
[844] Pri-Bar, I.; Alper, H. *J. Org. Chem.* ***1989***, *54*, 36.
[845] See Bumagin, N.A.; Nikitin, K.V.; Beletskaya, I.P. *Dokl. Chem.* ***1990***, *312*, 149.
[846] Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* ***2002***, *67*, 6232.
[847] Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 348–358.
[848] Albaneze-Walker, J.; Bazaral, C.; Leavey, T.; Dormer, P.G.; Murry, J.A. *Org. Lett.* ***2004***, *6*, 2097.
[849] Kormos, C.M.; Leadbeater, N.E. *Synlett* ***2006***, 1663.
[850] Cai, M.-Z.; Song, C.-S.; Huang, X. *J. Chem. Soc., Perkin Trans. 1* ***1997***, 2273.
[851] Beller, M.; Mägerlein, W.; Indolese, A.F.; Fischer, C. *Synthesis* ***2001***, 1098.
[852] Ramesh, C.; Kubota, Y.; Miwa, M.; Sugi, Y. *Synthesis* ***2002***, 2171.
[853] Ramesh, C.; Nakamura, R.; Kubota, Y.; Miwa, M.; Sugi, Y. *Synthesis* ***2003***, 501.
[854] Watson, D.A.; Fan, X.; Buchwald, S.L. *J. Org. Chem.* ***2008***, *73*, 7096.
[855] Ryu, I.; Kusano, K.; Masumi, N.; Yamazaki, H.; Ogawa, A.; Sonoda, N. *Tetrahedron Lett.* ***1990***, *31*, 6887.
[856] Yamashita, M.; Miyoshi, K.; Nakazono, Y.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* ***1982***, *55*, 1663.
[857] Nudelman, N.S.; Doctorovich, F. *Tetrahedron* ***1994***, *50*, 4651.
[858] Lee, S.W.; Kee, K.; Seomoon, D.; Kim, S.; Kim, H.; Kim, H.; Shim, E.; Lee, M.; Lee, S.; Kim, S.; Lee, P.H. *J. Org. Chem.* ***2004***, *69*, 4852.

a diaryl ketone.[859] Aryl iodides containing an *ortho* substituent that had a β-cyano group (which served as the source of a carbonyl group), were converted to bicyclic ketones with a Pd catalyst at 130 °C in aqueous DMF.[860]

Diaryl ketones can also be prepared by coupling aryl iodides with phenylboronic acid (**12-28**), in the presence of CO and a Pd catalyst.[861] This reaction has been extended to heteroaromatic systems, with the preparation of phenyl 4-pyridyl ketone from phenylboronic acid and 4-iodopyridine.[862] 2-Bromopyridine as coupled with phenylboronic acid, CO, and a Pd catalyst to give phenyl 2-pyridyl ketone.[863]

13-17 Arylation of Silanes

$$Ar{-}X + Ar'SiR_2 \longrightarrow Ar{-}SiR_3$$

In the presence of transition metal catalysts, such as Pd, trialkoxysilanes [$HSi(OR)_3$] react with aryl halides to give the corresponding arylsilane.[864] The influence of silicon substituents on the cross-coupling reaction has been studied.[865]. Cyclic alkoxysilanes are prepared using Pd-catalyzed cross-coupling reactions.[866] Vinylsilanes are coupled to aryl halides to give the aryl alkene.[867] Disilanes have also been employed, using a Pd catalyst.[868] Arylsilanes can be coupled to aryl iodides using a Pd catalyst[869] and in aqueous media.[870] Similar coupling of aryl halides with trialkylsilanes, $HSiR_3$,[871] in the presence of a Pd,[872] Rh,[873] PtO_2,[874] Ru,[875] Sc,[876] or Ir catalyst,[877] gave the arylsilane.

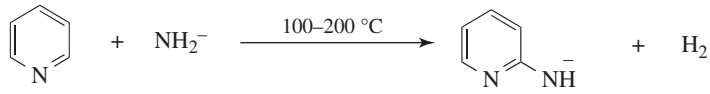
The metal-free catalytic silylation of aromatic compounds with various hydrosilanes was reported, using commercially available $B(C_6F_5)_3$ as a catalyst.[878] Functionalized arenes and heteroarenes were converted to the arylsilane derivative by reaction with $TMSCF_3$,

[859] Papoian, V.; Minehan, T. *J. Org. Chem.* ***2008***, *73*, 7376.
[860] Pletnev, A.A.; Larock, R.C. *J. Org. Chem.* ***2002***, *67*, 9428.
[861] Ishiyama, T.; Kizaki, H.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* ***1993***, *34*, 7595.
[862] Couve-Bonnaire, S.; Caprentier, J.-F.; Mortreux, A.; Castanet, Y. *Tetrahedron Lett.* ***2001***, *42*, 3689.
[863] Maerten, E.; Hassouna, F.; Couve-Bonnaire, S.; Mortreux, A.; Carpentiere, J.-F.; Castanet, Y. *Synlett* ***2003***, 1874.
[864] Cheng, C.; Hartwig, J.F. *Chem. Rev.* ***2015***, *115*, 8946; Komiyama, T.; Minami, Y.; Hiyama, T. *Synlett.* ***2017***, *28*, 1873. See also, Denmark, S.E.; Kallemeyn, J.M. *J. Am. Chem. Soc.* ***2006***, *128*, 15958; Seganish, W.M.; DeShong, P. *Org. Lett.* ***2004***, *6*, 4379.
[865] Denmark, S.E.; Neuville, L.; Christy, M.E.L.; Tymonko, S.A. *J. Org. Chem.* ***2006***, *71*, 8500.
[866] Nakao, Y.; Imanaka, H.; Sahoo, A.K.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc.* ***2005***, *127*, 6952.
[867] Denmark, S.E.; Butler, C.R. *J. Am. Chem. Soc.* ***2008***, ***130***, 3690.
[868] McNeill, E.; Barder, T.E.; Buchwald, S.L. *Org. Lett.* ***2007***, *9*, 3785.
[869] Denmark, S.E.; Wu, Z. *Org. Lett.* ***1999***, *1*, 1495; Lee, J.-y.; Fu, G.C. *J. Am. Chem. Soc.* ***2003***, *125*, 5616.
[870] Denmark, S.E.; Ober, M.H. *Org. Lett.* ***2003***, *5*, 1357.
[871] See Xu, Z.; Huang, W.-S.; Zhang, J.; Xu, L.-W. *Synthesis* ***2015***, *47*, 3645.
[872] Yamamoto, Y.; Matsubara, H.; Murakami, K.; Yorimitsu, H.; Osuka, A. *Chem. Asian J.* ***2015***, *10*, 219.
[873] Omachi, H.; Itami, K. *Chem. Lett.* ***2009***, *38*, 186. For a mechanistic study, see Cheng, C.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2014***, *136*, 12064.
[874] Hamze, A.; Provot, O.; Alami, M.; Brion, J.-D. *Org. Lett.* ***2006***, *8*, 931.
[875] Sakurai, T.; Matsuoka, Y.; Hanataka, T.; Fukuyama, N.; Namikoshi, T.; Watanabe, S.; Murata, M. *Chem. Lett.* ***2012***, *41*, 374.
[876] Oyamada, J.; Nishiura M.; Hou, Z. *Angew. Chem. Int. Ed.* ***2011***, *50*, 10720.
[877] Cheng, C.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2015***, *137*, 592; Murai, M.; Takami, K.; Takai, K. *Chem. Eur. J.* ***2015***, *21*, 4566.
[878] Ma, Y.; Wang, B.; Zhang, L.; Hou, Z. *J. Am. Chem. Soc.* ***2016***, *138*, 3663.

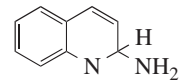
activated by alkali metal fluoride.[879] 2-Aryl pyridines reacted with $HSiFR_2$ in the presence of an Ir catalyst to give the 1-silyl-2-pyridylarene.[880]

13.C.ii. Hydrogen as Leaving Group[881]

13-18 Amination of Nitrogen Heterocycles



Pyridine and other heterocyclic nitrogen compounds can be aminated with alkali metal amides in a process called the *Chichibabin reaction*.[882] The attack is always in the 2 position unless both such positions are filled, in which case the 4 position is attacked. Substituted alkali metal amides, e.g., RNH^- and R_2N^-, have also been used. The mechanism is probably similar to that of **13-12**. The existence of intermediate ions, such as **8** (from quinoline) has been demonstrated by NMR spectra.[883]



8

A pyridyne type of intermediate was ruled out by several observations, including the facts that 3-ethylpyridine gave 2-amino-3-ethylpyridine[884] and that certain heterocycles that cannot form an aryne could nevertheless be successfully aminated. Nitro compounds do not give this reaction,[885] but they have been aminated ($ArH \rightarrow ArNH_2$ or ArNHR) via the vicarious substitution principle (see **13-17**), using 4-amino- or 4-alkylamino-1,2,4-triazoles as nucleophiles.[886] The vicarious leaving group in this case is the triazole ring. Note, however, that 3-nitropyridine was converted to 6-amino-3-nitropyridine by reaction with KOH, hydroxylamine, and $ZnCl_2$.[887]

Analogous reactions have been carried out with hydrazide ions, R_2NNH^-.[888] A mixture of NO_2 and O_3, with excess $NaHSO_3$, converted pyridine to 3-aminopyridine.[889] For other methods of aminating aromatic rings, see **11-4**.

[879] Sasaki, M.; Kondo, Y. *Org. Lett.* ***2015***, *17*, 848.
[880] Wakaki, T.; Kanai, M.; Kuninobu, Y. *Org. Lett.* ***2015***, *17*, 1758.
[881] See Chupakhin, O.N.; Postovskii, I.Ya. *Russ. Chem. Rev.* ***1976***, *45*, 454. See Chupakhin, O.N.; Charushin, V.N.; van der Plas, H.C. *Tetrahedron* ***1988***, *44*, 1.
[882] See Vorbrüggen, H. *Adv. Heterocycl. Chem.* ***1990***, *49*, 117; McGill, C.K.; Rappa, A. *Adv. Heterocycl. Chem.* ***1988***, *44*, 1. See Jeffrey, J.L.; Sarpong, R. *Org. Lett.* ***2012***, *14*, 5400; Mastalir, M.; Pittenauer, E.; Allmaier, G.; Kirchner, K. *Tetrahedron Lett.* ***2016***, *57*, 333.
[883] Wozniak, M.; Baránski, A.; Nowak, K.; van der Plas, H.C. *J. Org. Chem.* ***1987***, *52*, 5643.
[884] Ban, Y.; Wakamatsu, T. *Chem. Ind. (London)* ***1964***, 710.
[885] See Levitt, L.S.; Levitt, B.W. *Chem. Ind. (London)* ***1975***, 520.
[886] Katritzky, A.R.; Laurenzo, K.S. *J. Org. Chem.* ***1986***, *51*, 5039; ***1988***, *53*, 3978.
[887] Bakke, J.M.; Svensen, H.; Trevisan, R. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 376.
[888] Kauffmann, T.; Hansen, J.; Kosel, C.; Schoeneck, W. *Liebigs Ann. Chem.* ***1962***, *656*, 103.
[889] Suzuki, H.; Iwaya, M.; Mori, T. *Tetrahedron Lett.* ***1997***, *38*, 5647.

The reaction of various aromatic and heteroaromatic compounds with *N*-fluorobenzenesulfonimide gave the imide derivative in the presence of CuBr and 6,6′-dimethyl-2,2′-bipyridyl.[890]

There are no *Organic Syntheses* references, but see OS **V**, 977, for a related reaction.

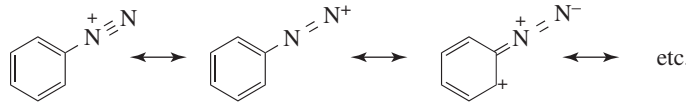
13.C.iii. Nitrogen as Leaving Group

The diazonium group can be replaced by a number of groups.[891] Some of these are nucleophilic substitutions, with S_N1 mechanisms (Sec. 10.A.ii), but others are free-radical reactions and are treated in Chapter 14. The solvent in diazonium group reactions is usually water. With other solvents it has been shown that the S_N1 mechanism is favored by solvents of low nucleophilicity, while those of high nucleophilicity favor free-radical mechanisms.[892] The N_2^+ group[893] can be replaced by Cl^-, Br^-, and CN^- by a nucleophilic mechanism (see OS **IV**, 182). It must be kept in mind that the N_2^+ group can activate the removal of another group on the ring.

13-19 Diazotization

$$Ar{-}NH_2 + HONO \longrightarrow Ar{-}\overset{+}{N}{\equiv}N$$

When primary aromatic amines are treated with nitrous acid, diazonium salts are formed.[894] The reaction also occurs with aliphatic primary amines, but aliphatic diazonium ions are extremely unstable, even in solution (Sec. 10.G.iii). Aromatic diazonium ions are more stable, because of the resonance interaction between the nitrogen atoms and the ring, as shown.



9 **10**

Incidentally, **9** contributes more than **10**, as shown by bond-distance measurements.[895] In benzenediazonium chloride, the C—N distance is ~1.42 Å, and the N—N distance ≈ 1.08 Å,[896] and these values fit more closely to a single bond and a triple bond than to two double bonds (see Table 1.5). Even aromatic diazonium salts are unstable at temperatures other than about <5 °C. A few are more stable, such as the diazonium salt obtained from sulfanilic acid, which is stable up to 10 or 15 °C. Diazonium salts are usually prepared

[890] Kawakami, T.; Murakami, K.; Itami, K. *J. Am. Chem. Soc.* ***2015***, *137*, 2460.

[891] See Wulfman, D.S. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, pp. 286–297.

[892] Szele, I.; Zollinger, H. *Helv. Chim. Acta* ***1978***, *61*, 1721.

[893] See Pérez, P. *J. Org. Chem.* ***2003***, *68*, 5886.

[894] See in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, Wiley, NY, ***1978***, the articles by Hegarty, A.F. pt. 2, pp. 511–591, and Schank, K. pt. 2, pp. 645–657; Godovikova, T.I.; Rakitin, O.A.; Khmel'nitskii, L.I. *Russ. Chem. Rev.* ***1983***, *52*, 440; Challis, B.C.; Butler, A.R. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 305–320. Butler, A.R. *Chem. Rev.* ***1975***, *75*, 241.

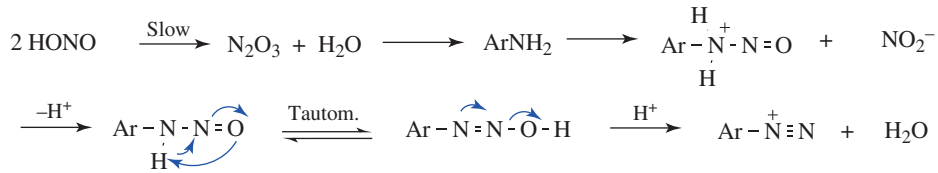
[895] See Sorriso, S. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, pp. 95–105.

[896] Rømming, C. *Acta Chem. Scand.* ***1963***, *17*, 1444; Sorriso, S. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, p. 98; Ball, R.G.; Elofson, R.M. *Can. J. Chem.* ***1985***, *63*, 332.

in aqueous solution and *used without isolation*.[897] While it is possible to prepare solid diazonium salts (see **13-22**), *many dry diazonium salts are explosive* if not handled with great care and extreme caution should be exercised. The stability of aryl diazonium salts can be increased by crown ether complexion.[898]

For aromatic amines, the reaction is very general. Since aliphatic amines do not react with nitrous acid below a pH of about 3, it is even possible, by working at a pH ~ 1, to diazotize an aromatic amine without disturbing an aliphatic amino group in the same molecule.[899] If an aliphatic amino group is α to a COOR, CN, CHO, COR, and so on and has a hydrogen, treatment with nitrous acid gives not a diazonium salt, but a *diazo compound*[900] (e.g., $EtO_2C{-}CH{=}N^+{=}N$) Such diazo compounds can also be prepared, often more conveniently, by treatment of the substrate with isoamyl nitrite ($Me_2CHCH_2CH_2ONO$) and a small amount of acid.[901] Certain heterocyclic amines also give diazo compounds rather than diazonium salts.[902]

Despite the fact that diazotization takes place in acid solution, the actual reactive species is not the salt of the amine, but the small amount of free amine present.[903] Because aliphatic amines are stronger bases than aromatic ones, at pH values < 3, there is not enough free amine present for the aliphatic amines to be diazotized, while the aromatic amines still undergo the reaction. In dilute acid the actual attacking species is N_2O_3, which acts as a carrier of NO^+. Evidence is that the reaction is second order in nitrous acid and, at sufficiently low acidities, the amine does not appear in the rate expression.[904] Under these conditions the mechanism is that shown.



Other evidence exists for this mechanism.[905] Other attacking species can be NOCl and $H_2NO_2^+$ and, at high acidities, even NO^+. Nucleophiles (e.g., Cl^-, SCN^-, thiourea) catalyze the reaction by converting the HONO to a better electrophile, for example:[906]

$$HNO_2 + Cl^- + H^+ \rightarrow NOCl + H_2O$$

[897] See Wulfman, D.S. in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, pp. 247–339.
[898] Korzeniowski, S.H.; Leopold, A.; Beadle, J.R.; Ahern, M.F.; Sheppard, W.A.; Khanna, R.K.; Gokel, G.W. *J. Org. Chem.* ***1981***, *46*, 2153, and references cited therein; Bartsch, R.A. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wiley, NY, ***1983***, pp. 889–915.
[899] Kornblum, N.; Iffland, D.C. *J. Am. Chem. Soc.* ***1949***, *71*, 2137.
[900] See Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***. For reviews, see Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, the articles by Regitz, M., pt. 2, pp. 659–708, 751–820, and Wulfman, D.S.; Linstrumelle, G.; Cooper, C.F., pt. 2, pp. 821–976.
[901] Takamura, N.; Mizoguchi, T.; Koga, K.; Yamada, S. *Tetrahedron* ***1975***, *31*, 227.
[902] Butler, R.N. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, p. 305.
[903] Challis, B.C.; Larkworthy, L.F.; Ridd, J.H. *J. Chem. Soc.* ***1962***, 5203.
[904] See Hughes, E.D.; Ingold, C.K.; Ridd, J.H. *J. Chem. Soc.* ***1958***, 58, 65, 77, 88.
[905] See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 95–109; Ridd, J.H. *Q. Rev. Chem. Soc.* ***1961***, *15*, 418 (pp. 422).
[906] Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 84–93.

There are many preparations of diazonium salts listed in *Organic Syntheses*, but they are always prepared for use in other reactions. They are listed under the reactions in which they are used. The preparation of aliphatic diazo compounds can be found in OS **III**, 392; **IV**, 424. See also, OS **VI**, 840.

13-20 Hydroxylation of Aryldiazonium Salts

$$ArN_2^+ + H_2O \longrightarrow ArOH$$

This reaction is formally analogous to **13-1**, but with a N_2^+ leaving group rather than a halide. Water is usually present whenever diazonium salts are made, but at these temperatures (0–5 °C) the reaction proceeds very slowly. When it is *desired* to have OH replace the diazonium group, the excess nitrous acid is destroyed and the solution is usually boiled. Some diazonium salts require even more vigorous treatment, for example, boiling with aqueous sulfuric acid or with trifluoroacetic acid containing potassium trifluoroacetate.[907] The reaction can be performed on solutions of any diazonium salts, but hydrogensulfates are preferred to chlorides or nitrates, since in these cases there is competition from the nucleophiles Cl^- or NO_3^-.

A better method, which is faster, avoids side reactions, takes place at room temperature, and gives higher yields, consists of adding Cu_2O to a dilute solution of the diazonium salt dissolved in a solution containing a large excess of $Cu(NO_3)_2$.[908] Aryl radicals are intermediates when this method is used. It has been shown that aryl radicals are at least partly involved when ordinary hydroxy de-diazoniation is carried out in weakly alkaline aqueous solution.[909] Decomposition of arenediazonium tetrafluoroborates in F_3CSO_2OH gives aryl triflates directly, in high yields.[910]

OS **I**, 404; **III**, 130, 453, 564; **V**, 1130.

13-21 Replacement by Sulfur-Containing Groups

$$ArN_2^+ + HS^- \longrightarrow ArSH$$
$$ArN_2^+ + S^{2-} \longrightarrow ArSAr$$
$$ArN_2^+ + RS^- \longrightarrow ArSR$$
$$ArN_2^+ + SCN^- \longrightarrow ArSCN + ArNCS$$

These reactions are convenient methods for incorporating a sulfur-containing group onto an aromatic ring. With $Ar'S^-$, diazosulfides Ar—N=N—S—Ar′ are intermediates,[911] which can in some cases be isolated.[912] Thiophenols can be made as shown above, but more often the diazonium ion is treated with $EtO–CS_2^-$ or S_2^{2-}, which give the expected products, and these are easily convertible to thiophenols. Aryldiazonium salts are prepared by the reaction of an aniline derivative with an alkyl nitrite (RONO); when formed in the presence of dimethyl disulfide (MeS—SMe), the product is the thioether, Ar—S—Me.[913] Aryl triflates

[907] Horning, D.E.; Ross, D.A.; Muchowski, J.M. *Can. J. Chem.* ***1973***, *51*, 2347.
[908] Cohen, T.; Dietz Jr., A.G.; Miser, J.R. *J. Org. Chem.* ***1977***, *42*, 2053.
[909] Dreher, E.; Niederer, P.; Rieker, A.; Schwarz, W.; Zollinger, H. *Helv. Chim. Acta* ***1981***, *64*, 488.
[910] Yoneda, N.; Fukuhara, T.; Mizokami, T.; Suzuki, A. *Chem. Lett.* ***1991***, 459.
[911] Abeywickrema, A.N.; Beckwith, A.L.J. *J. Am. Chem. Soc.* ***1986***, *108*, 8227, and references cited therein.
[912] See Price, C.C.; Tsunawaki, S. *J. Org. Chem.* ***1963***, *28*, 1867.
[913] Allaire, F.S.; Lyga, J.W. *Synth. Commun.* ***2001***, *31*, 1857.

have been converted to the aryl thiol using NaST(P5) and a palladium catalyst, followed by treatment with tetrabutylammonium fluoride[914] (see also, **13-21**).

Thiocyanates have been generated from unactivated aryl halides using charcoal-supported copper(I) thiocyanate.[915] The visible light-promoted, aerobic, metal-free C3 thiocyanation of indoles[916] or of imidazoheterocycles[917] has been reported.

OS **II**, 580; **III**, 809 (but see OS **V**, 1050). Also see, OS **II**, 238.

Diazonium salts can be converted to sulfonyl chlorides by treatment with sulfur dioxide in the presence of $CuCl_2$.[918] The use of $FeSO_4$ and Cu metal instead of $CuCl_2$ gives sulfinic acids ($ArSO_2H$).[919]

OS **V**, 60; **VII**, 508.

13-22 Replacement by Halogen

$$ArN_2^+ + CuX \longrightarrow Ar{-}X$$

Treatment of diazonium salts with CuCl or CuBr leads to aryl chlorides or aryl bromides, respectively. In either case, the reaction is called the *Sandmeyer reaction*.[920] The reaction can also be carried out with copper and HBr or HCl, in which case it is called the *Gatterman reaction* (not to be confused with **11-18**). However, a Cu-catalyzed Sandmeyer bromination reaction is known.[921] The Sandmeyer reaction is not useful for the preparation of fluorides or iodides, but for bromides and chlorides it is of wide scope and is probably the best way of introducing bromine or chlorine into an aromatic ring. The yields are usually high.

The mechanism is believed to involve formation of an aryl radical.[922] The first step involves a reduction of the diazonium ion by the cuprous ion, which results in the formation of an aryl radical. In the second step, the aryl radical abstracts halogen from cupric chloride, reducing it. CuX is regenerated and is thus a true catalyst.

$$ArN_2X + CuX \longrightarrow Ar\bullet + N_2 + CuX_2$$
$$Ar\bullet + CuX_2 \longrightarrow Ar{-}X + CuX$$

Aryl bromides and aryl chlorides can be prepared from primary aromatic amines in one step by several procedures,[923] including treatment of the amine (i) with *tert*-butyl nitrite and anhydrous $CuCl_2$ or $CuBr_2$ at 65 °C,[924] and (ii) with *tert*-butyl thionitrite or *tert*-butyl

[914] Arnould, J.C.; Didelot, M.; Cadilhac, C.; Pasquet, M.J. *Tetrahedron Lett.* ***1996***, *37*, 4523.
[915] Clark, J.H.; Jones, C.W.; Duke, C.V.A.; Miller, J.M. *J. Chem. Soc., Chem. Commun.* ***1989***, 81. See also, Yadav, J.S.; Reddy, B.V.S.; Shubashree, S.; Sadashiv, K. *Tetrahedron Lett.* ***2004***, *45*, 2951.
[916] Fan, W.; Yang, Q.; Xu, F.; Li, P. *J. Org. Chem.* ***2014***, *79*, 10588.
[917] Mitra, S.; Ghosh, M.; Mishra, S.; Hajra, A. *J. Org. Chem.* ***2015***, *80*, 8275.
[918] Gilbert, E.E. *Synthesis* ***1969***, 1 (p. 6).
[919] Wittig, G.; Hoffmann, R.W. *Org. Synth.* **V**, 60.
[920] Rate constants for this reaction have been determined. See Hanson, P.; Hammond, R.C.; Goodacre, P.R.; Purcell, J.; Timms, A.W. *J. Chem. Soc., Perkin Trans. 2* ***1994***, 691.
[921] Beletskaya, I.P.; Sigeev, A.S.; Peregudov, A.S.; Petrovskii, P.V. *Synthesis* ***2007***, 2534.
[922] Galli, C. *J. Chem. Soc., Perkin Trans. 2* ***1984***, 897. See also, Hanson, P.; Jones, J.R.; Gilbert, B.C.; Timms, A.W. *J. Chem. Soc., Perkin Trans. 2* ***1991***, 1009.
[923] Also see Brackman,W.; Smit, P.J. *Recl. Trav. Chim. Pays-Bas* ***1966***, *85*, 857; Cadogan, J.I.G.; Roy, D.A.; Smith, D.M. *J. Chem. Soc. C* ***1966***, 1249.
[924] Doyle, M.P.; Siegfried, B.; Dellaria Jr., J.F. *J. Org. Chem.* ***1977***, *42*, 2426.

thionitrate and $CuCl_2$ or $CuBr_2$ at room temperature.[925] A further advantage is that cooling to 0 °C is not needed. A mixture of Me_3SiCl and $NaNO_2$ was used to convert aniline to chlorobenzene in a related reaction.[926] It is noted that the reaction of aryl diazonium salts with CuCN to give benzonitrile derivatives is also called the *Sandmeyer reaction*. It is usually conducted in neutral solution to avoid liberation of HCN.

OS **I**, 135, 136, 162, 170; **II**, 130; **III**, 185; **IV**, 160. Also see, OS **III**, 136; **IV**, 182. For the reaction with CuCN see OS **I**, 514.

One of the best methods for the introduction of iodine into aromatic rings (see **13-6**) is the reaction of diazonium salts with iodide ions.[927] When other diazonium reactions are carried out in the presence of these ions, halides are usually side products. Aniline has also been converted to fluorobenzene by treatment with *t*-BuONO and SiF_4 followed by heating.[928]

The actual attacking species is probably not only I^-, if it is I^- at all. The iodide ion is oxidized (by the diazonium ion, nitrous acid, or some other oxidizing agent) to iodine, which in a solution containing iodide ions is converted to I_3^-; this is the actual attacking species, at least partly. This conclusion was deduced by isolation of $ArN_2^+ I_3^-$ salts, which, on standing, gave ArI.[929] From this experiment, it can be inferred that the reason the other halide ions give poor results is *not* that they are poor nucleophiles but *rather* they are poor reducing agents (compared with iodide). There is also evidence for a free-radical mechanism.[930]

OS **II**, 351, 355, 604; **V**, 1120.

Heating diazonium tetrafluoroborates ($ArN_2^+ BF_4^-$; the *Schiemann* or *Balz-Schiemann reaction*) is by far the best way to introduce fluorine into an aromatic ring.[931] In the most common procedure, the tetrafluoroborate salts are prepared by diazotizing as usual with nitrous acid and HCl and then adding a cold aqueous solution of $NaBF_4$, HBF_4, or NH_4BF_4. A precipitate forms, which is dried, and the salt is heated in the dry state (*CAUTION*!). These salts are unusually stable for diazonium salts, and the reaction is usually successful. (Since diazonium salts are generally unstable, care should be exercised any time a diazonium salt is dried.) In general, any aromatic amine that can be diazotized will form a BF_4^- salt, usually with high yields. The diazonium fluoroborates can be formed directly from primary aromatic amines with *tert*-butyl nitrite and BF_3-etherate.[932] The reaction has also been carried out on $ArN_2^+ PF_6^-$ $ArN_2^+ SbF_6^-$, and $ArN_2^+ AsF_6^-$ salts, in many cases with better yields.[933] Aryl chlorides and bromides are commonly prepared by the *Sandmeyer reaction*. In an alternative procedure, aryl fluorides are prepared by treatment of aryltriazenes Ar—N=N—NR_2 with 70% HF in pyridine.[934] The mechanism is of the S_N1 type. That aryl cations are intermediates was shown by several experiments:[935]

[925] Oae, S.; Shinhama, K.; Kim, Y.H. *Bull. Chem. Soc. Jpn.* ***1980***, *53*, 1065.
[926] Lee, J.G.; Cha, H.T. *Tetrahedron Lett.* ***1992***, *33*, 3167.
[927] See Krasnokutskaya, E.A.; Semenischeva, N.I.; Filimonov, V.D.; Knochel, P. *Synthesis* ***2007***, 81; Filimonov, V.D.; Semenischeva, N.I.; Krasnokutskaya, E.A.; Tretyakov, A.N.; Hwang, H.Y.; Chi, K.W. *Synthesis* ***2008***, 185.
[928] Tamura, M.; Shibakami, M.; Sekiya, A. *Eur. J. Org. Chem.* ***1998***, 725.
[929] Carey, J.G.; Millar, I.T. *Chem. Ind. (London)* ***1960***, 97.
[930] Packer, J.E.; Taylor, R.E.R. *Aust. J. Chem.* ***1985***, *38*, 991; Abeywickrema, A.N.; Beckwith, A.L.J. *J. Org. Chem.* ***1987***, *52*, 2568.
[931] See Suschitzky, H. *Adv. Fluorine Chem.* ***1965***, *4*, 1.
[932] Doyle, M.P.; Bryker, W.J. *J. Org. Chem.* ***1979***, *44*, 1572.
[933] Sellers, C.; Suschitzky, H. *J. Chem. Soc. C* ***1968***, 2317.
[934] Rosenfeld, M.N.; Widdowson, D.A. *J. Chem. Soc., Chem. Commun.* ***1979***, 914. For another alternative procedure, see Yoneda, N.; Fukuhara, T.; Kikuchi, T.; Suzuki, A. *Synth. Commun.* ***1989***, *19*, 865.
[935] See also, Swain, C.G.; Sheats, J.E.; Harbison, K.G. *J. Am. Chem. Soc.* ***1975***, *97*, 783, 796; Becker, H.G.O.; Israel, G. *J. Prakt. Chem.* ***1979***, *321*, 579.

If an aryl cation is an intermediate in the Schiemann reaction, compounds containing *meta*-directing groups, that is *meta*-directing for *electrophilic* substitutions, should be *meta*-arylated and those containing *ortho*/*para*-directing groups should be *ortho*- and *para*-arylated, since an aryl cation should behave in this respect like any electrophile (see Chapter 11). Experiments have shown[936] that such orientation is observed, demonstrating that the Schiemann reaction has a positively charged intermediate. The attacking species, in at least some instances, is not F^- but BF_4^-.[937]

OS **II**, 188, 295, 299; **V**, 133.

13-23 Replacement of the Diazonium Group by Nitro

$$ArN_2^+ + NaNO_2 \xrightarrow{Cu^+} ArNO_2$$

Nitro compounds can be formed in good yields by treatment of diazonium salts with sodium nitrite in the presence of cuprous ion. The reaction occurs only in neutral or alkaline solution. This is not usually called the *Sandmeyer reaction*, although it was discovered by Sandmeyer. Tetrafluoroborate (BF_4^-) is often used as the negative ion since the diminished nucleophilicity avoids competition from the chloride ion.[938] If electron-withdrawing groups are present, the catalyst is not needed; $NaNO_2$ alone gives nitro compounds in high yields.[939]

OS **II**, 225; **III**, 341.

13-24 Conversion of Amines to Azo Compounds

$$ArNH_2 + Ar'NO \xrightarrow{HOAc} Ar{-}N{=}N{-}Ar'$$

Aromatic nitroso compounds combine with primary arylamines in glacial acetic acid to give symmetrical or unsymmetrical azo compounds (the *Mills reaction*).[940] A wide variety of substituents may be present in both aryl groups. Unsymmetrical azo compounds have also been prepared by the reaction between aromatic nitro compounds, $ArNO_2$, and *N*-acyl aromatic amines, Ar′NHAc.[941] The use of phase-transfer catalysis increased the yields. The nano-Pd-catalyzed reaction of aromatic nitro compounds and KOH gave aromatic azo compounds.[942] Heating aryl nitro compounds and aniline derivatives with KOH gave the corresponding diaryl azo compound.[943]

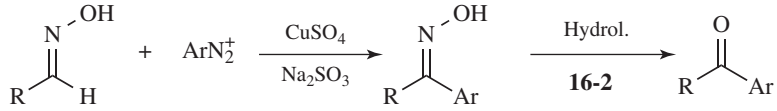
13-25 Methylation, Vinylation, and Arylation of Diazonium Salts

$$ArN_2^+ + Me_4Sn \xrightarrow[MeCN]{Pd(OAc)_2} ArMe$$

[936] Makarova, L.G.; Matveeva, M.K.; Gribchenko, E.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1958***, 1399.
[937] Swain, C.G.; Rogers, R.J. *J. Am. Chem. Soc.* ***1975***, *97*, 799.
[938] See Singh, P.R.; Kumar, R.; Khanna, R.K. *Tetrahedron Lett.* ***1982***, *23*, 5191.
[939] Bagal, L.I.; Pevzner, M.S.; Frolov, A.N. *J. Org. Chem. USSR* ***1969***, *5*, 1767.
[940] See Boyer, J.H. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, ***1969***, pp. 278–283.
[941] Ayyangar, N.R.; Naik, S.N.; Srinivasan, K.V. *Tetrahedron Lett.* ***1989***, *30*, 7253.
[942] Hu, L.; Cao, X.; Shi, L.; Qi, F.; Guo, Z.; Lu, J.; Gu, H. *Org. Lett.* ***2011***, *13*, 5640.
[943] Zhao, R.; Tan, C.; Xie, Y.; Gao, C.; Liu, H.; Jiang,Y. *Tetrahedron Lett.* ***2011***, *52*, 3805.

A methyl group can be introduced onto an aromatic ring by treatment of diazonium salts with Me_4Sn and a Pd catalyst.[944] The reaction has been performed with Me, Cl, Br, and NO_2 groups on the ring. A vinylic group can be introduced by using $CH_2{=}CHSnBu_3$. When an aryl amine is treated with *tert*-butyl hyponitrite (*t*-BuONO) and allyl bromide, the nitrogen is displaced to the give allyl aryl compound.[945]

13-26 Conversion of Diazonium Salts to Aldehydes, Ketones, or Carboxylic Acids

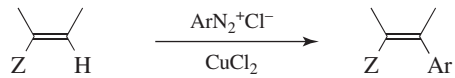


Diazonium salts react with oximes to give aryl oximes, which are easily hydrolyzed to aldehydes (R = H) or ketones.[946] A copper sulfate/sodium sulfite catalyst is essential. In most cases higher yields (40–60%) are obtained when the reaction is used for aldehydes than for ketones. In another method[947] for achieving the conversion $ArN_2^+ \rightarrow ArCOR$, diazonium salts are treated with R_4Sn and CO with palladium acetate as catalyst.[948] In a different kind of reaction, silyl enol ethers of aryl ketones $Ar'C(OSiMe_3){=}CHR$ react with solid diazonium fluoroborates ($ArN_2^+ BF_4^-$) to give ketones ($ArCHRCOAr'$).[949] This sequence is, in effect, an arylation of the aryl ketone.

Carboxylic acids can be prepared in moderate to high yields by treatment of diazonium fluoroborates with CO and palladium acetate[950] or $CuCl_2$.[951] The mixed anhydride ArCOOCOMe is an intermediate that can be isolated. Other mixed anhydrides can be prepared by the use of other salts instead of sodium acetate.[952] An arylpalladium compound is probably an intermediate.[368]

OS **V**, 139.

13-27 Arylation of Activated Alkenes by Diazonium Salts: Meerwein Arylation



Alkenes activated by an electron-withdrawing group (Z may be C=C, halogen, C=O, Ar, CN, etc.) can be arylated by treatment with a diazonium salt and a $CuCl_2$[953] catalyst in what is called the *Meerwein arylation reaction*.[954] Addition of ArCl to the double bond [to give Z(Cl)C—CHAr] is a side reaction (**15-42**). In an improved procedure, an arylamine is treated

[944] Kikukawa, K.; Kono, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* ***1983***, *48*, 1333.
[945] Ek, F.; Wistrand, L.-G.; Frejd, T. *J. Org. Chem.* ***2003***, *68*, 1911.
[946] Beech, W.F. *J. Chem. Soc.* ***1954***, 1297.
[947] See Citterio, A.; Serravalle, M.; Vimara, E. *Tetrahedron Lett.* ***1982***, *23*, 1831.
[948] Kikukawa, K.; Idemoto, T.; Katayama, A.; Kono, K.; Wada, F.; Matsuda, T. *J. Chem. Soc., Perkin Trans. 1* ***1987***, 1511.
[949] Sakakura, T.; Hara, M.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* ***1985***, 1545.
[950] Nagira, K.; Kikukawa, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* ***1980***, *45*, 2365.
[951] Olah, G.A.; Wu, A.; Bagno, A.; Prakash, G.K.S. *Synlett* ***1990***, 596.
[952] Kikukawa, K.; Kono, K.; Nagira, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* ***1981***, *46*, 4413.
[953] See Ganushchak, N.I.; Obushak, N.D.; Luka, G.Ya. *J. Org. Chem. USSR* ***1981***, *17*, 765.
[954] Dombrovskii, A.V. *Russ. Chem. Rev.* ***1984***, *53*, 943; Rondestvedt Jr., C.S. *Org. React.* ***1976***, *24*, 225; Kindt, S.; Heinrich, M.R. *Synthesis* ***2016***, *48*, 1597.

with an alkyl nitrite (generating ArN_2^+ *in situ*) and a copper(II) halide in the presence of the alkene.[955]

The mechanism of reaction with an alkene is probably of the free-radical type, with Ar• as seen in **13-22** and then (i) halogen transfer to give aryl addition with a β-chloro or (ii) elimination to give the styrene derivative.[956] Even when the addition pathway is taken, however, the substitution product may still be formed by subsequent elimination of HCl. Note that radical reactions are presented in Chapter 14, but the coupling of an alkene with an aromatic compound containing a leaving group prompted its placement here. Note the similarity to the *Heck reaction* (**13-13**).

OS **IV**, 15.

Esters with a distal terminal alkene unit were coupled with aryldiazonium tetrafluoroborates with a Pd catalyst to give the styryl derivative with high (*E*) selectivity.[957] The use of a Ru photoredox catalyst allows visible light to mediate the α-arylation of enol acetates by aryl diazonium salts.[958] The Pd-catalyzed cross coupling of diazo compounds with vinyl boronic acids gave 1,3-dienes.[959]

A Heck-type reaction of alkenes with aryldiazonium salts using a Pd catalyst gave the aryl alkene in neat water.[960] The coupling of 4-phenol diazonium salts with styrenes gave 4′-hydroxy stilbenes using a Pd catalyst.[961] The flow diazotization (Sec. 7.D) of aniline derivatives has been reported for the Pd-catalyzed cross coupling of ethyl acrylate to give the γ-arylated alkene product.[962]

13-28 Arylation of Aromatic Compounds by Diazonium Salts

$$ArH + Ar'N_2^+ X^- \xrightarrow{OH^-} Ar{-}Ar'$$

When the normally acidic solution of a diazonium salt is made alkaline, the aryl portion of the diazonium salt can couple with another aromatic ring. Known as the *Gomberg reaction* or the *Gomberg-Bachmann reaction*,[963] it has been performed on several types of aromatic rings and on quinones. Yields are not high (usually < 40%) because of the many side reactions undergone by diazonium salts, although higher yields have been obtained under phase-transfer conditions.[964] The conditions of the *Meerwein reaction* (**13-27**), treatment of the solution with a Cu–Fe catalyst, have also been used, as has the addition of sodium nitrite in DMSO (to benzenediazonium tetrafluoroborate).[965] When the Gomberg-Bachmann reaction is performed intramolecularly, either by the alkaline solution or by the copper ion procedure, it is called the *Pschorr reaction*[966] and yields are usually somewhat higher. Still

[955] Doyle, M.P.; Siegfried, B.; Elliott, R.C.; Dellaria Jr., J.F. *J. Org. Chem.* ***1977***, *42*, 2431.

[956] Dickerman, S.C.; Vermont, G.B. *J. Am. Chem. Soc.* ***1962***, *84*, 4150; Morrison, R.T.; Cazes, J.; Samkoff, N.; Howe, C.A. *J. Am. Chem. Soc.* ***1962***, *84*, 4152.

[957] Werner, E.W.; Sigman, M.S. *J. Am. Chem. Soc.* ***2011***, *133*, 9692.

[958] Hering, T.; Hari, D.P.; König, B. *J. Org. Chem.* ***2012***, *77*, 10347.

[959] Xia, Y.; Xia, Y.; Liu, Z.; Zhang, Y.; Wang, J. *J. Org. Chem.* ***2014***, *79*, 7711.

[960] Salabert, J.; Sebastián, R.M.; Vallribera, A.; Cívicos, J.F.; Nájera, C. *Tetrahedron* ***2013***, *69*, 2655.

[961] Schmidt, B.; Elizarov, N.; Berger, R.; Hölter, F. *Org. Biomol. Chem.* ***2013***, *11*, 3674.

[962] Nalivela, K.S.; Tilley, M.; McGuire, M.A.; Organ, M.G. *Chem. Eur. J.* ***2014***, *20*, 6603.

[963] See Bolton, R.; Williams, G.H. *Chem. Soc. Rev.* ***1986***, *15*, 261; Hey, D.H. *Adv. Free-Radical Chem.* ***1966***, *2*, 47. Also see Vernin, G.; Dou, H.J.; Metzger, J. *Bull. Soc. Chim. Fr.* ***1972***, 1173.

[964] Beadle, J.R.; Korzeniowski, S.H.; Rosenberg, D.E.; Garcia-Slanga, B.J.; Gokel, G.W. *J. Org. Chem.* ***1984***, *49*, 1594.

[965] Kamigata, N.; Kurihara, T.; Minato, H.; Kobayashi, M. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 3152.

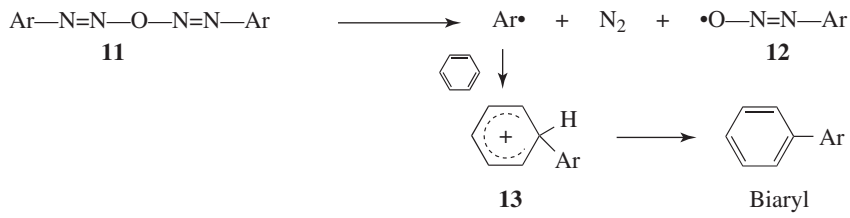
[966] For a review, see Abramovitch, R.A. *Adv. Free-Radical Chem.* ***1966***, *2*, 87.

higher yields have been obtained by carrying out the Pschorr reaction electrochemically.[967] The Pschorr reaction has been carried out for Z = CH=CH, CH_2CH_2, NH, C=O, CH_2, and quite a few others. A rapid and convenient way to diazotize the amine substrate uses isopropyl nitrite in the presence of sodium iodide, in which case the ring-closed product is formed in one step.[968] Palladium-catalyzed arylation of arenediazonium salts is known.[969]

A Cu-catalyzed modification of Gomberg-Bachmann-Hey reaction gave biaryls by diazotization of anilines with a *p*-TSA and $NaNO_2$ system at 50 °C, using aromatic liquids as solvents.[970] The ferrous salt-promoted homocoupling of arenediazonium salts gave biaryls.[971] Arenediazonium salts react with benzoic acids to give the *ortho* arylation product using an Ir catalyst.[972] A Au catalyst was used for the cross coupling of aryldiazonium salts with arylboronic acids, under photoredox conditions.[973] Aniline derivatives were arylated using aryl diazoacetates.[974] Aryldiazonium salts were coupled to heteroarenes photochemically in the presence of eosin.[975]

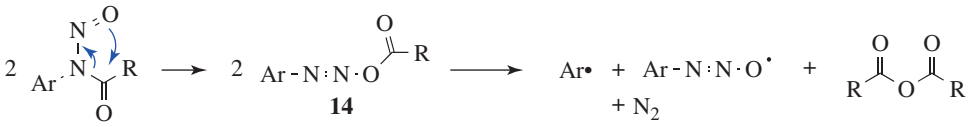
Other compounds with nitrogen–nitrogen bonds have been used instead of diazonium salts. Among these are *N*-nitroso amides [ArN(NO)COR], triazenes,[976] and azo compounds. Still another method involves treatment of an aromatic primary amine directly with an alkyl nitrite in an aromatic substrate as solvent.[977]

In each case, the mechanism involves generation of an aryl radical from a covalent azo compound. In acid solution, diazonium salts are ionic and their reactions are polar. When they cleave, the product is an aryl cation (Sec. 13.A.i). However, in neutral or basic solution, diazonium ions are converted to covalent compounds, and these cleave to give free radicals (Ar• and Z•). Note that radical reactions are presented in Chapter 14, but the coupling of an aromatic ring with an aromatic compound containing a leaving group prompted its placement here. Under Gomberg-Bachmann conditions, the species that cleaves is the anhydride, **11**.[978] The aryl radical thus formed attacks the substrate to give the aryl cation[979] (intermediate **13**), from which the radical **12** abstracts hydrogen to give the product, a biaryl.



[967] Elofson, R.M.; Gadallah, F.F. *J. Org. Chem.* ***1971***, *36*, 1769.
[968] Chauncy, B.; Gellert, E. *Aust. J. Chem.* ***1969***, *22*, 993. See also, Duclos Jr., R.I.; Tung, J.S.; Rapoport, H. *J. Org. Chem.* ***1984***, *49*, 5243.
[969] Robinson, M.K.; Kochurina, V.S.; Hanna Jr., J.M. *Tetrahedron Lett.* ***2007***, *48*, 7687.
[970] Chaturbhuj, G.U.; Akamanchi, K.G. *Tetrahedron Lett.* ***2011***, *52*, 4950.
[971] Ding, Y.; Cheng, K.; Qi, C.; Song, Q. *Tetrahedron Lett.* ***2012***, *53*, 6269.
[972] Huang, L.; Hackenberger, D.; Gooßen, L.J. *Angew. Chem. Int. Ed.* ***2015***, *54*, 12607.
[973] Cornilleau, T.; Hermange, P.; Fugquet, E. *Chem. Commun.* ***2016***, *52*, 10040.
[974] Pratsch, G.; Wallaschkowski, T.; Heinrich, M.R. *Chem. Eur. J.* ***2012***, *18*, 11555.
[975] Hari, D.P.; Schroll, P.; König, B. *J. Am. Chem. Soc.* ***2012***, *134*, 2958.
[976] See Butler, R.N.; O'Shea, P.D.; Shelly, D.P. *J. Chem. Soc., Perkin Trans. 1*, ***1987***, 1039.
[977] Fillipi, G.; Vernin, G.; Dou, H.J.; Metzger, J.; Perkins, M.J. *Bull. Soc. Chim. Fr.* ***1974***, 1075.
[978] Eliel, E.L.; Saha, J.G.; Meyerson, S. *J. Org. Chem.* ***1965***, *30*, 2451.
[979] For an alternative method to generate aryl cations, see Milanesi, S.; Fagnoni, M.; Albini, A. *J. Org. Chem.* ***2005***, *70*, 603.

N-Nitroso amides probably rearrange to *N*-acyloxy compounds (**14**), which cleave to give aryl radicals.[980]

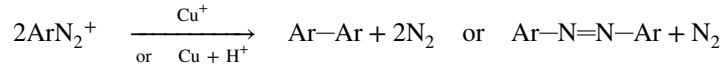


There is evidence that the reaction with alkyl nitrites also involves attack by aryl radicals.[981]

The *Pschorr reaction* can take place by two different mechanisms, depending on conditions: (i) attack by an aryl radical (as in the *Gomberg-Bachmann reaction*) or (ii) attack by an aryl cation (similar to the S_N1 mechanism discussed in Sec. 13.A.ii).[982] Under certain conditions, the ordinary *Gomberg-Bachmann reaction* can also involve attack by aryl cations.[983]

OS **I**, 113; **IV**, 718.

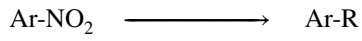
13-29 Aryl Dimerization with Diazonium Salts



When diazonium salts are treated with cuprous ion (or with Cu and acid, in which case it is called the *Gatterman method*), two products are possible. If the ring contains electron-withdrawing groups, the main product is the biaryl, but the presence of electron-donating groups leads mainly to the azo compound. This reaction is different from **13-28** (and from **19-14**) in that *both* aryl groups in the product originate from ArN_2^+, that is, hydrogen is not a leaving group in this reaction. The mechanism probably involves free radicals.[984]

OS **I**, 222; **IV**, 872. Also see, OS **IV**, 273.

13-30 Replacement of Nitro



In some cases, the nitrogen group of an aromatic nitro compound can be replaced with an alkyl group. The reaction of 1,4-dinitrobenzene with potassium *tert*-butoxide in the presence of BEt_3, for example, gave 4-ethylnitrobenzene.[985]

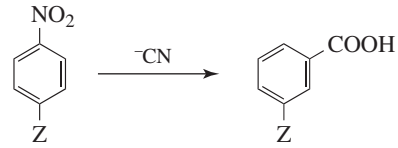
Other nucleophiles can replace a nitrogen-containing group. The reaction of hydroxide with Ar—Y, where Y = nitro,[986] azide, NR_3^+, and so on, gives the corresponding phenol.

[980] Cadogan, J.I.G.; Murray, C.D.; Sharp, J.T. *J. Chem. Soc., Perkin Trans. 2*, ***1976***, 583, and references cited therein.
[981] Gragerov, I.P.; Levit, A.F. *J. Org. Chem. USSR* ***1968***, *4*, 7.
[982] See Gadallah, F.F.; Cantu, A.A.; Elofson, R.M. *J. Org. Chem.* ***1973***, *38*, 2386.
[983] See Burri, P.; Zollinger, H. *Helv. Chim. Acta* ***1973***, *56*, 2204; Eustathopoulos, H.; Rinaudo, J.; Bonnier, J.M. *Bull. Soc. Chim. Fr.* ***1974***, 2911; Zollinger, H. *Acc. Chem. Res.* ***1973***, *6*, 335 (pp. 338).
[984] See Cohen, T.; Lewarchik, R.J.; Tarino, J.Z. *J. Am. Chem. Soc.* ***1974***, *96*, 7753.
[985] Palani, N.; Jayaprakash, K.; Hoz, S. *J. Org. Chem.* ***2003***, *68*, 4388.
[986] See Knudsen, R.D.; Snyder, H.R. *J. Org. Chem.* ***1974***, *39*, 3343.

This latter reaction works with alkoxide nucleophiles to give the corresponding aryl ether. The nitro can be replaced with chloro by use of NH_4Cl, PCl_5, $SOCl_2$, HCl, Cl_2, or CCl_4. Some of these reagents operate only at high temperatures and the mechanism is not always nucleophilic substitution. Activated aromatic nitro compounds can be converted to fluorides with fluoride ion.[987]

13.C.iv. Rearrangements

13-31 The von Richter Rearrangement



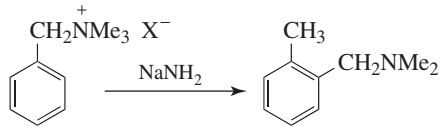
When aromatic nitro compounds are treated with cyanide ion, the nitro group is displaced and a carboxyl group enters with *cine* substitution (Sec. 13.A.iii), always *ortho* to the displaced group, never *meta* or *para*. The scope of this reaction, called the *von Richter rearrangement*, is variable.[988] As with other nucleophilic aromatic substitutions, the reaction gives best results when electron-withdrawing groups are in *ortho* and *para* positions, but yields are low, usually <20% and never >50%.

At one time it was believed that a nitrile, ArCN, was an intermediate, since cyanide is the reagent and nitriles are hydrolyzable to carboxylic acids under the reaction conditions (**16-4**). However, a remarkable series of results proved this belief to be in error. Bunnett and Rauhut demonstrated[989] that α-naphthyl cyanide is *not* hydrolyzable to α-naphthoic acid under conditions at which β-nitronaphthalene undergoes the von Richter rearrangement to give α-naphthoic acid. This proved that the nitrile couldn't be an intermediate. It was subsequently demonstrated that N_2 is a major product of the reaction.[990] It had previously been assumed that all the nitrogen in the reaction was converted to ammonia, which would be compatible with a nitrile intermediate, since ammonia is a hydrolysis product of nitriles. At the same time it was shown that NO_2^+ is not a major product. The discovery of nitrogen indicated that a N—N bond must be formed during the course of the reaction. Rosenblum proposed a mechanism in accord with all the facts.[989]

The 2-nitrobenzamide intermediate is a stable compound, and it was prepared and subjected to the conditions of the von Richter rearrangement, and this experiment gave the correct product.[991] When 4-chloro or 4-bromonitrobenzene was treated with cyanide in $H_2{}^{18}O$, half the oxygen in the product was labeled, showing that one of the oxygen atoms of the carboxyl group came from the nitro group and one from the solvent, as required by this mechanism.[992]

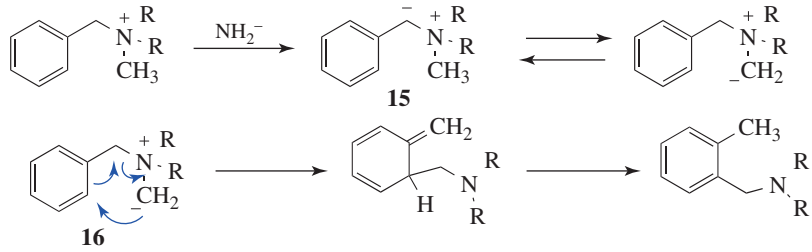
[987] Effenberger, F.; Streicher, W. *Chem. Ber.* ***1991***, *124*, 157.
[988] For a review, see Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 326–335.
[989] Bunnett, J.F.; Rauhut, M.M. *J. Org. Chem.* ***1956***, *21*, 934, 944.
[990] Rosenblum, M. *J. Am. Chem. Soc.* ***1960***, *82*, 3796.
[991] Ibne-Rasa, K.M.; Koubek, E. *J. Org. Chem.* ***1963***, *28*, 3240.
[992] Samuel, D. *J. Chem. Soc.* ***1960***, 1318. For other evidence, see Cullen, E.; L'Ecuyer, P. *Can. J. Chem.* ***1961***, *39*, 144, 155, 382; Ullman, E.F.; Bartkus, E.A. *Chem. Ind. (London)* ***1962***, 93.

13-32 The Sommelet-Hauser Rearrangement



Benzylic quaternary ammonium salts undergo a rearrangement called the *Sommelet-Hauser rearrangement* when treated with alkali metal amides.[993] Since the product is a benzylic tertiary amine, it can be further alkylated and the product again subjected to the rearrangement. This process can be continued around the ring until an *ortho* position is blocked.[994]

The rearrangement occurs with high yields and can be performed with various groups present in the ring.[995] The reaction is most often carried out with three methyl groups on the nitrogen, but other groups can also be used. Note, though, that if a β hydrogen is present, *Hofmann elimination* (**17-6**) often competes. The *Stevens rearrangement* (**18-21**) is also a competing process.[996] When both rearrangements are possible, the Stevens rearrangement is favored at high temperatures and the Sommelet-Hauser at low temperatures.[997] The mechanism is:



The benzylic hydrogen is most acidic and is the one that first loses a proton to give the ylid **15**. However, **16**, which is present in a smaller amount, is the species that undergoes the rearrangement, shifting the equilibrium in its favor. This mechanism is an example of a [2,3]-sigmatropic rearrangement (see **18-35**). Another mechanism that might be proposed is one in which a methyl group actually breaks away (in some form) from the nitrogen and then attaches itself to the ring. That this is not so was shown by a product study.[998] If the second mechanism were true, **17** should give 1-(2,6-dimethylphenyl)-*N*,*N*-dimethylmethanamine, but the first mechanism predicts the formation of 1-(2,3-dimethylphenyl)-*N*,*N*-dimethylmethanamine, which is what was actually obtained.[999]

[993] See Pine, S.H. *Org. React.* ***1970***, *18*, 403; Lepley, A.R.; Giumanini, A.G. *Mech. Mol. Migr.* ***1971***, *3*, 297; Wittig, G. *Bull. Soc. Chim. Fr.* ***1971***, 1921; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, ***1973***, pp. 81–88; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 316–326. Also see, Klunder, J.M. *J. Heterocycl. Chem.* ***1995***, *32*, 1687.

[994] Beard, W.Q.; Hauser, C.R. *J. Org. Chem.* ***1960***, *25*, 334.

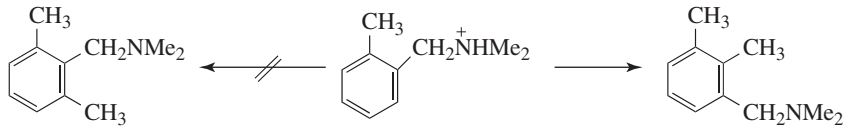
[995] Jones, G.C.; Beard, W.Q.; Hauser, C.R. *J. Org. Chem.* ***1963***, *28*, 199.

[996] See, however, Nakano, M.; Sato, Y. *J. Org. Chem.* ***1987***, *52*, 1844; Shirai, N.; Sato, Y. *J. Org. Chem.* ***1988***, *53*, 194.

[997] Wittig, G.; Streib, H. *Liebigs Ann. Chem.* ***1953***, *584*, 1.

[998] See Puterbaugh, W.H.; Hauser, C.R. *J. Am. Chem. Soc.* ***1964***, *86*, 1105; Pine, S.H.; Sanchez, B.L. *Tetrahedron Lett.* ***1969***, 1319; Shirai, N.; Watanabe, Y.; Sato, Y. *J. Org. Chem.* ***1990***, *55*, 2767.

[999] Kantor, S.W.; Hauser, C.R. *J. Am. Chem. Soc.* ***1951***, *73*, 4122.

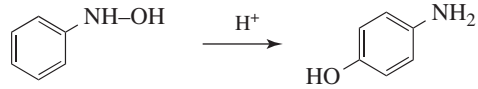


17

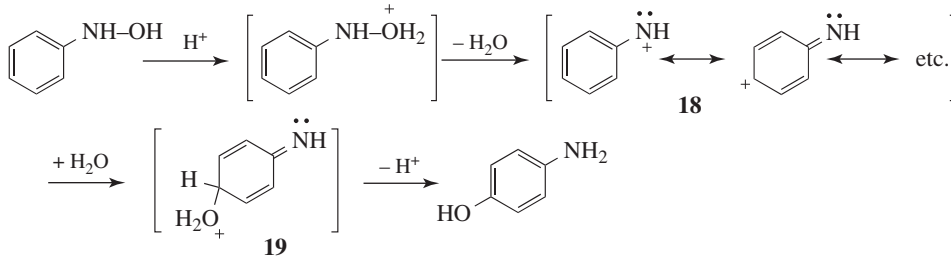
The mechanism as shown can lead only to an *ortho* product. However, a small amount of *para* product has been obtained in some cases.[1000] A mechanism[1001] in which there is a dissociation of the ArC—N bond (similar to the ion-pair mechanism of the *Stevens rearrangement*, **18-21**) has been invoked to explain the *para* products that are observed. Dialkylation using the Sommelet-Hauser protocol is known.[1002]

OS **IV**, 585.

13-33 Rearrangement of Aryl Hydroxylamines



Aryl hydroxylamines treated with acids rearrange to aminophenols.[1003] Although this reaction (known as the *Bamberger rearrangement*) is similar in appearance to **11-28** to **11-32**, the attack on the ring is not electrophilic but nucleophilic. The rearrangement is intermolecular, with the following mechanism:



18

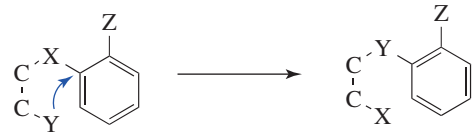
19

Among the evidence[1004] for this mechanism are the facts that other products are obtained when the reaction is run in the presence of competing nucleophiles, for example, *p*-ethoxyaniline is produced when ethanol is present, and that when the *para* position is blocked, compounds similar to **19** are isolated. In the case of 2,6-dimethylphenylhydroxylamine, the intermediate nitrenium ion **18** was trapped, and its lifetime in solution was measured.[1005] The reaction of **19** with water was found to be diffusion controlled.[1006]

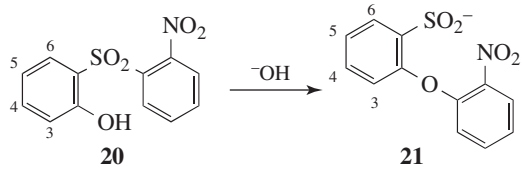
OS **IV**, 148.

[1000] Pine, S.H. *Tetrahedron Lett.* ***1967***, 3393; Pine, S.H. *Org. React.* ***1970***, *18*, 403 (p. 418).
[1001] Bumgardner, C.L. *J. Am. Chem. Soc.* ***1963***, *85*, 73.
[1002] Tayama, E.; Sato, R.; Takedachi, K.; Iwamoto, H.; Hasegawa, E. *Tetrahedron* ***2012***, *68*, 4710.
[1003] See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 182–190.
[1004] Also see Kohnstam, G.; Petch, W.A.; Williams, D.L.H. *J. Chem. Soc., Perkin Trans. 2* ***1984***, 423; Sternson, L.A.; Chandrasakar, R. *J. Org. Chem.* ***1984***, *49*, 4295, and references cited therein.
[1005] Fishbein, J.C.; McClelland, R.A. *J. Am. Chem. Soc.* ***1987***, *109*, 2824.
[1006] Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1661.

13-34 The Smiles Rearrangement



The *Smiles rearrangement* actually comprises a group of rearrangements that follow the pattern shown above.[1007] A specific example is the reaction of **20** with hydroxide to give **21**.

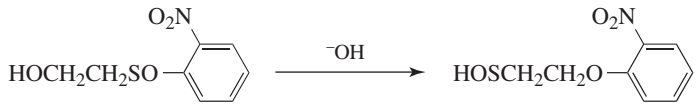


20 **21**

Smiles rearrangements are simply intramolecular nucleophilic substitutions. In the example given, SO_2Ar is the leaving group and ArO^- the nucleophile, and the nitro group serves to activate its *ortho* position. Halogens also serve as activating groups.[1008] The ring at which the substitution takes place is nearly always activated, usually by *ortho* or *para* nitro groups. Here X is usually S, SO, SO_2,[1009] O, or CO_2, and Y is usually the conjugate base of OH, NH_2, NHR, or SH. The reaction has even been carried out with $Y = CH_2^-$ (phenyllithium was the base here).[1010]

The reaction rate is greatly enhanced by substitution in the 6 position of the attacking ring, for steric reasons. For example, a methyl, chloro, or bromo group in the 6 position of **20** caused the rate to be $\sim 10^5$ times faster than when the same groups were in the 4 position,[1011] although electrical effects should be similar at these positions. The enhanced rate comes about because the most favorable conformation the molecule can adapt to suit the bulk of the 6 substituent is also the conformation required for the rearrangement. Thus, less entropy of activation is required.

Although the Smiles rearrangement is usually carried out on compounds containing two rings, this need not be the case, as in the formation of **22**.[1012]



22

[1007] See Truce, W.E.; Kreider, E.M.; Brand, W.W. *Org. React.* ***1971***, *18*, 99; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 307–316; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, ***1973***, pp. 120–126. See Reyes-González, J.; Gómez, R.M.; Cortés-Guzmán, F. *J. Phys. Org. Chem.* ***2012***, *25*, 230.

[1008] Grundon, M.F.; Matier, W.L. *J. Chem. Soc., B* ***1966***, 266; Schmidt, D.M.; Bonvicino, G.E. *J. Org. Chem.* ***1984***, *49*, 1664.

[1009] See Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Wiley, NY, ***1968***, pp. 262–274.

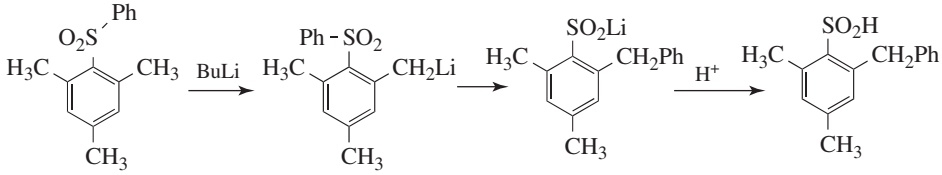
[1010] Truce, W.E.; Robbins, C.R.; Kreider, E.M. *J. Am. Chem. Soc.* ***1966***, *88*, 4027; Drozd, V.N.; Nikonova, L.A. *J. Org. Chem. USSR* ***1969***, *5*, 313.

[1011] Bunnett, J.F.; Okamoto, T. *J. Am. Chem. Soc.* ***1956***, *78*, 5363.

[1012] Kent, B.A.; Smiles, S. *J. Chem. Soc.* ***1934***, 422.

In this case the sulfenic acid (**22**) is unstable[1013] and the actual products isolated were the corresponding sulfinic acid (RSO_2H) and disulfide (R_2S_2).

In the Smiles rearrangement, the nucleophile Y is most often the conjugate base of SH, SO_2NHR, SO_2NH_2, NH_2, NHR, OH, or OR. There are few examples where Y is a carbanion, and the most common example is probably the *Truce-Smiles rearrangement,* where L–YH is an *o*-tolyl group.[1014] The prototypical Truce-Smiles rearrangement requires use of a strong base to form the benzylic carbanion that undergoes the rearrangement. When sulfone **23** was treated with butyllithium, for example, deprotonation led to the benzylic lithium compound **24**. Truce-Smiles rearrangement led to **25**, and hydrolysis gave the sulfinic acid, **26**.[1015]



23 **24** **25** **26**

Truce-Smiles rearrangements with stabilized benzylic carbanions are known,[1015] and rearrangements of carbanions in general fall under this category.[1016] Relatively few examples have been reported, however.[1017] Truce-Smiles rearrangements of sulfones that proceed through a six-membered transition state have been reported.[1018] In another example, displacement of an activated aryl fluoride with *o*-hydroxyacetophenone gave a product that was *C*-arylated adjacent to the ketone.[1019] Phenols were converted to anilines via a Smiles rearrangement.[1020] A benzyne Truce-Smiles rearrangement is known.[1021]

[1013] For a stable sulfenic acid, see Nakamura, N. *J. Am. Chem. Soc.* ***1983***, *105*, 7172.
[1014] Truce, W.E.; Ray Jr., W.J.; Norman, O.L.; Eickemeyer, D.B. *J. Am. Chem. Soc.* ***1958***, *80*, 3625. Henderson, A.R.P.; Kosowan, J.R.; Wood, T.E. *Can. J. Chem.* ***2017***, *95*, 483.
[1015] Erickson, W.R.; McKennon, M.J. *Tetrahedron Lett.* ***2000***, *41*, 4541.
[1016] Fukazawa, Y.; Kato, N.; Ito, S. *Tetrahedron Lett.* ***1982***, *23*, 437.
[1017] Hirota, T.; Tomita, K.; Sasaki, K.; Okuda, K.; Yoshida, M.; Kashino, S. *Heterocycles* ***2001***, *55*, 741.
[1018] Truce, W.E.; Hampton, D.C. *J. Org. Chem.* ***1963***, *28*, 2276.
[1019] Mitchell, L.H.; Barvian, N.C. *Tetrahedron Lett.* ***2004***, *45*, 5669.
[1020] Xie, Y.-S.; Vijaykumar, B.V.D.; Jang, K.; Shin, H.-H.; Zuo, H.; Shin, D.-S. *Tetrahedron Lett.* ***2013***, *54*, 5151.
[1021] Holden, C.M.; Sohel, S.M.A.; Greaney, M.F. *Angew. Chem. Int. Ed.* ***2016***, *55*, 2450.

CHAPTER 14

Radical Reactions

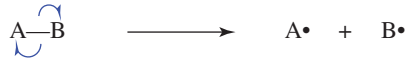
This chapter discusses many types of radical reactions, including reactions in which radicals may be intermediates. Radicals are increasingly important in organic synthesis.[1] The formation, fate, and properties of radicals were introduced in Sec. 5.C. Additional information concerning radicals may be found in Sec. 7.A, in the discussion of photochemical processes.

For the most part, this chapter discusses radical substitution reactions, although some radical coupling reactions are discussed.[2] Free-radical additions to unsaturated compounds and rearrangements are discussed in Chapters 15 and 18, respectively. Fragmentation reactions are covered, in part, in Chapter 17. In addition, many of the oxidation–reduction reactions considered in Chapter 19 involve free-radical mechanisms. Several important types of free-radical reactions do not usually lead to reasonable yields of pure products and are not generally treated in this book.

14.A. MECHANISMS

14.A.i. Radical Mechanisms in General[3]

A free-radical process (or just a radical process) consists of at least two steps. Any radical reaction first involves the *formation* of free radicals, usually by homolytic cleavage of a bond, that is, a cleavage in which each fragment retains one electron:



[1] Rowlands, G.J. *Tetrahedron* ***2009***, *65*, 8603; ***2010***, *66*, 1593. See Domingo, L.R.; Pérez, P. *Org. Biomol. Chem.* ***2013***, *11*, 4350.

[2] Liu, C.; Liu, D.; Lei, A. *Acc. Chem. Res.* ***2014***, *47*, 3459; Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A.K.; Lei, A. *Chem. Rev.* ***2017***, *117*, 9016.

[3] Nonhebel, D.C.; Tedder, J.M.; Walton, J.C. *Radical*, Cambridge University Press, Cambridge, ***1979***; Nonhebel, D.C.; Walton. J.C. *Free-Radical Chemistry*, Cambridge University Press, London, ***1974***; Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***; Pryor, W.A. *Free Radicals*, McGraw-Hill, NY, ***1966***. See Huyser, E.S. in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 1–59; Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***; Davies, D.I.; Parrott, M.J. *Free Radicals in Organic Synthesis*, Springer, NY, ***1978***; Curran, D.P. *Synthesis* ***1988***, 417, 489; Ramaiah, M. *Tetrahedron* ***1987***, *43*, 3541.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

This reaction is called an *initiation* step. It may happen spontaneously or may be induced by heat[4] or light (Sec. 5.C.ii), depending on the type of bond.[5] Peroxides,[6] including hydrogen peroxide, dialkyl, diacyl, alkyl acyl peroxides, and peroxyacids are the most common source of free radicals. However, other organic compounds with low-energy bonds, such as azo compounds, are also used. Chlorine, bromine, and various ketones[7] (see Chapter 7) are most commonly cleaved by light. Radicals can also be formed by a one-electron transfer (loss or gain),[8] for example:

$$A^+ + e^- \rightarrow A\bullet$$

One-electron transfers usually involve inorganic ions or electrochemical processes.[9]

Dialkyl peroxides (ROOR) or alkyl hydroperoxides (ROOH) decompose to hydroxy radicals (HO•)[10] or alkoxy radicals (RO•)[11] when heated. Cumene hydroperoxide ($PhCMe_2OOH$), bi-*tert*-butylperoxide ($Me_3COOCMe_3$),[12] and benzoyl peroxide [$(PhCO)O_2$] undergo homolytic cleavage at temperatures compatible with many organic reactions, and they are reasonably soluble in organic solvents.[13] In general, when a peroxide decomposes, the oxygen radical remains in a "cage" for $\sim 10^{-11}$ seconds before diffusing away.[14] The radical can recombine (dimerize), or react with other molecules.

Azo compounds, characterized by a —N=N— bond, are free-radical precursors that liberate nitrogen gas (N≡N) upon decomposition. Azobisisobutyronitrile (AIBN, **1**) is a well-known example, which decomposes to give nitrogen gas and the cyano-stabilized radical, **2**.[15] Homolytic dissociation of symmetrical diazo compounds may be stepwise.[16] A derivative has been developed that decomposes at room temperature:

[4] See Engel, P.S.; Pan, L.; Ying, Y.; Alemany, L.B. *J. Am. Chem. Soc.* ***2001***, *123*, 3706.

[5] See Fokin, A.A.; Schreiner, P.R. *Chem. Rev.* ***2002***, *102*, 1551.

[6] See Dai, Q.; Jiang, Y.; Yu, J.-T.; Cheng, J. *Synthesis* ***2016***, *48*, 329.

[7] For radical formation via triplet ketone-formation and catalyzed C—H functionalization reactions, see Chen, C. *Org. Biomol. Chem.* ***2016***, *14*, 8641.

[8] For the role of *t*-BuO, see Barham, J.P.; Coulthard, G.; Emery, K.J.; Doni, E.; Cumine, F.; Nocera, G.; John, M.P.; Berlouis, L.E.A.; McGuire, T.; Tuttle, T.; Murphy, J.A. *J. Am. Chem. Soc.* ***2016***, *138*, 7402.

[9] For a review of bond formation and bond dissociation, see Houmam, A. *Chem. Rev.* ***2008***, *108*, 2180. See Fuchigami, T.; Atobe, M.; Inagi, S. *Fundamentals and Applications of Organic Electrochemistry. Synthesis, Materials, Devices*, Wiley, Hoboken ***2014***. For a discussion of ionic liquids as electrolyte for organic reactions, see Kathiresan, M.; Velayutham, D. *Chem. Commun.* ***2015***, *51*, 17499.

[10] See Jiang, D.; Barata-Vallejo, S.; Golding, B.T.; Ferreri, C.; Chatgilialogiu, C. *Org. Biomol. Chem.* ***2012***, *10*, 1102.

[11] For a table of approximate decomposition temperatures, see Lazár, M.; Rychly, J.; Klimo, V.; Pelikán, P.; Valko, L. *Free Radicals in Chemistry and Biology*, CRC Press, Washington, DC, ***1989***, p 12. See Salamone, M.; Bietti, M. *Synlett* ***2014***, *25*, 1803.

[12] Lazár, M.; Rychly, J.; Klimo, V.; Pelikán, P.; Valko, L. *Free Radicals in Chemistry and Biology*, CRC Press, Washington, DC, ***1989***, p 13.

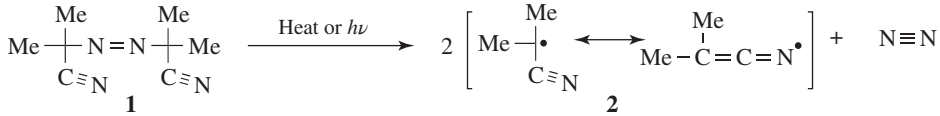
[13] Hydrogen bonding affects the persistency of alkyl peroxy radicals. See Mugnaini, V.; Lucarini, M. *Org. Lett.* ***2007***, *9*, 2725. For the use of cyclopentyl methyl ether, see Kobayashi, S.; Kuroda, H.; Ohtsuka, Y.; Kashihara, T.; Masuyama, A.; Watanabe, K. *Tetrahedron* ***2013***, *69*, 2251.

[14] For reactions of heteroatom-centered radicals, see Taniguchi, T. *Synthesis* ***2017***, *49*, 3511.

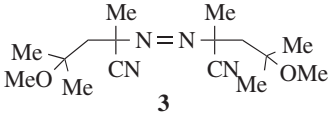
[15] Yoshino, K.; Ohkatsu, J.; Tsuruta, T. *Polym. J.* ***1977***, *9*, 275; von J. Hinz, A.; Oberlinner, A.; Rüchardt, C. *Tetrahedron Lett.* ***1973***, 1975.

[16] Dannenberg, J.J.; Rocklin, D. *J. Org. Chem.* ***1982***, *47*, 4529. See Dol, C.; Bertrand, M.P.; Gastaldi, S.; Besson, E. *Tetrahedron* ***2016***, *72*, 7744.

2,2′-azobis-(2,4-dimethyl-4-methoxyvaleronitrile), **3**.[17] Water-soluble azo compounds are known, and can be used as radical initiators.[18]



1 **2**



3

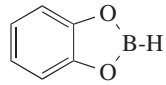
Alkyl hypochlorites (R—O—Cl) generate chlorine radicals (Cl•) and alkoxy radicals (RO•) when heated.[19] Heating *N*-alkoxydithiocarbamates is another useful source of alkoxy radicals, RO•.[20] Alkoxy radicals, particularly those derived from cyclic compounds, may undergo β-scission reactions to give carbonyl derivatives.[21]

It has been known for many years that boron compounds participate in radical reactions.[22] Trialkylboranes (R_3B; see **15-23**, **12-27**), such as triethylborane (Et_3B), can be used to initiate radical reactions. Indeed, Et_3B is widely used.[23] In radical reactions, Et_3B functions as both a radical initiator and also as a chain propagation agent.[24] Reactions are usually run in open vessels exposed to oxygen or under an oxygen atmosphere. It is known that O_2 reacts with BEt_3 to give $Et_2BOO•$ and Et• in the initiation step, and then an atom transfer reaction with an alkyl iodide[25] gives the alkyl radical, R•. In a second step, Et• reacts with R—I to give R• and Et—I. Trialkylborane/water-mediated radical reactions are also known.[26] 1-Chloroalkyl radicals have been generated from organoboranes.[27]

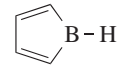
In general, the order of reactivity is $R_3B > R_2BOR > RB(OR)_2$ where R = alkyl.[28] Boronic acids are less reactive, presumably due to π bonding between B and O.[23] However, *B*-alkylcatecholboranes are very reactive, and are highly useful for initiating radical reactions.[29] Reaction conditions usually involve addition of catecholborane (**4**, abbreviated CatBH), and the *B*-alkyl derivative is presumably generated *in situ* by reaction with an

[17] Kita, Y.; Sano, A.; Yamaguchi, T.; Oka, M.; Gotanda, K.; Matsugi, M. *Tetrahedron Lett.* ***1997***, *38*, 3549.
[18] Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H; Oshima, K. *Tetrahedron Lett.* ***1999***, *40*, 519.
[19] Davies, D.I.; Parrott, M.J. *Free Radicals in Organic Synthesis*, Springer-Verlag, Berlin, ***1978***, p. 9; Chattaway, F.D.; Baekeberg, O.G. *J. Chem. Soc.* ***1923***, *123*, 2999.
[20] Kim, S.; Lim, C.J.; Song, S.-E.; Kang, H.-Y. *Synlett* ***2001***, 688.
[21] See Bietti, M.; Lanzalunga, O.; Salamone, M. *J. Org. Chem.* ***2005***, *70*, 417.
[22] See Ollivier, C.; Renaud, P. *Chem. Rev.* ***2001***, *101*, 3415.
[23] Renaud, P.; Beauseigneur, A.; Brecht-Forster, A.; Becattini, B.; Darmency, V.; Kandhasamy, S.; Montermini, F.; Ollivier, C.; Panchaud, P.; Pozzi, D.; Scanlan, E.M.; Schaffner, A.-P.; Weber, V. *Pure Appl. Chem.* ***2007***, *79*, 223; Yorimitsu, H.; Oshima, K. in *Radicals in Organic Synthesis*, Vol. 1, Renaud, P.; Sibi, M.P. (eds.), Wiley-VCH, Weinheim, ***2001***, p. 11.
[24] See Darmency, V.; Renaud, P. *Top. Curr. Chem.* ***2006***, *263*, 71.
[25] For I-transfer reactions, see Monks, B.M.; Cook, S.P. *Angew. Chem. Int. Ed.* ***2013***, *52*, 14214.
[26] Medeiros, M.R.; Schacherer, L.N.; Spiegel, D.A.; Wood, J.L. *Org. Lett.* ***2007***, *9*, 4427.
[27] Xu, G.; Lüthy, M.; Habegger, J.; Renaud, P. *J. Org. Chem.* ***2016***, *81*, 1506.
[28] Davies, A.G.; Roberts, B.P. *Free Radicals*, Vol. 1, Kochi, J.K. (ed.), Wiley, NY, ***1973***, p. 457; Baban, J.A.; Goodchild, N.J.; Roberts, B.P. *J. Chem. Soc., Perkin Trans. 2* ***1986***, 157.
[29] Darmency, V.; Renaud, P. *Top. Curr. Chem.* ***2006***, *263*, 71.

alkene.[30] It is noted that borole derivatives (the B analog of pyrrole, **5**) have been used to initiate radical reactions.[31]



4



5

Aldehydes can be a source of acyl radicals (•C═O) via reaction with transition metal salts such as Mn(III) acetate or Fe(II) compounds.[32] α,β-Unsaturated acyl radicals are subject to an isomerization that generates α-ketenyl radicals.[33] Another useful variation employs imidoyl radicals as synthons for unstable aryl radicals.[34] The formation of chirality in the reactions of α-amide radicals has been reported.[35]

An important step in radical reactions involves the *destruction* of free radicals. This usually happens by a process opposite to the first, namely, a combination of two like or unlike radicals to form a new bond:[36]

$$A\bullet + B\bullet \rightarrow A{-}B$$

This type of step is called *termination* because the product of the reaction is a neutral compound and not a radical.[37] Note that this reaction constitutes a radical coupling process. The termination step rarely follows initiation because most radicals are very reactive, and there are several radical processes that occur faster than the termination step. In the usual situation, in which the concentration of radicals is low, a radical is more likely to react with a molecule rather than another radical (i.e., the radical coupling reaction is usually slower). When a radical (which has an odd number of electrons) reacts with a molecule (which has an even number), the total number of electrons in the products must be odd. In other words, the product is another radical. When a radical reacts with a π bond, R• + C═C, the product is a free radical, R—C—C•. This is called *radical addition*. Another reaction constitutes an *atom-transfer reaction*. The abstraction of an atom such as hydrogen atom from an alkyl fragment gives two particles, R—H and the new radical R′•:

$$R\bullet + R'{-}H \rightarrow R{-}H + R'\bullet$$

This type of atom-transfer reaction is called a *hydrogen-transfer reaction*. Once again, the product is a free radical. This type of step is called *propagation*, since the newly formed radical can now react with another molecule and produce another radical, and so on, until

[30] See Garrett, C.E.; Fu, G.C. *J. Org. Chem.* ***1996***, *61*, 3224.
[31] Montgomery, I.; Parsons, A.F.; Ghelfi, F.; Roncaglia, F. *Tetrahedron Lett.* ***2008***, *49*, 628.
[32] Davies, D.I.; Parrott, M.J. *Free Radicals in Organic Synthesis*, Springer-Verlag, Berlin, ***1978***, p. 69; Nikishin, G.I.; Vinogradov, M.G.; Il'ina, G.P. *Synthesis* ***1972***, 376.
[33] Matsubara, H.; Ryu, I.; Schiesser, C.H. *J. Org. Chem.* ***2005***, *70*, 3610.
[34] Fujiwara, S.-i.; Matsuya, T.; Maeda, H.; Shin-ike, T.; Kambe, N.; Sonoda, N. *J. Org. Chem.* ***2001***, *66*, 2183.
[35] Sasmal, A.; Taniguchi, T.; Wipf, P.; Curran, D.P. *Can. J. Chem.* ***2013***, *91*, 1. Also see Salamone, M.; Mangiacapra, L.; Bietti, M. *J. Org. Chem.* ***2015***, *80*, 1149.
[36] For a review of stereochemistry, see Porter, N.A.; Krebs, P.J. *Top. Stereochem.* ***1988***, *18*, 97.
[37] Another type of termination step is *disproportionation* (Sec. 5.C.ii).

two radicals undergo coupling and terminate the sequence. The process of initiation, propagation, and then termination constitutes what is called a *chain reaction*,[38] and there may be hundreds or thousands of propagation steps between an initiation and a termination. Two other types of propagation reactions do not involve a molecule at all. These are (i) cleavage of a radical into, necessarily, a radical and a molecule and (ii) rearrangement of one radical to another (see Chapter 18). When radicals are highly reactive, for example, alkyl radicals, chains are long, since reactions occur with many molecules; but with radicals of low reactivity, aryl radicals for example, the radical may be unable to react with anything until it meets another radical, so that chains are short. Alternatively, the reaction may be a nonchain process. In any particular chain process, there are usually a wide variety of propagation and termination steps so there may be many products.

$$\mathrm{R{-}CH_2\bullet} + n\text{-}\mathrm{Bu_3Sn{-}H} \longrightarrow \mathrm{R{-}CH_2{-}H} + n\text{-}\mathrm{Bu_3Sn\bullet}$$
$$n\text{-}\mathrm{Bu_3Sn\bullet} + n\text{-}\mathrm{Bu_3Sn\bullet} \longrightarrow n\text{-}\mathrm{Bu_3Sn{-}Sn}n\text{-}\mathrm{Bu_3}$$

Such reactions are often difficult to treat kinetically.[39]

Is it possible to terminate a radical reaction under controlled conditions? The answer is yes, using an atom-transfer reaction. When a carbon radical (R•) is generated in the presence of tributyltin hydride (n-Bu_3SnH), a hydrogen atom is transferred to the radical to give R—H and a new radical, n-Bu_3Sn•. The tin radical usually undergoes rapid coupling to another tin radical to give n-Bu_3Sn—Sn-n-Bu_3, which effectively terminates the chain radical process. The carbon radical is *reduced* (R• → R—H) as a result of the hydrogen atom transfer, and the tin dimer can be removed from the reaction. Again, hydrogen atom transfer[40] is simply a variation of the radical reaction known as atom transfer. Silanes, such as triethylsilane (Et_3SiH), have also been used as an effective radical reducing agent.[41] The rate constants for the reaction of both tributytin hydride and $(Me_3Si)_3Si$—H with acyl radical have been measured and the silane quenches the radical faster than the tin hydride.[42] Thermolysis of *bis*-(tri-*n*-butylstannyl)benzopinacolate has also been used as a source of n-Bu_3Sn•, used to mediate radical reactions.[43]

The following are some general characteristics of free-radical reactions:[44]

1. Reactions are fairly similar whether they are occurring in the vapor or liquid phase, but solvation of free radicals in solution does cause some differences.[45]
2. They are largely unaffected by the presence of acids or bases or by changes in the polarity of solvents, except that nonpolar solvents may suppress competing ionic reactions.

[38] See Walling, C. *Tetrahedron* ***1985***, *41*, 3887.
[39] See Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***, pp. 39–65.
[40] For a discussion of barriers to degenerate hydrogen transfer, see Isborn, C.; Hrovat, D.A.; Borden, W.T.; Mayer, J.M.; Carpenter, B.K. *J. Am. Chem. Soc.* ***2005***, *127*, 5794. For a discussion of hydrogen atom transfer from phenols, see Nielsen, M.F.; Ingold, K.U. *J. Am. Chem. Soc.* ***2006***, *128*, 1172.
[41] Chatgilialoglu, C.; Ferreri, C.; Lucarini, M. *J. Org. Chem.* ***1993***, *58*, 249. See Yella, R.; Hoz, S. *Org. Lett.* ***2014***, *16*, 3876.
[42] Chatgilialoglu, C.; Lucarini, M. *Tetrahedron Lett.* ***1995***, *36*, 1299.
[43] Hart, D.J.; Krishnamurthy, R.; Pook, L.M.; Seely, F.L. *Tetrahedron Lett.* ***1993***, *34*, 7819.
[44] See Beckwith, A.L.J. *Chem. Soc. Rev.* ***1993***, *22*, 143 for a discussion of selectivity in radical reactions.
[45] See Mayo, F.R. *J. Am. Chem. Soc.* ***1967***, *89*, 2654.

3. They are initiated or accelerated by typical free-radical sources, such as the peroxides or diazo compounds noted above, or by light. In the latter case, the concept of quantum yield applies (Sec. 7.A.viii). Quantum yields can be quite high, for example, 1000, if each quantum generates a long chain, or low, in the case of nonchain processes.
4. Their rates are decreased or the reactions are suppressed entirely by substances that scavenge free radicals, for example, nitric oxide, molecular oxygen, or benzoquinone. These substances are called *inhibitors*.[46] Note that there are *C*-centered radicals in thermal equilibrium with their dimers that show poor reactivity with molecular oxygen but good reactivity with peroxyl radicals.[47]

14.A.ii. Free-Radical Substitution Mechanisms[48]

In a free-radical substitution reaction that transforms R—X to R—Y, there must first be homolytic cleavage of the substrate RX so that R• and X• radicals are produced.

$$\text{R—X} \longrightarrow \text{R•} + \text{X•}$$

This can happen by a spontaneous cleavage, or it can be caused by light or heat. More often, there is no actual cleavage, but R• is produced by an *abstraction* of another atom, X, by a radical W• produced by adding a compound, such as peroxide, that spontaneously forms free radicals.

$$\text{R—X} + \text{W•} \longrightarrow \text{R•} + \text{W—X}$$

Such a compound is called an *initiator* (see above). Once R• is formed, it can react with A—B to form R—A and a new radical B•, the products in this system.

$$\text{R•} + \text{A—B} \longrightarrow \text{R—A} + \text{B•}$$

Such an atom abstraction is known as an *atom transfer*.

Coupling is another reaction of radicals in which one radical reacts with another (R• + Y•) to form the neutral product R—Y.

$$\text{R•} + \text{Y•} \longrightarrow \text{R—Y}$$

In a reaction with a moderately long chain, much more of the product will be produced by abstraction than by coupling.

The cleavage steps have been called S_H1 (H for homolytic), and abstraction steps have been called S_H2; reactions can be classified as S_H1 or S_H2 on the basis of whether RX is converted to R by spontaneous cleavage or reaction with a radical source (W•).[49] Most chain substitution mechanisms follow the pattern cleavage then atom transfer. Chains are long and reactions go well where both cleavage and atom-transfer processes are energetically favored (no worse that slightly endothermic; Sec. 14.B.i, 14.C.i). The IUPAC designation of a chain reaction that follows this pattern is $A_rD_R + A_RD_r$ (R stands for radical).

[46] See Denisov, E.T.; Khudyakov, I.V. *Chem. Rev.* ***1987***, *87*, 1313.
[47] Korth, H.-G. *Angew. Chem. Int. Ed.* ***2008***, *47*, 5274.
[48] See Poutsma, M.L. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 113–158.
[49] Eliel, E.L. in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, pp. 142–143.

With certain radicals the transition state in an abstraction reaction has some polar character. Consider the abstraction of hydrogen from the methyl group of toluene by a bromine atom. Since bromine is more electronegative than carbon, it is reasonable to assume that there is a separation of charge in the transition state, with a partial negative charge on the halogen and a partial positive charge on the carbon:

$$\overset{\delta+}{\mathrm{PhCH_2}}\bullet\bullet\bullet\bullet\bullet\bullet\bullet\bullet\bullet\mathrm{H}\bullet\bullet\bullet\bullet\bullet\bullet\bullet\bullet\bullet\bullet\bullet\mathrm{Br}^{\delta-}$$

Evidence for the polar character of the transition state is that electron-withdrawing groups in the *para* position of toluene (which would destabilize a positive charge) decrease the rate of hydrogen abstraction by bromine while electron-donating groups increase it.[50] However, substituents have a smaller effect here ($\rho \approx -1.4$) than they do in reactions where a completely ionic intermediate is involved, e.g., the S_N1 mechanism (Sec. 10.A.ii). Other evidence for polar transition states in radical abstraction reactions is mentioned in Sec. 14.B.i, category 4. For abstraction by radicals such as methyl or phenyl, polar effects are very small or completely absent. For example, rates of hydrogen atom abstraction from ring-substituted toluenes by methyl radical were relatively unaffected by the presence of electron-donating or electron-withdrawing substituents.[51] Those radicals (e.g., Br•) that have a tendency to abstract electron-rich hydrogen atoms are called *electrophilic radicals*.

When the reaction step R—X → R• takes place at a stereogenic carbon, *racemization is almost always observed because free radicals do not retain configuration*. Exceptions to this rule are found with cyclopropyl substrates, where both inversion[52] and retention[53] of configuration have been reported, and in the reactions mentioned in Sec. 14.A.iv. Enantioselective radical processes have been reviewed.[54]

14.A.iii. Mechanisms at an Aromatic Substrate[55]

When R in the reaction from R—X to R—Y is aromatic, the simple abstraction mechanism just discussed may be operating, especially in gas-phase reactions. However, mechanisms of this type cannot account for all reactions of aromatic substrates. In processes such as the following (see **13-28**, **14-16**, and **14-17**), an aryl radical forms and coupling leads to a biaryl:

$$\mathrm{Ar}\bullet + \mathrm{Ar{-}H} \rightarrow \mathrm{Ar{-}Ar}$$

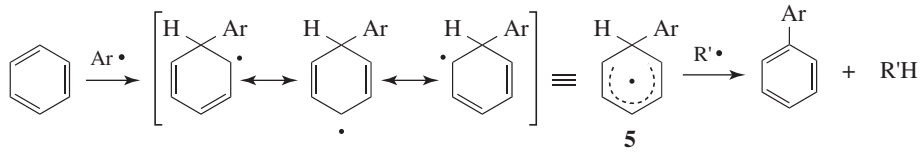
Coupling of this type can occur in solution, and generation of H• by the free-radical mechanism:

$$\mathrm{Ar}\bullet + \mathrm{Ar{-}H} \rightarrow \mathrm{Ar{-}Ar} + \mathrm{H}\bullet$$

is very unlikely (Sec. 14.B.i). Rather, the products can be explained by a mechanism similar to that of electrophilic and nucleophilic aromatic substitution. Initially, the aryl

[50] See Kim, S.S.; Choi, S.Y.; Kang, C.H. *J. Am. Chem. Soc.* ***1985***, *107*, 4234.
[51] See Pryor, W.A.; Tonellato, U.; Fuller, D.L.; Jumonville, S. *J. Org. Chem.* ***1969***, *34*, 2018.
[52] Altman, L.J.; Nelson, B.W. *J. Am. Chem. Soc.* ***1969***, *91*, 5163.
[53] Jacobus, J.; Pensak, D. *Chem. Commun.* ***1969***, 400.
[54] Sibi, M.P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* ***2003***, *103*, 3263.
[55] See Kobrina, L.S. *Russ. Chem. Rev.* ***1977***, *46*, 348; Perkins, M.J. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, 231–271; Bolton, R.; Williams, G.H. *Adv. Free Radical Chem.* ***1975***, *5*, 1; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, London, ***1974***, pp. 417–469.

radical attacks the ring in much the same way as would an electrophile or a nucleophile to generate **5**.

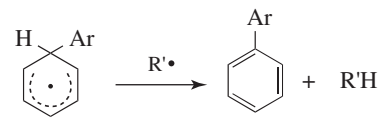


5

The intermediate radical **5** is relatively stable because of the resonance and the overall reaction leads to a biaryl product. Three pathways are available for **5**. Simple coupling leads to **6**, whereas disproportionation would give the biaryl product and **7**.

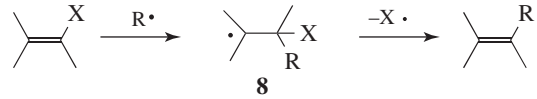
6 **7**

If a species (R′•) is present, abstraction of hydrogen lives the biaryl product directly.[56]



5

Coupling product **6** is a partially hydrogenated *o*-quaterphenyl (an *o,o′*-diphenylbiphenyl). Of course, the coupling need not be *ortho-ortho*, and other isomers can also be formed. Compounds of types **6** and **7** were isolated, which is taken as evidence for these steps.[57] However, under the reaction conditions dihydrobiphenyls like **7** are normally oxidized to the corresponding biphenyls. Other evidence for this mechanism is the detection of the intermediate **5** by CIDNP[58] and the absence of isotope effects. (Isotope effects would be expected if the rate-determining step were coupling of Ar• with Ar—H, which involves cleavage of the Ar—H bond.) In the mechanism just given, the rate-determining step is formation of **5**, and this reaction does not involve loss of hydrogen. The reaction between aromatic rings and the HO• radical takes place by the same mechanism. Intramolecular hydrogen transfer reactions of aryl radicals are known.[59] A similar mechanism has been shown for substitution at some vinylic[60] and acetylenic substrates, giving the substituted alkene via formation of the radical, **8**.[61]



8

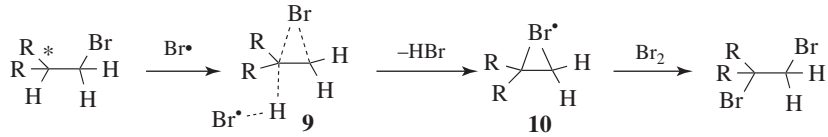
[56] See Narita, N.; Tezuka, T. *J. Am. Chem. Soc.* ***1982***, *104*, 7316.
[57] DeTar, D.F. *J. Am. Chem. Soc.* ***1967***, *89*, 4058. See also, Jandu, K.S.; Nicolopoulou, M.; Perkins, M.J. *J. Chem. Res. (S)* ***1985***, 88.
[58] Fahrenholtz, S.R.; Trozzolo, A.M. *J. Am. Chem. Soc.* ***1972***, *94*, 282.
[59] Curran, D.P.; Fairweather, N. *J. Org. Chem.* ***2003***, *68*, 2972.
[60] See Bach, R.D.; Baboul, A.G.; Schlegel, H.B. *J. Am. Chem. Soc.* ***2001***, *123*, 5787.
[61] Russell, G.A.; Ngoviwatchai, P. *Tetrahedron Lett.* ***1986***, *27*, 3479, and references cited therein.

The kinetics of radical heterolysis reactions that form alkene radical cations has been studied.[62] This mechanism is reminiscent of the nucleophilic tetrahedral mechanism at a vinylic carbon (Sec. 10.F).

There are a number of transition metal-mediated coupling reactions of aromatic substrates that probably proceed by radical coupling. It is likely that many of these reactions do *not* proceed by free radicals but rather by metal-mediated radicals or by ligand transfer at the metal. Reactions in these categories were presented in Chapter 13 for convenient correlation with other displacement reactions of aryl halides, aryl diazonium salts, and so on.

14.A.iv. Neighboring-Group Assistance in Free-Radical Reactions

In a few cases it has been shown that cleavage steps and abstraction steps were accelerated by the presence of neighboring groups. Photolytic halogenation (**14-1**) is a process that normally leads to mixtures of many products. However, bromination of carbon chains containing a bromine atom occurs with high regioselectivity. Bromination of alkyl bromides gave 84–94% substitution at the carbon adjacent to the bromine already in the molecule.[63] This result may seem surprising because, as will be seen (Sec. 14.B.i, category 3), positions close to a polar group, such as bromine, should actually be *deactivated* by the electron-withdrawing field effect of the bromine. However, the unusual regioselectivity is explained by a mechanism in which abstraction is assisted by a neighboring bromine atom, as in **9**.[64] In the normal mechanism, Br• abstracts a hydrogen atom from R—H, leaving R•. When a bromine is present in the proper position, it assists this process, giving a cyclic intermediate (a *bridged free radical*, **10**).[65] In the final step (very similar to $R\bullet + Br_2 \rightarrow RBr + Br\bullet$) the ring is broken. If this mechanism is correct, the configuration at the substituted carbon (marked *) should be retained.



Indeed, optically active 1-bromo-2-methylbutane gave 1,2-dibromo-2-methylbutane with retention of configuration.[64] When this reaction was carried out in the presence of DBr, the "recovered" 1-bromo-2-methylbutane was found to be deuterated in the 2 position, and its configuration was retained.[66] This result is just what would be predicted if some of the C═C—R that is present abstracted D from DBr. There is evidence that Cl can form bridged radicals,[67] although ESR spectra show that the bridging is not necessarily

[62] Horner, J.H.; Bagnol, L.; Newcomb, M. *J. Am. Chem. Soc.* ***2004***, *126*, 14979.
[63] Thaler, W.A. *J. Am. Chem. Soc.* ***1963***, *85*, 2607.
[64] Skell, P.S.; Tuleen, D.L.; Readio, P.D. *J. Am. Chem. Soc.* ***1963***, *85*, 2849; Huyser, E.S.; Feng, R.H.C. *J. Org. Chem.* ***1971***, *36*, 731. For another explanation, see Lloyd, R.V.; Wood, D.E. *J. Am. Chem. Soc.* ***1975***, *97*, 5986.
[65] See Kaplan, L. *Bridged Free Radicals*, Marcel Dekker, NY, ***1972***; Skell, P.S.; Traynham, J.G. *Acc. Chem. Res.* ***1984***, *17*, 160.
[66] Shea, K.J.; Skell, P.S. *J. Am. Chem. Soc.* ***1973***, *95*, 283.
[67] Everly, C.R.; Schweinsberg, F.; Traynham, J.G. *J. Am. Chem. Soc.* ***1978***, *100*, 1200; Wells, P.R.; Franke, F.P. *Tetrahedron Lett.* ***1979***, 4681.

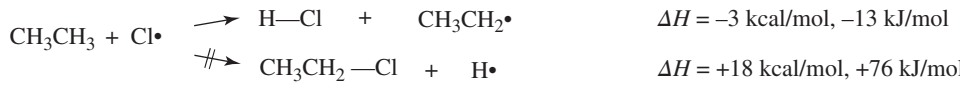
symmetrical.[68] Still more evidence for bridging by Br has been found in isotope effect and other studies.[69] However, evidence from CIDNP shows that the methylene protons of the β-bromoethyl radical are not equivalent, at least while the radical is present in the radical pair [PhCOO• •CH_2CH_2Br] within a solvent cage.[70] This evidence indicates that under these conditions $BrCH_2CH_2$• is not a symmetrically bridged radical, but it could be unsymmetrically bridged. A bridged intermediate has also been invoked, when a bromo group is in the proper position, in the *Hunsdiecker reaction*[71] (**14-24**), and in abstraction of iodine atoms by the phenyl radical.[72] Participation by other neighboring groups, e.g., SR, SiR_3, SnR_3, has also been reported.[73]

It is noted that a traditional explanation for the selectivity of bromine relative to chlorine is that abstraction of hydrogen by a bromine radical has a late transition state relative to abstraction of hydrogen by a chlorine radical. In a late transition state, the relative stability of the radical plays a greater role than the strength of the C—H bond. Since a tertiary radical is more stable than a secondary, which is more stable than a primary radical, bromination favors formation of the secondary radical over the primary, and a tertiary over secondary. This analysis is supported by the relative rates of hydrogen atom abstraction by Br• when compared to Cl•, where there is a large difference between 1°, 2°, and 3° for Br• and a small difference for Cl•. This effect is discussed in more detail in Sec. 14.B.i, categories 1–5.

14.B. REACTIVITY

14.B.i. Reactivity for Aliphatic Substrates[74]

In a chain reaction, the step that determines what the product will be is most often an abstraction (atom transfer) step. The atom abstracted by a free radical is almost never a tetravalent atom[75] or tervalent atom[76] (except in strained systems, Sec. 15.B.iv)[77] and seldom a divalent one.[78] Nearly always it is univalent, and for organic compounds, it is commonly hydrogen or halogen. Further, in a reaction between a chlorine radical and ethane, the formation of an ethyl radical is preferred (H atom transfer) to formation of a hydrogen atom radical (Cl atom transfer):



[68] Cooper, J.; Hudson, A.; Jackson, R.A. *Tetrahedron Lett.* ***1973***, 831; Chen, K.S.; Elson, I.H.; Kochi, J.K. *J. Am. Chem. Soc.* ***1973***, *95*, 5341.
[69] Howard, J.A.; Chenier, J.H.B.; Holden, D.A. *Can. J. Chem.* ***1977***, *55*, 1463. See, however, Tanner, D.D.; Blackburn, E.V.; Kosugi, Y.; Ruo, T.C.S. *J. Am. Chem. Soc.* ***1977***, *99*, 2714.
[70] Hargis, J.H.; Shevlin, P.B. *J. Chem. Soc., Chem. Commun.* ***1973***, 179.
[71] Applequist, D.E.; Werner, N.D. *J. Org. Chem.* ***1963***, *28*, 48.
[72] Danen, W.C.; Winter, R.L. *J. Am. Chem. Soc.* ***1971***, *93*, 716.
[73] Ingold, K.U.; Griller, D.; Nazran, A.S. *J. Am. Chem. Soc.* ***1985***, *107*, 208. See Reetz, M.T. *Angew. Chem. Int. Ed.* ***1979***, *18*, 173.
[74] See Tedder, J.M. *Angew. Chem. Int. Ed.* ***1982***, *21*, 401.
[75] Firouzbakht, M.L.; Ferrieri, R.A.; Wolf, A.P.; Rack, E.P. *J. Am. Chem. Soc.* ***1987***, *109*, 2213.
[76] See Back, R.A. *Can. J. Chem.* ***1983***, *61*, 916.
[77] See Jackson, R.A.; Townson, M. *J. Chem. Soc., Perkin Trans. 2* ***1980***, 1452.
[78] See Ingold, K.U.; Roberts, B.P. *Free-Radical Substitution Reactions*, Wiley, NY, ***1971***.

The principal reason for this preference is steric. A univalent atom is much more exposed to attack by the incoming radical than an atom with a higher valence. Also, in many cases, abstraction of a univalent atom is energetically more favored. For example, in the reaction given above, a C_2H_5—H bond is broken ($D = 100$ kcal mol^{-1}, 419 kJ mol^{-1}, from Table 5.3) whichever pathway is taken, but in the former case an H—Cl bond is formed ($D = 103$ kcal mol^{-1}, 432 kJ mol^{-1}) while in the latter case it is a C_2H_5—Cl bond ($D = 82$ kcal mol^{-1}, 343 kJ mol^{-1}). Thus the first reaction is favored because it is exothermic by 3 kcal mol^{-1} (100–103) [13 kJ mol^{-1} (419–432)], while the latter is endothermic by 18 kcal mol^{-1} (100–82) [76 kJ mol^{-1} (419–343)].[79] However, the steric reason is more important, because even in cases where ΔH is not very different for the two possibilities, the univalent atom is chosen.[80] *Ab initio* studies have probed the transition structures for radical hydrogen abstractions.[81]

Most studies of aliphatic reactivity have been made with hydrogen as the leaving atom and chlorine atoms as the abstracting species.[82] In these reactions, every hydrogen atom in the substrate is potentially replaceable and mixtures of several products may be obtained. However, the abstracting radical is not totally unselective, and some positions on a molecule lose hydrogen more easily than others. *Ab initio* studies have studied the factors controlling hydrogen abstraction by radicals.[83] For hydrogen abstraction by the *tert*-butoxy radical (*t*-Bu—O•) the factors that influence rate in their order of importance are structure of the radical > substituent effects[84] > solvent effects.[85] The position of attack will be discussed under several headings.[86]

1. *Alkanes*. If a tertiary hydrogen atom is present in an alkane, it is preferentially abstracted by almost any radical, with secondary hydrogen atoms being next preferred. This is in the same order as *D* values for these types of C—H bonds (Table 5.3). The extent of the preference depends on the selectivity of the abstracting radical and on the temperature. At high temperatures, and in the gas phase, selectivity for attack of Cl• at 3° > 2° > 1° hydrogen decreases,[87] as might be expected.[88] An example of the effect of radical selectivity is the comparison of fluorine atoms with bromine atoms. For the former, the ratio of primary to tertiary abstraction (of hydrogen) is 1:1.4, while for the less reactive bromine atom this ratio is 1:1600. With certain large radicals there is a steric factor that may change the selectivity pattern.

[79] The parameter ΔH for a free-radical abstraction reaction can be regarded simply as the difference in *D* values for the bond being broken and the one formed.

[80] Giese, B.; Hartung, J. *Chem. Ber.* ***1992***, *125*, 1777.

[81] Eksterowicz, J.E.; Houk, K.N. *Tetrahedron Lett.* ***1993***, *34*, 427; Damm, W.; Dickhaut, J.; Wetterich, F.; Giese, B. *Tetrahedron Lett.* ***1993***, *34*, 431.

[82] See Roberts, B.P.; Steel, A.J. *Tetrahedron Lett.* ***1993***, *34*, 5167. See Tanko, J.M.; Blackert, J.F. *J. Chem. Soc., Perkin Trans. 2* ***1996***, 1775.

[83] Zavitsas, A.A. *J. Chem. Soc., Perkin Trans. 2* ***1998***, 499.

[84] See Wen, Z.; Li, Z.; Shang, Z.; Cheng, J.-P. *J. Org. Chem.* ***2001***, *66*, 1466.

[85] Kim, S.S.; Kim, S.Y.; Ryou, S.S.; Lee, C.S.; Yoo, K.H. *J. Org. Chem.* ***1993***, *58*, 192.

[86] See Tedder, J.M. *Tetrahedron* ***1982***, *38*, 313; Kerr, J.A. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 18, Elsevier, NY, ***1976***, pp. 39–109; Russell, G.A. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 275–331; Rüchardt, C. *Angew. Chem. Int. Ed.* ***1970***, *9*, 830; Poutsma, M.L. *Methods Free-Radical Chem.* ***1969***, *1*, 79; Davidson, R.S. *Q. Rev. Chem. Soc.* ***1967***, *21*, 249; Pryor, W.A.; Fuller, D.L.; Stanley, J.P. *J. Am. Chem. Soc.* ***1972***, *94*, 1632.

[87] Hass, H.B.; McBee, E.T.; Weber, P. *Ind. Eng. Chem.* ***1936***, *28*, 333.

[88] With phenyl radicals: Kopinke, F.; Zimmermann, G.; Anders, K. *J. Org. Chem.* ***1989***, *54*, 3571.

For example, in the photochemical chlorination of 2-methylbutane in H_2SO_4 with *N*-chloro-di-*tert*-butylamine and *N*-chloro-*tert*-butyl-*tert*-pentylamine, the primary hydrogen atoms are abstracted 1.7 times *faster* than the tertiary hydrogen.[89] In this case, the attacking radicals (the radical ions $R_2NH^{\bullet+}$, see **14-1**) are bulky enough for steric hindrance to become a major factor.

Cyclopropylcarbinyl radicals (**11**) are alkyl radicals, but because of the cyclopropane ring with its relatively weak bonds, they undergo rapid ring opening to give butenyl radicals.[90] The rate constant for this process has been measured by picosecond radical kinetic techniques to be in the range of 10^7 M^{-1} s^{-1} for the parent[91] to 10^{10} M^{-1} s^{-1} for substituted derivatives.[92]

11

Cyclobutylcarbinyl radicals undergo the cyclobutylcarbinyl to 4-pentenyl radical process,[93] but examples are generally limited to the parent system and phenyl-substituted derivatives.[94] Cyclization of the 4-pentenyl radical is usually limited to systems where a stabilized radical can be formed.[95] The effect of substituents has been studied.[96] Note that 2-aziridinylmethyl radicals also undergo ring opening via C—N or C—C cleavage to give a nitrogen or carbon radical respectively, and the ring opening is strongly influenced by substituents at C1 rather than those on nitrogen.[97] An alkyl substituent at C1 generally leads to C—N cleavage, whereas a carbonyl substituent at C1 usually favors C—C cleavage.[97]

The rates of the ring-opening reaction of **5** and other substrates[98] have been determined using an indirect method for the calibration[99] of fast radical reactions, applicable for radicals with lifetimes as short as 1 ps.[100] This "radical clock"[101] method is based on the use of pyridine-2-thione-*N*-oxycarbonyl esters as radical precursors and radical trapping by the highly reactive thiophenol and benzeneselenol.[102] A number of radical clock substrates are known.[103] Other radical clock processes include: (i)

[89] Deno, N.C.; Fishbein, R.; Wyckoff, J.C. *J. Am. Chem. Soc.* ***1971***, *93*, 2065. See Dneprovskii, A.N.; Mil'tsov, S.A. *J. Org. Chem. USSR* ***1988***, *24*, 1836.

[90] Nonhebel, D.C. *Chem. Soc. Rev.* ***1993***, *22*, 347. For a discussion of solvent/counterion reorganization, see Tanko, J.M.; Gillmore, J.G.; Friedline, R.; Chahma, M. *J. Org. Chem.* ***2005***, *70*, 4170.

[91] Engel, P.S.; He, S.-L.; Banks, J.T.; Ingold, K.U.; Lusztyk, J. *J. Org. Chem.* ***1997***, *62*, 1210.

[92] Toy, P.H.; Newcomb, M. *J. Org. Chem.* ***1998***, *63*, 8609. See Martinez, F.N.; Schlegel, H.B.; Newcomb, M. *J. Org. Chem.* ***1998***, *63*, 3618 for *ab initio* studies to determine rate constants.

[93] See Jin, J.; Newcomb, M. *J. Org. Chem.* ***2007***, *72*, 5098. For a discussion of ring opening versus ring expansion in bicyclic cyclocarbinyl radicals, see Shi, J.; Chong, S.-S.; Fu, Y.; Guo, Q.-X.; Liu, L. *J. Org. Chem.* ***2008***, *73*, 974.

[94] Choi, S.-Y.; Horner, J.H.; Newcomb, M. *J. Org. Chem.* ***2000***, *65*, 4447.

[95] Cerreti, A.; D'Annibale, A.; Trogolo, C.; Umani, F. *Tetrahedron Lett.* ***2000***, *41*, 3261.

[96] Baker, J.M.; Dolbier Jr., W.R. *J. Org. Chem.* ***2001***, *66*, 2662.

[97] Wang, Y.-M.; Fu, Y.; Liu, L.; Guo, Q.-X. *J. Org. Chem.* ***2005***, *70*, 3633.

[98] Engel, P.S.; He, S.-L.; Banks, J.T.; Ingold, K.U.; Lusztyk, J. *J. Org. Chem.* ***1997***, *62*, 1210, 5656.

[99] See Hollis, R.; Hughes, L.; Bowry, V.W.; Ingold, K.U. *J. Org. Chem.* ***1992***, *57*, 4284.

[100] Newcomb, M.; Toy, P.H. *Acc. Chem. Res.* ***2000***, *33*, 449. See Horn, A.H.C.; Clark, T. *J. Am. Chem. Soc.* ***2003***, *125*, 2809.

[101] See Griller, D.; Ingold, K.U. *Acc. Chem. Res.* ***1980***, *13*, 317.

[102] Newcomb, M.; Johnson, C.C.; Manek, M.B.; Varick, T.R. *J. Am. Chem. Soc.* ***1992***, *114*, 10915.

[103] See Kumar, D.; de Visser, S.P.; Sharma, P.K.; Cohen, S.; Shaik, S. *J. Am. Chem. Soc.* ***2004***, *126*, 1907.

racemization of radicals with chiral conformations,[104] (ii) one-carbon ring expansion in cyclopentanones,[105] norcarane, and spiro[2,5]octane,[106] (iii) α- and β-thujone radical rearrangements,[107] (iv) cyclopropylcarbinyl radicals or alkoxycarbonyl radicals containing stabilizing substituents,[108] and (v) cyclobutylcarbinyl radicals.[109] *Ab initio* and density functional theory have been used to study radical clock reactions.[110]

2. *Alkenes*. When the substrate molecule contains a double bond, treatment with chlorine or bromine usually leads to addition rather than substitution, as described in **15-35**. However, for other radicals (and even for chlorine or bromine atoms when they react by hydrogen transfer) the position of attack is at the allylic carbon. Vinylic hydrogen atoms are practically never abstracted, and allylic hydrogen atoms are greatly preferred to other positions of the molecule. Allylic hydrogen abstraction from a cyclic alkenes is usually faster than abstraction from a acyclic alkenes.[111] This is generally attributed[112] to resonance stabilization of an allylic radical:

$$\text{C=C—C}\bullet \leftrightarrow \bullet\text{C—C=C}$$

As might be expected, allylic rearrangements (see **14-6**) are common in these cases.[113]

3. *Alkyl Side Chains of Aromatic Rings*. The preferential position of attack on a side chain is usually the one directly attached to the ring (the benzylic position). Both for active radicals, such as chlorine and phenyl, and for more selective ones, such as bromine, hydrogen exchange is faster than that at a primary carbon. For active radicals, hydrogen exchange at the benzylic position is slower than for tertiary positions, while for the selective ones it is faster. Two or three aryl groups on a carbon activate its hydrogen atoms even more, as would be expected from the resonance involved. These statements can be illustrated by the abstraction ratios shown:[114]

	Me—H	$MeCH_2$—H	Me_2CH—H	Me_3C—H	$PhCH_2$—H	Ph_2CH—H	Ph_3C—H
Br	0.0007	1	220	19,400	64,000	1.1×10^6	6.4×10^6
Cl	0.004	1	4.3	6.0	1.3	2.6	9.5

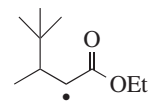
However, many anomalous results have been reported for these substrates. The benzylic position is not always the most favored. One thing certain is that *aromatic* hydrogen atoms are seldom abstracted if there are aliphatic ones to compete. (Note from Table 5.3, that *D* for Ph—H is higher than that for any C—H bond in an alkyl

[104] Rychnovsky, S.D.; Hata, T.; Kim, A.I.; Buckmelter, A.J. *Org. Lett.* ***2001***, *3*, 807.
[105] Chatgilialoglu, C.; Timokhin, V.I.; Ballestri, M. *J. Org. Chem.* ***1998***, *63*, 1327.
[106] See Auclair, K.; Hu, Z.; Little, D.M.; Ortiz de Montellano, P.R.; Groves, J.T. *J. Am. Chem. Soc.* ***2002***, *124*, 6020.
[107] He, X.; Ortiz de Montellano, P.R. *J. Org. Chem.* ***2004***, *69*, 5684.
[108] Beckwith, A.L.J.; Bowry, V.W. *J. Am. Chem. Soc.* ***1994***, *116*, 2710. See Cooksy, A.L.; King, H.F.; Richardson, W.H. *J. Org. Chem.* ***2003***, *68*, 9441.
[109] Jin, J.; Newcomb, M. *J. Org. Chem.* ***2008***, *73*, 4740.
[110] Jäger, C.M.; Hennemann, M.; Mieszała, A.; Clark, T. *J. Org. Chem.* ***2008***, *73*, 1536.
[111] Rothenberg, G.; Sasson, Y. *Tetrahedron* ***1998***, *54*, 5417.
[112] See, however, Kwart, H.; Brechbiel, M.; Miles, W.; Kwart, L.D. *J. Org. Chem.* ***1982***, *47*, 4524.
[113] See Wilt, J.W. in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 458–466.
[114] Russell, G.A. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, p. 289.

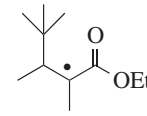
group.) Several $\sigma^{\bullet}$ scales (similar to the σ, σ^{+}, and σ^{-} scales discussed in Chapter 9) have been developed for benzylic radicals.[115]

4. *Compounds Containing Electron-Withdrawing Substituents*. In halogenations, electron-withdrawing groups greatly deactivate adjacent positions. Compounds of the type $Z{-}CH_2{-}CH_3$ are attacked predominantly or exclusively at the β position when Z is CO_2H, COCl, COOR, SO_2Cl, or CX_3. Compounds such as acetic acid and acetyl chloride are not attacked at all, in sharp contrast to electrophilic halogenations (**12-4** to **12-6**), where *only* the α position is substituted. This deactivation of α positions is also at variance with the expected stability of the resulting radicals, since they would be expected to be stabilized by resonance similar to that for allylic and benzylic radicals. This behavior is a result of the polar transition states discussed in Sec. 14.A.ii. Halogen atoms are electrophilic radicals and look for positions of high electron density. Hydrogen atoms on carbon atoms next to electron-withdrawing groups have low electron densities (because of the field effect of Z) and are therefore shunned. Radicals that are not electrophilic do not display this behavior. For example, the methyl radical is essentially nonpolar and does not avoid positions next to electron-withdrawing groups; relative rates of abstraction at the C-2 and C-3 carbons of propionic acid are (i) 1 for C-2 and 78 for C-3 (Me•) and (ii) 1 for C-2 and 0.02 for C-3 (Cl•).[116]

   It is possible to generate radicals adjacent to electron-withdrawing groups. Radical **12** can be generated and it undergoes coupling reactions with little selectivity. When **13** is generated, it rapidly disproportionates rather than couples, giving the corresponding alkene and alkane.[117] Such radicals have also been shown to have a conformational preference for orientation of the orbital containing the single electron. In such cases, hydrogen abstraction proceeds with good stereoselectivity.[118]



12



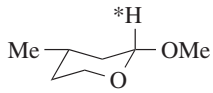
13

Some radicals, for example, *tert*-butyl,[119] benzyl,[120] and cyclopropyl,[121] are *nucleophilic* (they tend to abstract electron-poor hydrogen atoms).[122] The phenyl radical appears to have a very small degree of nucleophilic character.[123] For longer chains, the field effect continues, and the β position is also deactivated to attack by halogen, though much less so than the α position. It was noted previously (in

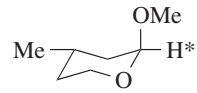
[115] See Fisher, T.H.; Dershem, S.M.; Prewitt, M.L. *J. Org. Chem.* ***1990***, *55*, 1040.
[116] Russell, G.A. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, p. 311.
[117] Porter, N.A.; Rosenstein, I.J. *Tetrahedron Lett.* ***1993***, *34*, 7865.
[118] Giese, B.; Damm, W.; Wetterich, F.; Zeitz, H.-G. *Tetrahedron Lett.* ***1992***, *33*, 1863.
[119] Pryor, W.A.; Tang, F.Y.; Tang, R.H.; Church, D.F. *J. Am. Chem. Soc.* ***1982***, *104*, 2885; Dütsch, H.R.; Fischer, H. *Int. J. Chem. Kinet.* ***1982***, *14*, 195.
[120] Clerici, A.; Minisci, F.; Porta, O. *Tetrahedron* ***1973***, *29*, 2775.
[121] Stefani, A.; Chuang, L.; Todd, H.E. *J. Am. Chem. Soc.* ***1970***, *92*, 4168.
[122] For nucleophilicity and electrophilicity indices developed for radicals, see De Vleeschouwer, F.; van Speybroeck, V.; Waroquier, M.; Geerlings, P.; De Proft, F. *Org. Lett.* ***2007***, *9*, 2721.
[123] Suehiro, T.; Suzuki, A.; Tsuchida, Y.; Yamazaki, J. *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 3324.

Sec. 14.A.ii) that abstraction of an α-hydrogen atom from ring-substituted toluenes can be correlated by the *Hammett equation*.

5. *Stereoelectronic Effects*. In Sec. 16.A.i, category 4, there is an example of a stereoelectronic effect. It has been shown that such effects are important where a hydrogen is abstracted from a carbon adjacent to a C—O or C—N bond. In such cases, hydrogen is abstracted from C—H bonds that have a relatively small dihedral angle (≈30°) with the unshared orbitals of the O or N much more easily than from those with a large angle (≈90°). For example, the starred hydrogen of **14** was abstracted about 8 times faster than the starred hydrogen of **15**.[124]



14



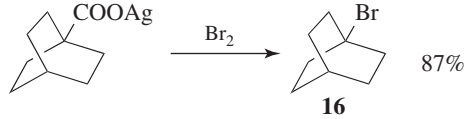
15

The presence of an OR or SiR_3 substituent β to the carbon bearing the radical accelerates the rate of halogen abstraction.[125] Tertiary arylcarbinyloxy radicals undergo β scission to give a ketone.[126] Abstraction of a halogen has been studied much less,[127] but the order of reactivity is RI > RBr > RCl ≫ RF.

There are now many cases where free-radical reactions are promoted by transition metals.[128]

14.B.ii. Reactivity at a Bridgehead[129]

Many free-radical reactions have been observed at bridgehead carbons, for example, the formation of bromide **16** (see **14-24**),[130] demonstrating that the free radical need not be planar. However, treatment of norbornane with sulfuryl chloride and benzoyl peroxide gave mostly 2-chloronorbornane, although the bridgehead position is tertiary.[131] So, while bridgehead free-radical substitution is possible, it is not preferred, presumably because of the strain involved.[132]

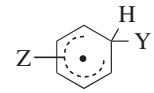


16

[124] Hayday, K.; McKelvey, R.D. *J. Org. Chem.* ***1976***, *41*, 2222. Also see Griller, D.; Bunce, N.J.; Cheung, H.K.Y.; Langshaw, J. *J. Org. Chem.* ***1986***, *51*, 5421.
[125] Roberts, B.P.; Steel, A.J. *J. Chem. Soc., Perkin Trans. 2* ***1994***, 2411.
[126] Bietti, M.; Gente, G.; Salamone, M. *J. Org. Chem.* ***2005***, *70*, 6820.
[127] See Danen, W.C. *Methods Free-Radical Chem.* ***1974***, *5*, 1.
[128] Iqbal, J.; Bhatia, B.; Nayyar, N.K. *Chem. Rev.* ***1994***, *94*, 519.
[129] See Bingham, R.C.; Schleyer, P.v.R. *Fortschr. Chem. Forsch.* ***1971***, *18*, 1 (see pp. 79–81).
[130] Grob, C.A.; Ohta, M.; Renk, E.; Weiss, A. *Helv. Chim. Acta* ***1958***, *41*, 1191.
[131] Roberts, J.D.; Urbanek, L.; Armstrong, R. *J. Am. Chem. Soc.* ***1949***, *71*, 3049. See also, Kooyman, E.C.; Vegter, G.C. *Tetrahedron* ***1958***, *4*, 382; Walling, C.; Mayahi, M.F. *J. Am. Chem. Soc.* ***1959***, *81*, 1485.
[132] See Koch, V.R.; Gleicher, G.J. *J. Am. Chem. Soc.* ***1971***, *93*, 1657.

14.B.iii. Reactivity in Aromatic Substrates

Free-radical substitution at an aromatic carbon seldom takes place by a mechanism in which a hydrogen atom is abstracted to give an aryl radical. Reactivity considerations here are similar to those in Chapters 11 and 13; i.e., which position on the ring will be attacked to give the intermediate, **17**.



17

The obvious way to obtain this information is to carry out reactions with various Z groups and to analyze the products for percent *ortho*, *meta*, and *para* isomers, as has so often been done for electrophilic substitution. However, this procedure is much less accurate in the case of free-radical substitutions because of the many side reactions. It may be, for example, that in a given case the *ortho* position is more reactive than the *para*, but the intermediate from the *para* attack may go on to product while that from *ortho* attack gives a side reaction. In such a case, analysis of the three products does not give a true picture of which position is most susceptible to attack. The following generalizations can nevertheless be drawn, although there has been much controversy over just how meaningful such conclusions are.[133]

1. All substituents increase reactivity at *ortho* and *para* positions over that of benzene. There is no great difference between electron-donating and electron-withdrawing groups.
2. Reactivity at *meta* positions is usually similar to that of benzene, perhaps slightly higher or lower. This fact, coupled with the preceding one, means that all substituents are activating and *ortho*/*para* directing; none are deactivating or (chiefly) *meta* directing.
3. Reactivity at *ortho* positions is usually somewhat greater than at *para* positions, except where a large group decreases *ortho* reactivity for steric reasons.
4. In direct competition, electron-withdrawing groups exert a somewhat greater influence than electron-donating groups. Arylation of *para*-disubstituted compounds XC_6H_4Y showed that substitution *ortho* to the group X became increasingly preferred as the electron-withdrawing character of X increases (with Y held constant).[134] The increase could be correlated with the Hammett σ_p values for X.
5. Substituents have a much smaller effect than in electrophilic or nucleophilic substitution; hence the partial rate factors (Sec. 11.C) are not great.[135] Partial rate factors for a few groups are given in Table 14.1.[136]
6. Although hydrogen is the leaving group in most free-radical aromatic substitutions, *ipso* attack (Sec. 11.B.iii) and *ipso* substitution (e.g., with Br, NO_2, or CH_3CO as the leaving group) have been found in certain cases.[137]

[133] Vidal, S.; Court, J.; Bonnier, J. *J. Chem. Soc., Perkin Trans. 2* ***1973***, 2071; Tezuka, T.; Ichikawa, K.; Marusawa, H.; Narita, N. *Chem. Lett.* ***1983***, 1013.
[134] Davies, D.I.; Hey, D.H.; Summers, B. *J. Chem. Soc. C* ***1970***, 2653.
[135] For a quantitative treatment, see Charton, M.; Charton, B. *Bull. Soc. Chim. Fr.* ***1988***, 199.
[136] Davies, D.I.; Hey, D.H.; Summers, B. *J. Chem. Soc. C* ***1971***, 2681.
[137] See Traynham, J.G. *J. Chem. Educ.* ***1983***, *60*, 937; *Chem. Rev.* ***1979***, *79*, 323; Tiecco, M. *Acc. Chem. Res.* ***1980***, *13*, 51; *Pure Appl. Chem.* ***1981***, *53*, 239.

TABLE 14.1 Partial rate factors for attack of substituted benzenes by phenyl radicals generated from Bz_2O_2 (Reaction 13-7)[136]

	Partial rate factor		
Z	***o***	***m***	***p***
H	1	1	1
NO_2	5.50	0.86	4.90
CH_3	4.70	1.24	3.55
CMe_3	0.70	1.64	1.81
Cl	3.90	1.65	2.12
Br	3.05	1.70	1.92
MeO	5.6	1.23	2.31

Reproduced from Davies, D.I.; Hey, D.H.; Summers, B. *J. Chem. Soc. C* ***1971***, 2681, with permission from the Royal Society of Chemistry.

Note that interconvertible 1,4-hydrogen atom shifts are possible in radicals derived from biaryls.[138]

14.B.iv. Reactivity in the Attacking Radical[139]

As seen above, some radicals are much more selective than others (Sec. 14.B.i). The bromine atom is so selective that when only primary hydrogen atoms are available, as in 2,2-dimethylpropane or *tert*-butylbenzene, the reaction is slow. Also, 2-methylpropane can be selectively brominated to give *tert*-butyl bromide in high yields. However, toluene reacts with bromine atoms instantly. Bromination of other alkylbenzenes, for example ethylbenzene and cumene (isopropylbenzene), takes place exclusively at the α position,[140] emphasizing the selectivity of Br•. The dissociation energy *D* of the C—H bond is more important for radicals of low reactivity than for highly reactive radicals, since the energy required for bond breaking in the transition state is greater. Thus, bromine shows a greater tendency than chlorine to attack α to an electron-withdrawing group because the energy of the C—H bond there is lower than in other places in the molecule.

Some radicals, for example, triphenylmethyl, are so unreactive that they abstract hydrogen atoms very poorly, if at all. Common free radicals have been discussed for their selectivity and approximate order of reactivity.[141] The bromine radical is nearly 708 times more reactive than the chlorine radical for removal of a tertiary alkyl hydrogen atom and is 4500 times more reactive than the fluorine radical. The methyl radical is 5.6 times more reactive than the chlorine radical, and the methoxy radical is 3 times more reactive than the chlorine radical for removal of a tertiary hydrogen atom. The activation energies for the reaction *i*-Pr• show that it is less active than Me• and *t*-Bu• is even less reactive.[142] It has been mentioned that some free radicals (e.g., chloro) are electrophilic and some (e.g., *tert*-butyl) are nucleophilic. It must be borne in mind that these tendencies are relatively slight compared with the electrophilicity of a positive ion or the nucleophilicity of a negative ion. The predominant character of a free radical is neutral, whether it has slight electrophilic or nucleophilic tendencies.

[138] Peng, L.; Scott, L.T. *J. Am. Chem. Soc.* ***2005***, *127*, 16518.
[139] See Trotman-Dickenson, A.F. *Adv. Free Radical Chem.* ***1965***, *1*, 1; Gray, P.; Herod, A.A.; Jones, A. *Chem. Rev.* ***1971***, *71*, 247.
[140] Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***, p. 97.
[141] Trotman-Dickenson, A.F. *Adv. Free Radical Chem.* ***1965***, *1*, 1.
[142] Kharasch, M.S.; Hambling, J.K.; Rudy, T.P. *J. Org. Chem.* ***1959***, *24*, 303.

14.B.v. The Effect of Solvent on Reactivity[143]

As noted earlier, the solvent usually has little effect on free-radical substitutions in contrast to ionic substitution reactions: indeed, reactions in solution are often quite similar in character to those in the gas phase, where there is no solvent at all. However, in certain cases the solvent *can* make an appreciable difference.

Chlorination of 2,3-dimethylbutane in aliphatic solvents gave ~60% $(CH_3)_2CHCH(CH_3)CH_2Cl$ and 40% $(CH_3)_2CHCCl(CH_3)_2$, while in aromatic solvents the ratio became about 10 : 90.[144] This result is attributed to complex formation between the aromatic solvent and the chlorine atom that makes the chlorine more selective.[145] This type of effect is not found in cases where the differences in ability to abstract the atom are caused by field effects of electron-withdrawing groups (Sec. 14.B.i). In such cases, aromatic solvents make little difference.[146] The aryl–Cl complex has been detected[147] as a very short-lived species by observation of its visible spectrum in the pulse radiolysis of a solution of benzene in CCl_4.[148]

Differences caused by solvents have also been reported in reactions of other radicals.[149] Some of the anomalous results obtained in the chlorination of aromatic side chains (Sec. 14.B.i) can also be explained by this type of complexing, in this case not with the solvent but with the reacting species.[150] Much smaller, but real, differences in selectivity have been found when the solvent in the chlorination of 2,3-dimethylbutane is changed from an alkane to CCl_4.[151] However, these differences are not caused by formation of a complex between Cl• and the solvent. There are cases, however, where the rate of reaction for trapping a radical depends on the polarity of the solvent, particularly in water.[152]

14.C. REACTIONS

The reactions in this chapter are classified according to leaving group.

14.C.i. Hydrogen as Leaving Group

A. Substitution by Halogen

14-1 Halogenation at an Alkyl Carbon[153]

$$\text{R—H} + \text{Halogenating agent} \longrightarrow \text{R—X}$$

[143] Reichardt, C.; Welton, T. *Solvents and Solvent Effects in Organic Chemisry*, 4th ed., Wiley-VCH, Weiheim, ***2011***, pp. 220–235; Martin, J.C. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 493–524; Huyser, E.S. *Adv. Free Radical Chem.* ***1965***, *1*, 77.

[144] Russell, G.A. *J. Am. Chem. Soc.* ***1958***, *80*, 4987, 4997, 5002; *J. Org. Chem.* ***1959***, *24*, 300.

[145] See also, Ingold, K.U.; Lusztyk, J.; Raner, K.D. *Acc. Chem. Res.* ***1990***, *23*, 219.

[146] Nagai, T.; Horikawa, Y.; Ryang, H.S.; Tokura, N. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 2771.

[147] See, however, Skell, P.S.; Baxter III, H.N.; Tanko, J.M.; Chebolu, V. *J. Am. Chem. Soc.* ***1986***, *108*, 6300. For arguments against this proposal, see Walling, C. *J. Org. Chem.* ***1988***, *53*, 305; Aver'yanov, V.A.; Shvets, V.F.; Semenov, A.O. *J. Org. Chem. USSR* ***1990***, *26*, 1261.

[148] Bühler, R.E. *Helv. Chim. Acta* ***1968***, *51*, 1558; Raner, K.D.; Lusztyk, J.; Ingold, K.U. *J. Phys. Chem.* ***1989***, *93*, 564.

[149] Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M.; Giordano, C. *J. Org. Chem.* ***1987***, *52*, 730.

[150] See Newkirk, D.D.; Gleicher, G.J. *J. Am. Chem. Soc.* ***1974***, *96*, 3543 and references cited therein.

[151] See Raner, K.D.; Lusztyk, J.; Ingold, K.U. *J. Org. Chem.* ***1988***, *53*, 5220.

[152] Tronche, C.; Martinez, F.N.; Horner, J.H.; Newcomb, M.; Senn, M.; Giese, B. *Tetrahedron Lett.* ***1996***, *37*, 5845.

[153] For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley-VCH, NY, ***1999***, pp. 611–617.

Alkanes can be chlorinated or brominated by treatment with chlorine or bromine in the presence of visible or UV light, or with heat.[154] These reactions require an added chemical reagent as the radical chain initiator, or exposure to light, or higher temperatures.[155] The reaction can also be applied to alkyl chains containing many functional groups. The chlorination reaction is usually not useful for preparative purposes precisely because it is so general: not only does substitution take place at virtually every alkyl carbon in the molecule, but di- and polychloro substitution almost invariably occur even if there is a large molar ratio of substrate to halogen. A visible light-induced monochlorination of cyclohexane with NaCl and Oxone in H_2O/CF_3CH_2OH gave chlorocyclohexane.[156] Note that benzylic halogenation, such as the *Wohl-Ziegler bromination*, is discussed in **14-3**.

When functional groups are present, the principles are those outlined in Sec. 14.B.i. Tertiary carbons are most likely to be functionalized and primary carbons least likely. Favored positions are those α to aromatic rings, while positions α to electron-withdrawing groups are least likely to be substituted. Hydrogen atoms α to an OR group are very readily replaced. Nevertheless, mixtures are nearly always obtained. Of course, if a *mixture* of chlorides is wanted, the reaction is usually quite satisfactory. For obtaining pure compounds, the chlorination reaction is essentially limited to substrates with only one type of replaceable hydrogen (e.g., ethane, cyclohexane, 2,2-dimethylpropane). With methylbenzenes and other substrates with methyl groups on aromatic rings, few cases are known where halogen atoms substitute at an aromatic position.[157] Of course, ring substitution *does* take place in the presence of a positive ion-forming catalyst (**11-10**). In addition to mixtures of various alkyl halides, traces of other products are obtained. These include H_2, alkenes, higher alkanes, lower alkanes, and halogen derivatives of these compounds. Solvent plays an important role in this process.[158]

The bromine atom is much more selective than the chlorine atom. As indicated in Sec. 14.B.iv, it is often possible to brominate tertiary and benzylic positions selectively. High regioselectivity can also be obtained where the neighboring-group mechanism (Sec. 14.A.iv) can operate. Reductive bromine atom transfer reactions have been reported.[159] Photobromination using molecular bromine has been done using flow conditions (Sec. 7.D).[160]

As already mentioned, halogenation can be performed with chlorine or bromine. Fluorine has also been used,[161] but seldom, because it is too reactive and hard to control.[162]

[154] See Poutsma, M.L. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 159–229; Huyser, E.S. in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 1, Wiley, NY, ***1973***, pp. 549–607; Poutsma, M.L. *Methods Free-Radical Chem.* ***1969***, *1*, 79 (chlorination); Thaler, W.A. *Methods Free-Radical Chem.* ***1969***, *2*, 121 (bromination).

[155] Hill, C.L. *Activation and Functionalization of Alkanes*, Wiley, NY, ***1989***.

[156] Zhao, M.; Lu, W. *Org. Lett.* ***2017***, *19*, 4560.

[157] Dermer, O.C.; Edmison, M.T. *Chem. Rev.* ***1957***, *57*, 77 (pp. 110–112). See Kooyman, E.C. *Adv. Free Radical Chem.* ***1965***, *1*, 137.

[158] Dneprovskii, A.S.; Kuznetsov, D.V.; Eliseenkov, E.V.; Fletcher, B.; Tanko, J.M. *J. Org. Chem.* ***1998***, *63*, 8860.

[159] Sumino, S.; Fusano, A.; Ryu, I. *Org. Lett.* ***2013***, *15*, 2826.

[160] Manabe, Y.; Kitawaki, Y.; Nagasaki, M.; Fukase, K.; Matsubara, H.; Hino, Y.; Fukuyama, T.; Ryu, I. *Chem. Eur. J.* ***2014***, *20*, 12750.

[161] Rozen, S. *Acc. Chem. Res.* ***1988***, *21*, 307; Purrington, S.T.; Kagen, B.S.; Patrick, T.B. *Chem. Rev.* ***1986***, *86*, 997 (pp. 1003–1005); Hudlicky, M. *The Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, ***1976***, pp. 67–91. For descriptions of the apparatus necessary for handling F2, see Vypel, H. *Chimia* ***1985***, *39*, 305.

[162] See Rozhkov, I.N. in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, ***1983***, pp. 805–825; Lagow, R.J.; Margrave, J.L. *Prog. Inorg. Chem.* ***1979***, *26*, 161. See also, Huang, H.; Lagow, R.J. *Bull. Soc. Chim. Fr.* ***1986***, 993.

The reactions of fluorinated organic radicals have been studied.[163] Fluorination often breaks carbon chains down into smaller units, a side reaction that sometimes becomes troublesome in chlorinations too. Fluorination[164] has been achieved by the use of chlorine trifluoride ClF_3 at −75 °C.[165] For example, cyclohexane gave 41% fluorocyclohexane and methylcyclohexane gave 47% 1-fluoro-1-methylcyclohexane. Fluoroxytrifluoromethane CF_3OF fluorinates tertiary positions of certain molecules in good yields with high regioselectivity.[166] Fluorine at −70 °C, diluted with N_2,[167] and bromine trifluoride at 25–35 °C[168] are also highly regioselective for tertiary positions. These reactions probably have an electrophilic mechanism[169] not a free-radical mechanism. In fact, the success of the F_2 reactions depends on the suppression of free-radical pathways, by dilution with an inert gas, by working at low temperatures, and/or by the use of radical scavengers. Fluorination of 1,3-dicarbonyl compounds and activated aromatic compounds was achieved under solvent-free conditions using Selectfluor/TEDA/BF_4.[170]

Iodine can be used if the activating light has a wavelength of 184.9 nm,[171] but iodinations using I_2 alone are seldom attempted, largely because the HI formed reduces the alkyl iodide. The direct free-radical halogenation of aliphatic hydrocarbons with iodine is significantly endothermic relative to the other halogens, and the requisite chain reaction does not occur.[172] The reaction of an alkane with *tert*-butylhypoiodite (*t*-BuOI) at 40 °C gave the iodoalkane in good yield.[173] The reaction of alkanes with iodine and $PhI(OAc)_2$ generates the iodoalkane.[174] A radical protocol was developed using CI_4 with base. For example, cyclohexane could be iodinated with CI_4 in the presence of powdered NaOH.[175] The reaction led to the use of iodoform on solid NaOH as the iodination reagent of choice. A base-induced bromination has been reported. Hydrogen peroxide/HBr in water has been used for radical bromination.[176]

When chlorination is carried out with *N*-haloamines and sulfuric acid (catalyzed by either UV light or metal ions), selectivity is much greater than with other reagents.[177] In particular, alkyl chains are chlorinated with high regioselectivity at the position next to the end of the chain (the $\omega - 1$ position).[178] Some typical selectivity values are given here:[179]

[163] Vallejo, S.B.; Postigo, A. *Eur. J. Org. Chem.* ***2012***, 1889.
[164] German, L.; Zemskov, S. *New Fluorinating Agents in Organic Synthesis*, Springer, NY, ***1989***.
[165] Brower, K.R. *J. Org. Chem.* ***1987***, *52*, 798.
[166] Alker, D.; Barton, D.H.R.; Hesse, R.H.; Lister-James, J.; Markwell, R.E.; Pechet, M.M.; Rozen, S.; Takeshita, T.; Toh, H.T. *Nouv. J. Chem.* ***1980***, *4*, 239.
[167] Rozen, S.; Gal, C. *J. Org. Chem.* ***1988***, *53*, 2803. See Ref. 153.
[168] Boguslavskaya, L.S.; Kartashov, A.V.; Chuvatkin, N.N. *J. Org. Chem. USSR* ***1989***, *25*, 1835.
[169] See, for example, Rozen, S.; Gal, C. *J. Org. Chem.* ***1987***, *52*, 2769.
[170] Stavber, G.; Zupan, M.; Stavber, S. *Tetrahedron Lett.* ***2007***, *4*8, 2671.
[171] Gover, T.A.; Willard, J.E. *J. Am. Chem. Soc.* ***1960***, *82*, 3816.
[172] Liguori, L.; Bjørsvik, H.-R.; Bravo, A.; Fontana, R.; Minisci, F. *Chem. Commun.* ***1997***, 1501.
[173] Montoro, R.; Wirth, T. *Org. Lett.* ***2003***, *5*, 4729.
[174] Barluenga, J.; González-Bobes, F.; González, J.M. *Angew. Chem. Int. Ed.* ***2002***, *41*, 2556.
[175] Schreiner, P.R.; Lauenstein, O.; Butova, E.D.; Fokin, A.A. *Angew. Chem. Int. Ed.* ***1999***, *38*, 2786.
[176] Podgoršek, A.; Stavber, S.; Zupan, M.; Iskra, J. *Tetrahedron Lett.* ***2006***, *47*, 7245.
[177] See Minisci, F. *Synthesis* ***1973***, 1; Deno, N.C. *Methods Free-Radical Chem.* ***1972***, *3*, 135; Sosnovsky, G.; Rawlinson, D.J. *Adv. Free Radical Chem.* ***1972***, *4*, 203.
[178] The $\omega - 1$ regioselectivity diminishes when the chains are >10 carbons; see Deno, N.C.; Jedziniak, E.J. *Tetrahedron Lett.* ***1976***, 1259; Konen, D.A.; Maxwell, R.J.; Silbert, L.S. *J. Org. Chem.* ***1979***, *44*, 3594.
[179] See, however, Deno, N.C.; Pohl, D.G. *J. Org. Chem.* ***1975***, *40*, 380.

Ref. [180]

$$\underset{1}{CH_3}-\underset{56}{CH_2}-\underset{29}{CH_2}-\underset{14}{CH_2}-CH_2-CH_2-CH_3$$

Ref. [181]

$$\underset{1}{CH_3}-\underset{92}{CH_2}-\underset{3}{CH_2}-\underset{1}{CH_2}-\underset{1}{CH_2}-\underset{2}{CH_2}-\underset{0}{CH_2}-\underset{0}{CH_2}-OH$$

Ref. [182]

$$\underset{3}{CH_3}-\underset{72}{CH_2}-\underset{20}{CH_2}-\underset{4}{CH_2}-\underset{1}{CH_2}-\underset{0}{CH_2}-COOMe$$

Furthermore, di- and polychlorination are much less prevalent. Dicarboxylic acids are predominantly chlorinated in the middle of the chain,[183] and adamantane and bicyclo[2.2.2]octane are predominantly chlorinated at the bridgeheads[184] by this procedure. The reasons for the high $\omega - 1$ specificity are not clearly understood.[185] Enhanced selectivity at a terminal position of *n*-alkanes has been achieved by absorbing the substrate onto a pentasil (five-membered ring) zeolite.[186]

In almost all cases, the mechanism involves a free-radical chain:

Initiation	X_2	$\xrightarrow{h\nu}$	$2X\bullet$
Propagation	$RH + X\bullet$	$\longrightarrow$	$R\bullet + XH$
	$R\bullet + X_2$	$\longrightarrow$	$RX + X\bullet$
Termination	$R\bullet + X\bullet$	$\longrightarrow$	RX

When the reagent is halogen, initiation occurs as shown above.[187] When it is another reagent, a similar cleavage occurs (catalyzed by light or, more commonly, peroxides), followed by propagation steps that do not necessarily involve abstraction by halogen. For example, the propagation steps for chlorination by *tert*-butyl hypochlorite (*t*-BuOCl) have been formulated as:[188]

$$RH + t\text{-BuO}\bullet \longrightarrow R\bullet + t\text{-BuOH}$$
$$R\bullet + t\text{-BuOCl} \longrightarrow RCl + t\text{-BuO}$$

[180] Bernardi, R.; Galli, R.; Minisci, F. *J. Chem. Soc. B* ***1968***, 324. See also, Fuller, S.E.; Lindsay Smith, J.R.; Norman, R.O.C.; Higgins, R. *J. Chem. Soc., Perkin Trans. 2* ***1981***, 545.

[181] Deno, N.C.; Billups, W.E.; Fishbein, R.; Pierson, C.; Whalen, R.; Wyckoff, J.C. *J. Am. Chem. Soc.* ***1971***, *93*, 438.

[182] Minisci, F.; Gardini, G.P.; Bertini, F. *Can. J. Chem.* ***1970***, *48*, 544.

[183] Kämper, F.; Schäfer, H.J.; Luftmann, H. *Angew. Chem. Int. Ed.* ***1976***, *15*, 306.

[184] Smith, C.V.; Billups, W.E. *J. Am. Chem. Soc.* ***1974***, *96*, 4307.

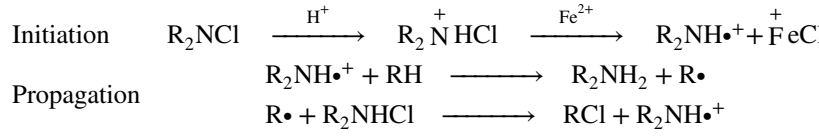
[185] See, however, Dneprovskii, A.S.; Mil'tsov, S.A.; Arbuzov, P.V. *J. Org. Chem. USSR* ***1988***, *24*, 1826. See also, Tanner, D.D.; Arhart, R.; Meintzer, C.P. *Tetrahedron* ***1985***, *41*, 4261.

[186] Turro, N.J.; Fehlner, J.R.; Hessler, D.P.; Welsh, K.M.; Ruderman, W.; Firnberg, D.; Braun, A.M. *J. Org. Chem.* ***1988***, *53*, 3731.

[187] There is evidence for radicals within a solvent cage, see Raner, K.D.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1988***, *110*, 3519; Tanko, J.M.; Anderson III, F.E. *J. Am. Chem. Soc.* ***1988***, *110*, 3525.

[188] See Walling, C.; McGuiness, J.A. *J. Am. Chem. Soc.* ***1969***, *91*, 2053. See also, Zhulin, V.M.; Rubinshtein, B.I. *Bull. Acad. Sci. USSR Div. Chem. Sci,* ***1977***, *26*, 2082.

and the abstracting radicals in the case of *N*-haloamines are the aminium radical cations $R_2NH\bullet^+$ (**11-5**), with the following mechanism (in the case of initiation by Fe^{2+}):[177]



The two propagation steps shown above for X_2 are those that lead directly to the principal products (RX and HX), but many other propagation steps are possible and many occur. Similarly, the only termination step shown is the one that leads to RX, but any two radicals (•H, $\bullet CH_3$, •Cl, $\bullet CH_2CH_3$) may combine in all combinations. Thus, products like H_2, higher alkanes, and higher alkyl halides can be accounted for.

When CH_4 and CH_2CD_2 are the substrates, the rate-determining step is removal of H by Cl•

$$CH_4 + Cl\bullet \rightarrow \bullet CH_3 + HCl$$

and an isotope effect of 12.1 was observed at 0 °C.[189] For chlorinations, there are about 10^4–10^6 propagations before a termination step takes place.

The order of reactivity of the halogens can be explained by energy considerations. For the substrate methane, ΔH values for the two principal propagation steps are shown:

	F_2	Cl_2	Br_2	I_2	F_2	Cl_2	Br_2	I_2
	kcal mol^{-1}				kJ mol^{-1}			
$CH_4 + X\bullet \rightarrow CH_3\bullet + HX$	−31	+2	+17	+34	−132	+6	+72	+140
$CH_4 + X_2 \rightarrow CH_3X + X\bullet$	−70	−26	−24	−21	−293	−113	−100	−87

In each case *D* for CH_3—H is 105 kcal mol^{-1} (438 kJ mol^{-1}), while *D* values for the other bonds involved are given in Table 14.2.[190] F_2 is so reactive[191] that neither UV light nor any other initiation is needed (total $\Delta H = -101$ kcal mol^{-1}, −425 kJ mol^{-1});[192] while Br_2 and I_2 essentially do not react with methane. The second step is exothermic in all four cases, but it cannot take place before the first, and it is this step that is very unfavorable for Br_2 and I_2. It is apparent that the most important single factor causing the order of halogen reactivity to be $F_2 > Cl_2 > Br_2 > I_2$ is the decreasing strength of the HX bond in the order HF > HCl > HBr > HI. The increased reactivity of secondary and tertiary positions is in accord with the decrease in *D* values for R—H in the order primary > secondary > tertiary (Table 5.3). (Note that for chlorination the first step is exothermic for practically all substrates other than CH_4, since most other aliphatic C—H bonds are weaker than those in

[189] Wiberg, K.B.; Motell, E.L. *Tetrahedron* ***1963***, *19*, 2009.

[190] Lide, D.R. (ed.), *Handbook of Chemistry and Physics*, 87th ed., CRC Press, Boca Raton, FL, ***2007***, pp. 5-4 to 5-42.

[191] See Johnson, G.L.; Andrews, L. *J. Am. Chem. Soc.* ***1980***, *102*, 5736.

[192] For F2 the following initiation step is possible: F2 + RH → R + F• + HF, first demonstrated by Miller Jr., W.T.; Koch Jr, S.D.; McLafferty, F.W. *J. Am. Chem. Soc.* ***1956***, *78*, 4992.

TABLE 14.2 Some *D* values[190]

	D	
Bond	kcal mol^{-1}	kJ mol^{-1}
H—F	136	570
H—Cl	103	432
H—Br	88	366
H—I	71	298
F—F	38	159
Cl—Cl	59	243
Br—Br	46	193
I—I	36	151
CH_3—F	108	452
CH_3—Cl	85	356
CH_3—Br	70	293
CH_3—I	57	238

Reprinted with permission from Lide, D.R. (Ed.), *Handbook of Chemistry and Physics*, 87th ed., CRC Press, Boca Raton, FL, ***2007***, pp. 5-4 to 5-42.

CH_4.) It is noted that the mechanism of triethylborane-initiated radical chain chlorination has been examined.[193]

Metal-mediated halogenation reactions are known. Heating alkenes with bromine in the presence of MnO_2 leads to monobromination.[194] Bromination and chlorination of alkanes and cycloalkanes can also take place by an electrophilic mechanism if the reaction is catalyzed by $AgSbF_6$.[195] The Ag-catalyzed chlorination is known.[196] Polycomponent metal-catalyzed fluorination reactions are known.[197] Direct chlorination at a vinylic position by an electrophilic mechanism has been achieved with benzeneseleninyl chloride PhSe(O)Cl and $AlCl_3$ or $AlBr_3$.[198] However, while some substituted alkenes give high yields of chloro substitution products, others (e.g., styrene) undergo addition of Cl_2 to the double bond (**15-39**).[164] The Pd-catalyzed fluorination has been reported.[199] Organocatalysts have been used for asymmetric fluorination.[200]

OS **II**, 89, 133, 443, 549; **III**, 737, 788; **IV**, 807, 921, 984; **V**, 145, 221, 328, 504, 635, 825; **VI**, 271, 404, 715; **VII**, 491; **VIII**, 161.

A different halogenation reaction is possible in which aldehydes can be directly converted to acyl chlorides by treatment with chlorine, but the reaction operates *only* when the aldehyde does not contain an α hydrogen and even then it is not very useful. When there is

[193] Pitts, C.R.; Ling, B.; Woltornist, R.; Liu, R.; Lectka, T. *J. Org. Chem.* ***2014***, *79*, 8895.
[194] Jiang, X.; Shen, M.; Tang, Y.; Li, C. *Tetrahedron Lett.* ***2005***, *46*, 487.
[195] Olah, G.A.; Renner, R.; Schilling, P.; Mo, Y.K. *J. Am. Chem. Soc.* ***1973***, *95*, 7686. See also, Olah, G.A.; Wu, A.; Farooq, O. *J. Org. Chem.* ***1989***, *54*, 1463.
[196] Ozawa, J.; Kanai, M. *Org. Lett.* ***2017***, *19*, 1430.
[197] Bloom, S.; Pitts, C.R.; Miller, D.C.; Haselton, N.; Holl, M.G.; Urheim, E.; Lectka, T. *Angew. Chem. Int. Ed.* ***2012***, *51*, 10580.
[198] Kamigata, N.; Satoh, T.; Yoshida, M. *Bull. Chem. Soc. Jpn.* ***1988***, *44*, 449.
[199] Miao, J.; Yang, K.; Kurek, M.; Ge, H. *Org. Lett.* ***2015***, *17*, 3738; Braun, M.-G.; Doyle, A.G. *J. Am. Chem. Soc.* ***2013***, *135*, 12990.
[200] Lin, J.-H.; Xiao, J.-C. *Tetrahedron Lett.* ***2014***, *55*, 6147.

an α hydrogen, α halogenation occurs instead. The mechanisms are probably of the free-radical type. *N*-Bromosuccinimide (NBS), with AIBN (Sec. 14.A.i) as a catalyst, has been used to convert aldehydes to acyl bromides.[201] Many other halogenation agents have been employed, and a common reagent is sulfuryl chloride SO_2Cl_2.[202] Among other reagents used have been *N*-bromosuccinimide (see **14-3**), CCl_4,[203] PCl_5,[204] and *N*-haloamines and sulfuric acid.[177] In all these cases, an initiator is required, usually peroxides or UV light.[205]

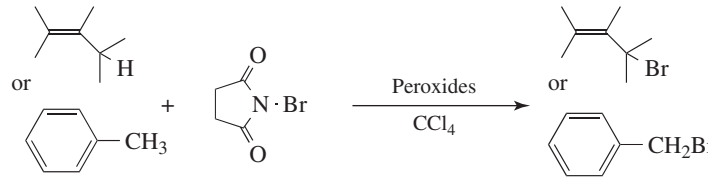
OS **I**, 155.

14-2 Halogenation at Silicon

$$R_3Si{-}H \longrightarrow R_3Si{-}X$$

Just as free radical halogenation occurs at the carbon of an alkane, via hydrogen abstraction to form the radical, a similar reaction occurs at silicon. When triisopropylsilane (i-$Pr_3Si{-}H$) reacts with *tert*-butyl hypochlorite at −10 °C, the product is triisopropylchlorosilane (i-$Pr_3Si{-}Cl$).[206]

14-3 Allylic and Benzylic Halogenation



This reaction is a special case of **14-1**, but is important enough to be treated separately.[207] Alkenes can be brominated in the allylic position and arenes in a benzylic position by a number of reagents, of which NBS[208] is by far the most common. When this reagent is used, the reaction is known as *Wohl-Ziegler bromination*.[209] A nonpolar solvent is used, most often CCl_4, but the reaction has also been done in an ionic liquid.[210] Other *N*-bromo amides have also been used. A radical initiator is needed, usually AIBN (**1**), but a peroxide such as di-*tert*-butyl peroxide, or benzoyl peroxide or, less often, UV light can be used. A light-induced benzylic bromination[211] has been reported using flow conditions, as

[201] Markó, I.E.; Mekhalfia, A. *Tetrahedron Lett.* ***1990***, *31*, 7237. For a related procedure, see Cheung, Y. *Tetrahedron Lett.* ***1979***, 3809.
[202] See Tabushi, I.; Kitaguchi, H. in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, ***1981***, pp. 336–396.
[203] See Hawari, J.A.; Davis, S.; Engel, P.S.; Gilbert, B.C.; Griller, D. *J. Am. Chem. Soc.* ***1985***, *107*, 4721.
[204] Wyman, D.P.; Wang, J.Y.C.; Freeman, W.R. *J. Org. Chem.* ***1963***, *28*, 3173.
[205] Schreiner, P.R.; Lauenstein, O.; Kolomitsyn, I.V.; Nadi, S.; Kokin, A.A. *Angew. Chem. Int. Ed.* ***1998***, *37*, 1895.
[206] Chawla, R.; Larson, G.L. *Synth. Commun.* ***1999***, *29*, 3499.
[207] See Nechvatal, A. *Adv. Free Radical Chem.* ***1972***, *4*, 175.
[208] See Pizey, J.S. *Synthetic Reagents*, Vol. 2, Wiley, NY, ***1974***, pp. 1–63.
[209] Wohl, A. *Ber. Deutsch. Chem. Gesell* ***1919***, *52*, 51; Ziegler, K.; Schenck, G.; Krockow, E.W.; Siebert, A.; Wenz, A.; Weber, H. *Justus Liebigs Ann. Chem.* ***1942***, *551*, 1.
[210] Togo, H.; Hirai, T. *Synlett* ***2003***, 702.
[211] Cantillo, D.; de Frutos, O.; Rincon, J.A.; Mateos, C.; Kappe, C.O. *J. Org. Chem.* ***2014***, *79*, 223.

has benzylic fluorination[212] (Sec. 7.D). Boron tribromide in CCl_4 has been used for benzylic bromination.[213] Benzylic dibromides have been prepared from benzylic alcohols using 1,3-dibromo-5,5-dimethylhydantoin in THF.[214] The radical bromination of unsymmetrical dimethylated pyridines proceeds with good regioselectivity.[215]

Allylic chlorination has also been carried out[216] with *N*-chlorosuccinimide (NCS) and either arylselenyl chlorides (ArSeCl), aryl diselenides (ArSeSeAr), or TsNSO as catalysts. Allylic chlorination has been carried out with *tert*-butyl hypochlorite[217] or with $NaClO/CeCl_3 \bullet 7H_2O$.[218] The regioselective and enantioselective fluorination of cyclic allylic halides using Pd catalysts[219] is known, and Mn catalysts[220] have been reported. Iron compounds catalyze benzylic fluorination.[221] Iodohydantoins were used for benzylic iodination.[222] The reaction of allylic systems with an excess of elemental iodine in DMA gave the allylic iodide.[223]

The reaction is usually quite specific at an allylic or benzylic position and good yields are obtained. However, when the allylic radical intermediate is unsymmetrical, allylic rearrangements can take place, so that mixtures of both possible products are obtained, for example 1-bromobut-2-ene and 3-bromobut-1-ene are formed from but-1-ene. When a double bond has two different allylic positions (e.g., $CH_3CH{=}CHCH_2CH_3$), a secondary position is substituted more readily than a primary. The relative reactivity of tertiary hydrogen is not clear, though many substitutions at allylic tertiary positions have been performed.[224] It is possible to brominate both sides of the double bond.[225] Because of the electron-withdrawing nature of bromine, the second bromine substitutes on the other side of the double bond rather than α to the first bromine. Use of the selenium catalysts produces almost entirely the allylic rearranged chlorides in high yields. With TsNSO the products are the unrearranged chlorides in lower yields. Dichlorine monoxide (Cl_2O), with no catalyst, also leads to allylic rearranged chlorides in high yields.[226] A free-radical mechanism is unlikely in these latter reactions.

Molecules with a benzylic hydrogen, such as toluene, react rapidly to give benzyl bromide (e.g., $PhCH_3 \rightarrow PhCH_2Br$).

N-Bromosuccinimide is a highly regioselective brominating agent at other positions, including positions α to a carbonyl group, α to a C≡C triple bond, or α to an aromatic ring (the benzylic position). When both a double and a triple bond are in the same molecule, the preferred position is α to the triple bond.[227]

[212] Cantillo, D.; de Frutos, O.; Rincón, J.A.; Mateos, C.; Kappe, C.O. *J. Org. Chem.* ***2014***, *79*, 8486.
[213] Chen, H.; Shen, L.; Lin, Y. *Synth. Commun.* ***2010***, *40*, 998.
[214] Radaram, B.; Levine, M. *Tetrahedron Lett.* ***2014***, *55*, 4905.
[215] Thapa, R.; Brown, J.; Balestri, T.; Taylor, R.T. *Tetrahedron Lett.* ***2014***, *55*, 6743.
[216] Hori, T.; Sharpless, K.B. *J. Org. Chem.* ***1979***, *44*, 4204.
[217] Walling, C.; Thaler, W.A. *J. Am. Chem. Soc.* ***1961***, *83*, 3877.
[218] Moreno-Dorado, F.J.; Guerra, F.M.; Manzano, F.L.; Aladro, F.J.; Jorge, Z.S.; Massanet, G.M. *Tetrahedron Lett.* ***2003***, *44*, 6691.
[219] Katcher, M.H.; Sha, A.; Doyle, A.G. *J. Am. Chem. Soc.* ***2011***, *133*, 15902.
[220] Liu, W.; Groves, J.T. *Angew. Chem. Int. Ed.* ***2013***, *52*, 6024.
[221] Bloom, S.; Pitts, C.R.; Woltornist, R.; Griswold, A.; Holl, M.G.; Lectka, T. *Org. Lett.* ***2013***, *15*, 1722.
[222] Combe, S.H.; Hosseini, A.; Song, L.; Hausmann, H.; Schreiner, P.R. *Org. Lett.* ***2017***, *19*, 6156.
[223] Yemets, S.V.; Shubina, T.E.; Krasutsky, P.A. *Org. Biomol. Chem.* ***2013***, *11*, 2891.
[224] Dauben Jr, H.J.; McCoy, L.L. *J. Org. Chem.* ***1959***, *24*, 1577.
[225] Ucciani, E.; Naudet, M. *Bull. Soc. Chim. Fr.* ***1962***, 871.
[226] Torii, S.; Tanaka, H.; Tada, N.; Nagao, S.; Sasaoka, M. *Chem. Lett.* ***1984***, 877.
[227] Peiffer, G. *Bull. Soc. Chim. Fr.* ***1963***, 537.

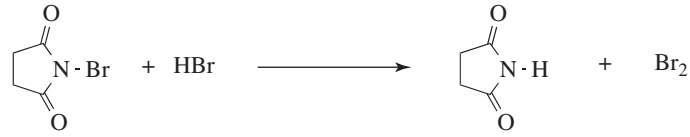
Dauben and McCoy demonstrated that the mechanism of allylic bromination is of the free-radical type,[228] showing that the reaction is very sensitive to free-radical initiators and inhibitors and indeed does not proceed at all unless at least a trace of initiator is present. Subsequent work indicated that the species that actually abstracts hydrogen from the substrate is the bromine atom. The reaction is initiated by small amounts of Br•, and the main propagation steps are

$$\text{Br}\bullet + \text{R}{-}\text{H} \rightarrow \text{R}\bullet + \text{HBr}$$

and then

$$\text{R}\bullet + \text{Br}{-}\text{Br} \rightarrow \text{R}{-}\text{Br} + \text{Br}\bullet$$

When NBS is used, the source of the Br_2 is a fast ionic reaction between NBS and the HBr:

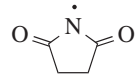


The function of the NBS is therefore to provide a source of Br_2, as shown in the reaction, in a low, steady state concentration, which effectively uses up the HBr liberated in step 1.[229] The main evidence for this mechanism is that NBS and Br_2 show similar selectivity[230] and that the various *N*-bromo amides also show similar selectivity,[231] which is consistent with the hypothesis that the same species is abstracting in each case.[232]

It may be asked why, if Br_2 is the reacting species, it does not add to the double bond, either by an ionic or by a free-radical mechanism (see **15-35**). Apparently, the concentration is too low. In bromination of a double bond, only one atom of an attacking bromine molecule becomes attached to the substrate, whether the addition is electrophilic or free radical. The other bromine atom comes from another bromine-containing molecule or ion. This is clearly not a problem in reactions with benzylic species since the benzene ring is not prone to such addition reactions. If the concentration is sufficiently low, there is a low probability that the proper species will be in the vicinity once the intermediate forms. The intermediate in either case reverts to the initial species and the allylic substitution competes successfully. If this is true, it should be possible to brominate an alkene in the allylic position without competition from addition, even in the absence of NBS or a similar compound, if a very low concentration of bromine is used and if the HBr is removed as it is formed so that it is not available to complete the addition step. This pathway has indeed been demonstrated.[233]

[228] Dauben Jr, H.J.; McCoy, L.L. *J. Am. Chem. Soc.* ***1959***, *81*, 4863.
[229] See Adam, J.; Gosselain, P.A.; Goldfinger, P. *Nature (London)* ***1953***, *171*, 704; *Bull. Soc. Chim. Belg.* ***1956***, *65*, 533.
[230] Walling, C.; Rieger, A.L.; Tanner, D.D. *J. Am. Chem. Soc.* ***1963***, *85*, 3129; Russell, G.A.; Desmond, K.M. *J. Am. Chem. Soc.* ***1963***, *85*, 3139; Pearson, R.; Martin, J.C. *J. Am. Chem. Soc.* ***1963***, *85*, 3142; Skell, P.S.; Tuleen, D.L.; Readio, P.D. *J. Am. Chem. Soc.* ***1963***, *85*, 2850.
[231] Incremona, J.H.; Martin, J.C. *J. Am. Chem. Soc.* ***1970***, *92*, 627.
[232] For other evidence, see Day, J.C.; Lindstrom, M.J.; Skell, P.S. *J. Am. Chem. Soc.* ***1974***, *96*, 5616.
[233] McGrath, B.P.; Tedder, J.M. *Proc. Chem. Soc.* ***1961***, 80.

When NBS is used to brominate nonalkenyl substrates, such as alkanes, another mechanism, involving abstraction of the hydrogen of the substrate by the succinimidyl radical[234] **18** can operate.[235] This mechanism is facilitated by certain solvents (e.g., CH_2Cl_2, $CHCl_3$, or MeCN) in which NBS is more soluble, and by the presence of small amounts of an alkene that lacks an allylic hydrogen (e.g., ethene). The alkene serves to scavenge any Br• that forms from the reagent. Among the evidence for the mechanism involving **18** are abstraction selectivities similar to those of Cl• atoms and the isolation of β-bromopropionyl isocyanate ($BrCH_2CH_2CONCO$), which is formed by ring opening of **18**.



18

OS **IV**, 108; **V**, 825; **VI**, 462; **IX**, 191.

B. Substitution by Oxygen

14-4 Hydroxylation at an Aromatic Carbon[236]

$$ArH + H_2O_2 + FeSO_4 \longrightarrow ArOH$$

The hydroxylation of aromatic rings (e.g., formation of a phenol derivative) was discussed in **13-1**. However, another procedure is known that involves radicals. A mixture of hydrogen peroxide and ferrous sulfate,[237] called *Fenton's reagent*,[238] can be used to hydroxylate aromatic rings, although yields are usually not high.[239] Biaryls are typical side products. A mixture of ferrous ion, oxygen, ascorbic acid, and ethylenetetraaminetetraacetic acid (*Udenfriend's reagent*),[240] and peroxy acids such as peroxynitrous and trifluoroperoxyacetic acids have been used.

Much work has been done on the mechanism of the reaction with Fenton's reagent, and it is known that free aryl radicals (formed by a process such as $HO• + ArH \rightarrow Ar• + H_2O$) are *not* intermediates. The mechanism is essentially that outlined in Sec. 14.A.iii, with HO• as the attacking species,[241] formed by $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{-}OH + HO•$. The rate-determining step is formation of HO• and not its reaction with the aromatic substrate.

See also, **11-26**.

[234] See Chow, Y.L.; Naguib, Y.M.A. *Rev. Chem. Intermed.* ***1984***, *5*, 325.

[235] Lüning, U.; Seshadri, S.; Skell, P.S. *J. Org. Chem.* ***1986***, *51*, 2071; Zhang, Y.; Dong, M.; Jiang, X.; Chow, Y.L. *Can. J. Chem.* ***1990***, *68*, 1668.

[236] See Vysotskaya, N.A. *Russ. Chem. Rev.* ***1973***, *42*, 851; Sangster, D.F. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 133–191.

[237] See Sosnovsky, G.; Rawlinson, D.J. in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1970***, pp. 269–336. See also, Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, NY, ***1981***.

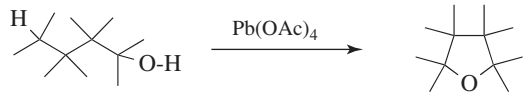
[238] See Walling, C. *Acc. Chem. Res.* ***1975***, *8*, 125.

[239] Yields can be improved with phase-transfer catalysis: Karakhanov, E.A.; Narin, S.Yu.; Filippova, T.Yu.; Dedov, A.G. *Doklad. Chem.* ***1987***, *292*, 81.

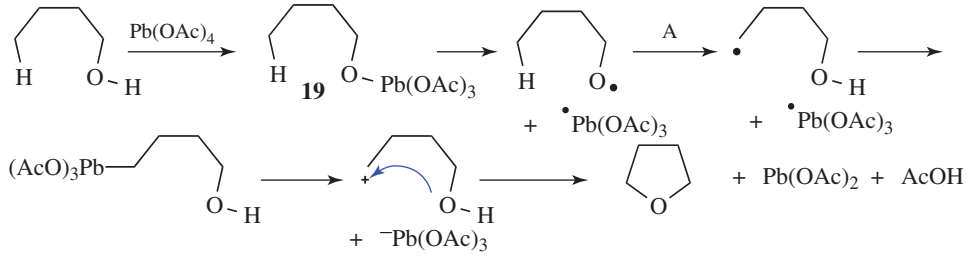
[240] Udenfriend, S.; Clark, C.T.; Axelrod, J.; Brodie, B.B. *J. Biol. Chem.* ***1954***, *208*, 731; Brodie, B.B.; Shore, P.A.; Udenfriend, S. *J. Biol. Chem.* ***1954***, *208*, 741. See also, Tamagaki, S.; Suzuki, K.; Tagaki, W. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 148, 153, 159.

[241] Brook, M.A.; Castle, L.; Lindsay Smith, J.R.; Higgins, R.; Morris, K.P. *J. Chem. Soc., Perkin Trans. 2* ***1982***, 687; Kunai, A.; Hata, S.; Ito, S.; Sasaki, K. *J. Am. Chem. Soc.* ***1986***, *108*, 6012.

14-5 Formation of Cyclic Ethers

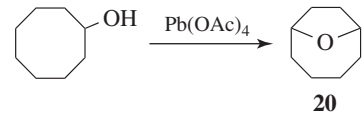


Alcohols with hydrogen in the δ position (C-3 relative to the carbon bearing the OH) can be cyclized with lead tetraacetate.[242] The reaction is usually carried out at ~80 °C (most often in benzene at reflux), but can also be done at room temperature if the reaction mixture is irradiated with UV light. Tetrahydrofurans are formed in high yields. Little or no four- and six-membered cyclic ethers (oxetanes and tetrahydropyrans, respectively) are obtained even when γ and ε-hydrogen atoms are present. The reaction has also been carried out with a mixture of halogen (Br_2 or I_2) and a salt or oxide of silver or mercury (especially HgO or AgOAc),[243] with iodosobenzene diacetate and I_2,[244] and with ceric ammonium nitrate (CAN).[245] The following mechanism is likely for the lead tetraacetate reaction:[246]



although **19** has never been isolated. The step marked **A** is a *1,5 internal hydrogen abstraction*. Such abstractions are well known (see **18-40**) and are greatly favored over 1,4 or 1,6 abstractions (the small amounts of tetrahydropyran formed result from 1,6 abstractions).[247]

Oxidation to the aldehyde or acid (**19-3** and **19-22**) and fragmentation of the substrate sometimes compete. When the OH group is on a ring of at least seven members, a transannular product can be formed, as in the cyclization reaction of octan-1-ol to **20**.[248]



20

[242] See Mihailovic, M.Lj.; Partch, R. *Sel. Org. Transform.* ***1972***, *2*, 97; Milhailovic, M.Lj.; Cekovic, Z. *Synthesis* ***1970***, 209; Butler, R.N. in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, ***1977***, pp. 277–419.

[243] Roscher, N.M.; Shaffer, D.K. *Tetrahedron* ***1984***, *40*, 2643. See Kalvoda, J.; Heusler, K. *Synthesis* ***1971***, 501. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 889–890.

[244] Furuta, K.; Nagata, T.; Yamamoto, H. *Tetrahedron Lett.* ***1988***, *29*, 2215.

[245] See Doyle, M.P.; Zuidema, L.J.; Bade, T.R. *J. Org. Chem.* ***1975***, *40*, 1454.

[246] Mihailovic, M.Lj.; Cekovic, Z.; Maksimovic, Z.; Jeremic, D.; Lorenc, Lj.; Mamuzic, R.I. *Tetrahedron* ***1965***, *21*, 2799.

[247] Mihailovic, M.Lj.; Cekovic, Z.; Jeremic, D. *Tetrahedron* ***1965***, *21*, 2813.

[248] Mihailovic, M.Lj.; Cekovic, Z.; Andrejevic, V.; Matic, R.; Jeremic, D. *Tetrahedron* ***1968***, *24*, 4947.

There are no references in *Organic Syntheses*, but see OS **V**, 692; **VI**, 958, for related reactions.

14-6 Formation of Hydroperoxides

$$RH + O_2 \longrightarrow R{-}O{-}O{-}H$$

The slow atmospheric oxidation (*slow* meaning without combustion) of C—H to C—O—O—H is called *autoxidation*.[249] The reaction occurs when compounds are allowed to stand in air and is catalyzed by light, so unwanted autoxidations can be greatly slowed by keeping the compounds in dark places. Most autoxidations proceed by free-radical chain processes that involve peroxyl radicals.[250] To suppress autoxidation, an antioxidant can be added that will prevent or retard the reaction with atmospheric oxygen.[251] Although some lactone compounds are sold as antioxidants, many radicals derived from lactones show poor or no reactivity toward oxygen.[251] The hydroperoxides produced often react further to give alcohols, ketones, and more complicated products, so the reaction is not often used for preparative purposes, although in some cases hydroperoxides have been prepared in good yield.[252] Foods, rubber, paint, lubricating oils, and so on deteriorate on exposure to the atmosphere over periods of time due to autoxidation. On the other hand, a useful application of autoxidation is the atmospheric drying of paints and varnishes.

As with other free-radical reactions of C—H bonds, some bonds are attacked more readily than others,[253] and these are the ones seen before (Sec. 14.B.i), although the selectivity is very low at high temperatures and in the gas phase. The reaction can be carried out successfully at tertiary (to a lesser extent, secondary), benzylic,[254] and allylic R (though allylic rearrangements are common).[255] 2-Phenylpropane reacted with oxygen to give $PhMe_2C{-}OOH$, for example. Another susceptible position is an aldehyde C—H, but the peroxy acids so produced are not easily isolated[256] since they are converted to the corresponding carboxylic acids (**19-23**). The α positions of ethers are also easily attacked by oxygen [RO—C—H → RO—C—OOH], but the resulting hydroperoxides are seldom isolated. However, this reaction constitutes a hazard in the storage of ethers since solutions of these hydroperoxides and their rearrangement products in ethers are potential spontaneous explosives.[257]

Oxygen itself (a diradical, •O—O•) is not reactive enough to be the species that actually abstracts the hydrogen. But if even a trace of free radical (say R′•) is produced by some

[249] The term autoxidation actually applies to any slow oxidation with atmospheric oxygen. See Goosen, A.; Morgan, D.H. *J. Chem. Soc., Perkin Trans. 2* ***1994***, 557. For reviews, see Sheldon, R.A.; Kochi, J.K. *Adv. Catal.* ***1976***, *25*, 272; Howard, W.G. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 3–62; Lloyd, W.G. *Methods Free-Radical Chem.* ***1973***, *4*, 1; Betts, J. *Q. Rev. Chem. Soc.* ***1971***, *25*, 265; Mayo, F.R. *Acc. Chem. Res.* ***1968***, *1*, 193.

[250] Ingold, K.U. *Acc. Chem. Res.* ***1969***, *2*, 1.

[251] Bejan, E.V.; Font-Sanchis, E.; Scaiano, J.C. *Org. Lett,* ***2001***, *3*, 4059.

[252] See Sheldon, R.A. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 161–200.

[253] See Korcek, S.; Chenier, J.H.B.; Howard, J.A.; Ingold, K.U. *Can. J. Chem.* ***1972***, *50*, 2285, and other papers in this series.

[254] See Santamaria, J.; Jroundi, R.; Rigaudy, J. *Tetrahedron Lett.* ***1989***, *30*, 4677.

[255] See Voronenkov, V.V.; Vinogradov, A.N.; Belyaev, V.A. *Russ. Chem. Rev.* ***1970***, *39*, 944.

[256] Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, p. 313.

[257] For methods of detection and removal of peroxides from ether solvents, see Gordon, A.J.; Ford, R.A. *The Chemist's Companion*, Wiley, NY, ***1972***, p. 437; Burfield, D.R. *J. Org. Chem.* ***1982***, *47*, 3821.

initiating process, *it reacts with oxygen*[258] to give R′—O—O•; and since this type of radical *does* abstract hydrogen, the chain is:

$$\begin{array}{rcl} \text{R}'\text{OO}\bullet + \text{RH} & \longrightarrow & \text{R}\bullet + \text{R}'\text{OOH} \\ \text{R}\bullet + \text{O}_2 & \xrightarrow[\text{etc.}]{} & \text{R—O—O}\bullet \end{array}$$

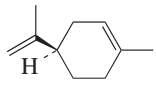
In at least some cases (in alkaline media)[259] the radical R• can be produced by formation of a carbanion and its oxidation (by O_2) to a radical such as allylic radical.[260] Autoxidations in alkaline media can also proceed by a different mechanism:[261]

$$\text{R—H} + \text{base} \rightarrow \text{R}^- + \text{O}_2 \rightarrow \text{ROO}^-$$

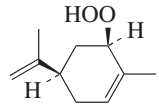
When alkenes are treated with oxygen that has been photosensitized (Sec. 7.A.vi, category 6), they are substituted by OOH in the allylic position in a synthetically useful reaction.[262] Although superficially similar to autoxidation, this reaction is clearly different because 100% allylic rearrangement always takes place. The reagent here is not the ground-state oxygen (a triplet), but an excited singlet state[263] (in which all electrons are paired; *singlet oxygen*). The function of the photosensitization is to promote the oxygen to this singlet state. Singlet oxygen can also be produced by nonphotochemical means,[264] for example, by the reaction between H_2O_2 and NaOCl[265] or between ozone and triphenyl phosphite.[266] Calcium peroxide diperoxohydrate ($CaO_2 \bullet 2H_2O_2$) has been reported as a storable compound used for the chemical generation of singlet oxygen.[267] The oxygen generated by either photochemical or nonphotochemical methods reacts with alkenes in the same way;[268] this is evidence that singlet oxygen is the reacting species in the photochemical reaction and not some hypothetical complex between triplet oxygen and the photosensitizer, as had previously been suggested. The fact that 100% allylic rearrangement always takes place is incompatible with a free-radical mechanism. Further evidence that free radicals are not involved comes from the treatment of optically active limonene

[258] See Schwetlick, K. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 2007.
[259] Sosnovsky, G.; Zaret, E.H. in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, pp. 517–560.
[260] See Russell, G.A.; Bemis, A.G. *J. Am. Chem. Soc.* ***1966***, *88*, 5491.
[261] Gersmann, H.R.; Bickel, A.F. *J. Chem. Soc. B* ***1971***, 2230.
[262] See Frimer, A.A.; Stephenson, L.M. in Frimer, A.A. *Singlet O2*, Vol. 2, CRC Press, Boca Raton, FL, ***1985***, pp. 67–91; Wasserman, H.H.; Ives, J.L. *Tetrahedron* ***1981***, *37*, 1825; Gollnick, K.; Kuhn, H.J. in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 287–427; Denny, R.W.; Nickon, A. *Org. React.* ***1973***, *20*, 133; Adams, W.R. in Augustine, R.L. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1969***, pp. 65–112.
[263] Frimer, A.A. *Singlet* O_2, 4 Vols., CRC Press, Boca Raton, FL, ***1985***; Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***; Frimer, A.A. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 201–234; Gorman, A.A.; Rodgers, M.A.J. *Chem. Soc. Rev.* ***1981***, *10*, 205.
[264] See Turro, N.J.; Ramamurthy, V. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 1–23; Murray, R.W. in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 59–114; Adam, W.; Cilento, G. *Chemical and Biological Generation of Excited States*, Academic Press, NY, ***1982***.
[265] Foote, C.S.; Wexler, S. *J. Am. Chem. Soc.* ***1964***, *86*, 3879.
[266] See Bartlett, P.D.; Mendenhall, G.D.; Durham, D.L. *J. Org. Chem.* ***1980***, *45*, 4269.
[267] Pierlot, C.; Nardello, V.; Schrive, J.; Mabille, C.; Barbillat, J.; Sombret, B.; Aubry, J.-M. *J. Org. Chem.* ***2002***, *67*, 2418.
[268] Foote, C.S.; Wexler, S.; Ando, W.; Higgins, R. *J. Am. Chem. Soc.* ***1968***, *90*, 975. See also, McKeown, E.; Waters, W.A. *J. Chem. Soc. B* ***1966***, 1040.

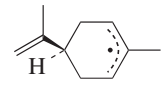
(**21**) with singlet oxygen. Among other products is the optically active hydroperoxide **22**, though if **23** were an intermediate, it could not give an optically active product since it possesses a plane of symmetry.[269] In contrast, autoxidation of **21** gave optically inactive **22** (a mixture of four diastereomers in which the two pairs of enantiomers are present as racemic mixtures).



21



22



23

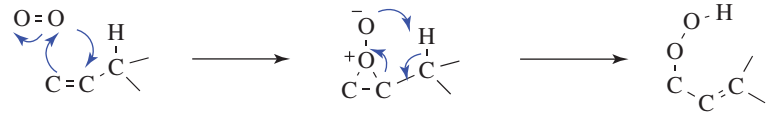
As this example shows, singlet oxygen reacts faster with more highly substituted alkenes than with less highly substituted alkenes. The order of alkene reactivity is tetrasubstituted > trisubstituted > disubstituted. Electron-withdrawing substituents deactivate the alkene.[270] In simple trisubstituted alkenes, there is a general preference for the hydrogen to be removed from the more highly congested side of the double bond.[271] With *cis*-alkenes of the form RCH═CHR′, the hydrogen is removed from the larger R group.[272] Many functional groups in an allylic position cause the hydrogen to be removed from that side rather than the other (geminal selectivity).[273] Also, in alkyl-substituted alkenes, the hydrogen that is preferentially removed is the one geminal to the larger substituent on the double bond.[274]

Several mechanisms have been proposed for the reaction with singlet oxygen.[275] One of these is a pericyclic mechanism, *similar to that of the ene synthesis* (**15-19**).

Pericyclic mechanism

However, there is strong evidence against this mechanism,[276] and a more likely mechanism involves addition of singlet oxygen to the double bond to give a perepoxide (**24**),[277] followed by internal proton transfer.[278] Still other proposed mechanisms involve diradicals or dipolar intermediates.[279]

[269] See Schenck, G.O.; Neumüller, O.; Ohloff, G.; Schroeter, S. *Liebigs Ann. Chem.* ***1965***, *687*, 26.
[270] See Foote, C.S.; Denny, R.W. *J. Am. Chem. Soc.* ***1971***, *93*, 5162.
[271] Rautenstrauch, V.; Thommen, W.; Schulte-Elte, K.H. *Helv. Chim. Acta* ***1986***, *69*, 1638 and references cited therein.
[272] Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *Tetrahedron Lett.* ***1989***, *30*, 4875.
[273] Clennan, E.L.; Chen, X.; Koola, J.J. *J. Am. Chem. Soc.* ***1990***, *112*, 5193, and references cited therein.
[274] Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *J. Am. Chem. Soc.* ***1990***, *112*, 6417.
[275] See Frimer, A.A.; Stephenson, L.M. in Frimer, A.A. *Singlet O2*, Vol. 2, CRC Press, Boca Raton, FL, ***1985***, pp. 80–87; Stephenson, L.M.; Grdina, M.J.; Orfanopoulos, M. *Acc. Chem. Res.* ***1980***, *13*, 419; Gollnick, K.; Kuhn, H.J; Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 288–341; Frimer, A.A. *Chem. Rev.* ***1979***, *79*, 359; Foote, C.S. *Pure Appl. Chem.* ***1971***, *27*, 635; Gollnick, K. *Adv. Photochem.* ***1968***, *6*, 1; Kearns, D.R. *Chem. Rev.* ***1971***, *71*, 395.
[276] Asveld, E.W.H.; Kellogg, R.M. *J. Org. Chem.* ***1982***, *47*, 1250.
[277] See Mitchell, J.C. *Chem. Soc. Rev.* ***1985***, *14*, 399 (pp. 401).
[278] See Davies, A.G.; Schiesser, C.H. *Tetrahedron Lett.* ***1989***, *30*, 7099; Orfanopoulos, M.; Smonou, I.; Foote, C.S. *J. Am. Chem. Soc.* ***1990***, *112*, 3607.
[279] See Jefford, C.W. *Helv. Chim. Acta* ***1981***, *64*, 2534.



24

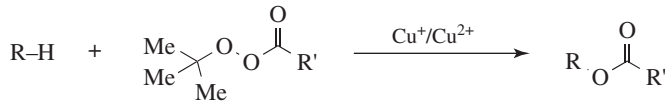
OS **IV**, 895.

14-7 Formation of Peroxides

$$RH + R'OOH \xrightarrow{CuCl} ROOR'$$

Peroxy groups (ROO) can be introduced into susceptible organic molecules by treatment with a hydroperoxide in the presence of cuprous chloride or other catalysts, for example, Co and Mn salts.[280] Very high yields can be obtained. The type of hydrogen replaced is similar to that with NBS (**14-3**), that is, mainly benzylic, allylic, and tertiary. The mechanism is therefore of the free-radical type, involving ROO• formed from ROOH and the metal ion. Biologically important chiral endoperoxides have been prepared by the catalytic peroxidation of conjugated aldehydes.[281]

14-8 Acyloxylation



Susceptible positions of organic compounds can be directly acyloxylated[282] by *tert*-butyl peroxyesters, the most frequently used being acetic and benzoic (R′ = Me or Ph).[283] The reaction requires a catalyst (cuprous ion is the actual catalyst, but a trace is all that is necessary, and such traces are usually present in cupric compounds, so that these are often used) and without the catalyst the reaction is not selective. Susceptible positions are similar to those in **14-5**: benzylic, allylic, and the α position of ethers and sulfides. Terminal alkenes are substituted almost entirely in the 3 position, that is, with only a small amount of allylic rearrangement, but internal alkenes generally give mixtures containing a large amount of allylic-shift products. If the reaction with alkenes is carried out in an excess of another acid R″CO_2H, the ester produced is of *that* acid ROCOR″. Aldehydes react to give anhydrides.

[280] See Sosnovsky, G.; Rawlinson, D.J. in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1970***, pp. 153–268. See also, Murahashi, S.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* ***1990***, *112*, 7820; Sheldon, R.A. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, p. 161.

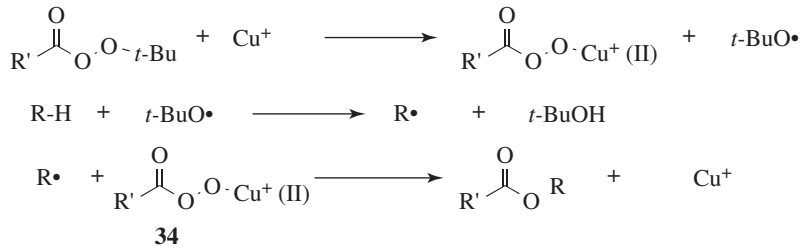
[281] Hu, L.; Lu, X.; Deng, L. *J. Am. Chem. Soc.* ***2015***, *137*, 8400.

[282] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1625–1630 *ff*, 1661–1663.

[283] See Rawlinson, D.J.; Sosnovsky, G. *Synthesis* ***1972***, 1; Sosnovsky, G.; Rawlinson, D.J. in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, pp. 585–608; Doumaux Jr, A.R. in Augustine, R.L. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***, pp. 141–185.

Acyloxylation has also been achieved with metallic acetates, such as lead tetraacetate,[284] mercuric acetate,[285] and palladium(II) acetate.[286] In the case of the lead and mercuric acetates, not only does the reaction take place at allylic and benzylic positions and at those positions α to an OR or SR group, but also at positions α to the carbonyl groups of aldehydes, ketones, or esters and at positions α to two carbonyl groups (ZCH_2Z'). It is likely that in the latter cases it is the enol forms that react. Ketones can be α-acyloxylated indirectly by treatment of various enol derivatives with metallic acetates, for example, silyl enol ethers with silver carboxylate/iodine,[287] enol thioethers with lead tetraacetate,[288] and enamines[289] with lead tetraacetate.[290] Lead tetraacetate even acyloxylates alkanes, in a slow reaction (10 days to 2 weeks), with tertiary and secondary positions greatly favored over primary ones.[291] α,β-Unsaturated ketones can be acyloxylated in good yields in the α′ position with manganese triacetate.[292] Palladium acetate converts alkenes to vinylic and/or allylic acetates.[293] Acyloxylation of certain alkanes has also been reported with palladium(II) acetate.[294]

Studies of the mechanism of the cuprous-catalyzed reaction show that the most common mechanism is the one shown.[295]



34

This mechanism, involving a free radical R•, is compatible with the allylic rearrangements found.[296] The fact that *tert*-butyl peroxyesters labeled with ^{18}O in the carbonyl oxygen gave an ester with 50% of the label in each oxygen[297] is in accord with coupling of R• with intermediate **34**, in which the Cu is ionically bound, so that the oxygen atoms are essentially equivalent. Other evidence is that *tert*-butoxy radicals have been trapped with

[284] See Butler, R.N. in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, p. 277.
[285] Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 190–208; Rawlinson, D.J.; Sosnovsky, G. *Synthesis* ***1973***, 567.
[286] Byström, S.E.; Larsson, E.M.; Åkermark, B. *J. Org. Chem.* ***1990***, *55*, 5674.
[287] Rubottom, G.M.; Mott, R.C.; Juve Jr., H.D. *J. Org. Chem.* ***1981***, *46*, 2717.
[288] Trost, B.M.; Tanigawa, Y. *J. Am. Chem. Soc.* ***1979***, *101*, 4413.
[289] See Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, pp. 251–258.
[290] See Butler, R.N. *Chem. Ind. (London)* ***1976***, 499.
[291] See Mosher, M.W.; Cox, J.L. *Tetrahedron Lett.* ***1985***, *26*, 3753.
[292] Demir, A.S.; Sayrac, T.; Watt, D.S. *Synthesis* ***1990***, 1119.
[293] See Rylander, P.N. *Organic Synthesis with Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 80–87; Jira, R.; Freiesleben, W. *Organomet. React.* ***1972***, *3*, 1 (pp. 44–84); Heck, R.F. *Fortschr. Chem. Forsch.* ***1971***, *16*, 221 (pp. 231–237); Tsuji, J. *Adv. Org. Chem.* ***1969***, *6*, 109 (pp. 132–143).
[294] See Sen, A.; Gretz, E.; Oliver, T.F.; Jiang, Z. *New J. Chem.* ***1989***, *13*, 755.
[295] Kochi, J.K.; Mains, H.E. *J. Org. Chem.* ***1965***, *30*, 1862. See also, Beckwith, A.L.J.; Zavitsas, A.A. *J. Am. Chem. Soc.* ***1986***, *108*, 8230.
[296] Goering, H.L.; Mayer, U. *J. Am. Chem. Soc.* ***1964***, *86*, 3753.
[297] Denney, D.B.; Denney, D.Z.; Feig, G. *Tetrahedron Lett.* ***1959***, Vol. 1, Issue 15, p. 19.

dienes.[298] Much less is known about the mechanisms of the reactions with other metal acetates.[299]

Free-radical acyloxylation of aromatic substrates[300] has been accomplished with a number of reagents, including copper(II) acetate,[301] silver(II) complexes,[302] and cobalt(III) trifluoroacetate.[303]

OS **III**, 3; **V**, 70, 151; **VIII**, 137.

C. Substitution by Sulfur

14-9 Chlorosulfonation

$$R{-}H + SO_2 + Cl_2 \xrightarrow{h\nu} RSO_2Cl$$

The chlorosulfonation of organic molecules with chlorine and sulfur dioxide is called the *Reed reaction*.[304] In its scope and the range of products obtained, the reaction is similar to **14-1**. The mechanism is also similar, except that there are two additional main propagation steps:

$$R\bullet + SO_2 \longrightarrow R{-}SO_2\bullet$$
$$R{-}SO_2\bullet + Cl_2 \longrightarrow R{-}SO_2Cl + Cl\bullet$$

Chlorosulfenation[305] can be accomplished by treatment with SCl_2 and UV light:

$$RH + SCl_2 \xrightarrow{h\nu} RSCl$$

D. Substitution by Nitrogen

14-10 The Direct Conversion of Aldehydes to Amides

$$ArCHO \xrightarrow[\text{NBS-AIBN}]{NH_3} ArCONH_2$$

Aliphatic and aromatic aldehydes have been converted to the corresponding amides with ammonia or a primary or secondary amine, NBS, and a catalytic amount of AIBN (Sec. 14.A.i).[306] In a reaction of more limited scope, amides are obtained from aromatic and α,β-unsaturated aldehydes by treatment with dry ammonia gas and nickel peroxide.[307] Best

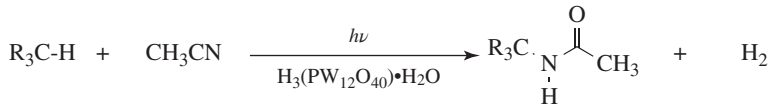
[298] Kochi, J.K. *J. Am. Chem. Soc.* ***1962***, *84*, 2785, 3271; Story, P.R. *Tetrahedron Lett.* ***1962***, 401.
[299] See, for example, Jones, S.R.; Mellor, J.H. *J. Chem. Soc., Perkin Trans. 2* ***1977***, 511.
[300] See Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1985***, pp. 177–180, 351–355.
[301] Takizawa, Y.; Tateishi, A.; Sugiyama, J.; Yoshida, H.; Yoshihara, N. *J. Chem. Soc., Chem. Commun.* ***1991***, 104. See also, Kaeding, W.W.; Kerlinger, H.O.; Collins, G.R. *J. Org. Chem.* ***1965***, *30*, 3754.
[302] Nyberg, K.; Wistrand, L.G. *J. Org. Chem.* ***1978***, *43*, 2613.
[303] See DiCosimo, R.; Szabo, H. *J. Org. Chem.* ***1986***, *51*, 1365.
[304] See Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 126–131.
[305] Müller, E.; Schmidt, E.W. *Chem. Ber.* ***1964***, *97*, 2614; See Kühle, E. *Synthesis* ***1971***, 563, 617.
[306] Markó, I.E.; Mekhalfia, A. *Tetrahedron Lett.* ***1990***, *31*, 7237. See Ekoue-Kovi, K.; Wolf, C. *Chem. Eur. J.* ***2008***, *14*, 6302.
[307] Nakagawa, K.; Onoue, H.; Minami, K. *Chem. Commun.* ***1966***, 17.

yields (80–90%) are obtained at −25 to −20 °C. In the nickel peroxide reaction the corresponding alcohols ($ArCH_2OH$) have also been used as substrates.

Oxidative amidation of aldehydes has been done using $AgIO_3$ in the presence of a CuI catalyst.[308] Similar oxidative amidation was accomplished using H_2O_2 and a Pd catalyst.[309] Amides were prepared from aldehydes using NBS with a Cu catalyst.[310] Hypervalent iodine with a Fe catalyst has also been used.[311] Oxidative amidation of aromatic aldehydes using Oxone and ball milling without solvent gave the corresponding amide.[312]

Treatment of an aldehyde with iodine in aqueous ammonia, followed by oxidation with aqueous hydrogen peroxide, generates a primary amide.[313] Secondary amines react with aldehydes to give an amide using a Pd catalyst[314] or a Rh catalyst.[315] Thioamides $RCSNR'_2$ have been prepared in good yield from thioaldehydes (produced *in situ* from phosphoranes and sulfur) and secondary amines.[316]

14-11 Amidation and Amination at an Alkyl Carbon



When alkanes bearing a tertiary hydrogen are exposed to UV light in acetonitrile containing a heteropolytungstic acid, they are converted to an amide.[317] The oxygen in the product comes from the tungstic acid. When the substrate bears two adjacent tertiary hydrogen atoms, alkenes are formed (by loss of two hydrogen atoms), rather than amides (**19-2**). Amidyl radicals can be generated by other means.[318]

N-Methoxybenzamide reacts with ethers, with a Ni catalyst and di-*tert*-butyl peroxide, to give the *N*-(α-alkoxy) derivative via radical–radical coupling.[319] The activation of remote C—H bonds by photoredox-catalyzed radical translocation via *O*- and *N*-centered radicals has been reported.[320] The α-C—H amination of ketones by reaction with amines using ammonium iodide as the catalyst and sodium percarbonate as the co-oxidant has been developed.[321] The Cu-catalyzed reaction of benzylic or simple hydrocarbons with benzamide and 2 equivalents of di-*tert*-butyl peroxide gave the corresponding amide.[322] A similar reaction has been reported using tetrabutylammonium iodide with TBHP as the oxidant.[323] A

[308] Yoo, W.-J.; Li, C.-J. *J. Am. Chem. Soc.* ***2006***, *128*, 13064.
[309] Suto, Y.; Yamagiwa, N.; Torisawa, Y. *Tetrahedron Lett.* ***2008***, *49*, 5732.
[310] Wang, L.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem. Eur. J.* ***2008***, *14*, 10722.
[311] Fang, C.; Qian, W.; Bao, W. *Synlett* ***2008***, 2529.
[312] Gao, J.; Wang, G.-W. *J. Org. Chem.* ***2008***, *73*, 2955.
[313] Shie, J.-J.; Fang, J.-M. *J. Org. Chem.* ***2003***, *68*, 1158.
[314] Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Synthesis* ***1983***, 474.
[315] Tillack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* ***2001***, 523.
[316] Okuma, K.; Komiya, Y.; Ohta, H. *Chem. Lett.* ***1988***, 1145.
[317] Renneke, R.F.; Hill, C.L. *J. Am. Chem. Soc.* ***1986***, *108*, 3528.
[318] Moutrille, C.; Zard, S.Z. *Chem. Commun.* ***2004***, 1848.
[319] Zhou, L.; Tang, S.; Qi, X.; Lin, C.; Liu, K.; Liu, C.; Lan, Y.; Lei, A. *Org. Lett.* ***2014***, *16*, 3404.
[320] Hu, X.-Q.; Chen, J.-R.; Xiao, W.-J *Angew. Chem. Int. Ed.* ***2017***, *56*, 1960.
[321] Jiang, Q.; Xu, B.; Zhao, A.; Jia, J.; Liu, T.; Guo, C. *J. Org. Chem.* ***2014***, *79*, 8750.
[322] Zeng, H.-T.; Huang, J.-M. *Org. Lett.* ***2015***, *17*, 4276.
[323] Xue, Q.; Xie, J.; Li, H.; Cheng, Y.; Zhu C. *Chem. Commun.* ***2013***, *49*, 3700.

Cu-catalyzed amidation reaction has been reported.[324] The visible-light photoredox-catalyzed reaction using DCA (9,10-dicyanoanthracene) as a visible light-absorbing photoredox catalyst and using *N*-methoxyacetamide as the nitrogen source gave the amide derivative.[325]

14-12 Substitution by Nitro

In a reaction termed a "nitro-Hunsdiecker" (see **14-24**), vinyl carboxylic acids (conjugated acids) are treated with nitric acid and a catalytic amount of AIBN (**1**). The product is the vinyl nitro compound, generated via decarboxylation of a radical intermediate.[326]

Aryl halides are converted to aromatic nitro compounds via a Cu-catalyzed reaction with nitrite salts (Ar—X → Ar—NO_2).[327] Ceric ammonium nitrate in acetonitrile also facilitates this reaction.[328] Conjugated amides were coupled via the γ carbon to give good yields of the dimeric diamide, with an excess of samarium (II) iodide, and with modest enantioselectivity using a chiral additive.[329]

E. Substitution by Carbon

In these reactions a new carbon–carbon bond is formed. These reaction may be given the collective title *coupling reactions*. In each case, an alkyl or aryl radical is generated and then combines with another radical (a termination process) or reacts with an aromatic ring or alkene to give the coupling product.[330]

14-13 Simple Coupling at a Susceptible Position

$$2\,RH \longrightarrow R{-}R$$

Alkane and alkyl substrates R—H are treated with peroxides, which decompose to give a radical that abstracts a hydrogen from R—H to give R•, which dimerizes by radical coupling. Dialkyl and diacyl peroxides have been used, as well as Fenton's reagent (see **14-4**). This reaction is far from general, although in certain cases respectable yields have been obtained. Among susceptible positions are those at a tertiary carbon,[331] as well as those α to a phenyl group (especially if there is also an α-alkyl or α-chloro group),[332] an ether

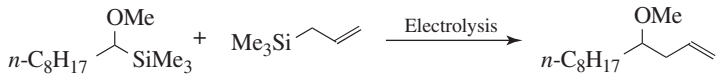
[324] Wu, X.; Zhao, Y.; Zhang, G.; Ge, H. *Angew. Chem. Int. Ed.* ***2014***, *53*, 3706.
[325] Pandey, G.; Laha, R. *Angew. Chem. Int. Ed.* ***2015***, *54*, 14875.
[326] Das, J.P.; Sinha, P.; Roy, S. *Org. Lett.* ***2002***, *4*, 3055.
[327] Saito, S.; Koizumi, Y. *Tetrahedron Lett.* ***2005***, *46*, 4715.
[328] Rao, A.S.; Srinivas, P.V.; Babu, K.S.; Rao, J.M. *Tetrahedron Lett.* ***2005***, *46*, 8141.
[329] Kikukawa, T.; Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.* ***1999***, *40*, 7497.
[330] See Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Elsmsford, NY, ***1986***.
[331] Meshcheryakov, A.P.; Érzyutova, E.I. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1966***, 94.
[332] Johnston, K.M.; Williams, G.H. *J. Chem. Soc.* ***1960***, 1168.

group,[333] a carbonyl group,[334] a cyano group,[335] a dialkylamino group,[336] or a carboxylic ester group (either the acid or alcohol side).[337] Cross coupling is possible in some cases. When toluene was heated with allyl bromide, in the presence of di-*tert*-butyl peroxide, 4-phenylbut-1-ene was formed quantitatively.[338]

Alkanes can be dimerized by vapor-phase mercury photosensitization[339] in a synthetically useful process that produces H_2 as a byproduct. Best results are obtained for coupling at tertiary positions, but compounds lacking tertiary hydrogen atoms (e.g., cyclohexane) also give good yields. Dimerization of *n*-alkanes gives secondary–secondary coupling in a nearly statistical distribution, with primary positions essentially unaffected. When a mixture of compounds is treated, cross-dimerization and homodimerization take place statistically. Even with the limitation on yield implied by the statistical process, cross-dimerization is still useful when one of the reactants is an alkane, because the products are easy to separate, and because of the few other ways to functionalize an alkane. The cross coupling of an alkane with trioxane is especially valuable, because hydrolysis of the product (**10-6**) gives an aldehyde, thus achieving the conversion RH → RCHO. The mechanism probably involves abstraction of H by the excited Hg atom, and coupling of the resulting radicals. Acylation of a tertiary alcohol gave the *tert*-alkyl *N*-phthalimidoyl oxalate, and subsequent exposure to visible light, with a $Ru(bpy)_3(PF_6)$ catalyst, gave the tertiary carbon radical, which gave reductive coupling with alkenes or substitution reactions with allylic and vinylic halides.[340]

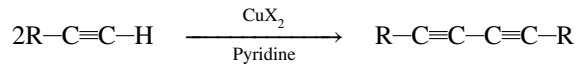
OS **IV**, 367; **V**, 1026; **VII**, 482.

14-14 Coupling at a Susceptible Position Via Silanes



Under electrochemical conditions it is possible to couple two silanes. The reaction of 1-trimethylsilyl-1-methoxynonane and allyltrimethylsilane, for example, gave the corresponding homoallylic ether.[341]

14-15 Coupling of Alkynes[342]



Terminal alkynes can be coupled by heating with stoichiometric amounts of cupric salts in pyridine or a similar base. This reaction, which produces symmetrical diynes

[333] Pfordte, K.; Leuschner, G. *Liebigs Ann. Chem.* ***1961***, *643*, 1.
[334] Hawkins, E.G.E.; Large, R. *J. Chem. Soc., Perkin Trans. 1* ***1974***, 280.
[335] Kharasch, M.S.; Sosnovsky, G. *Tetrahedron* ***1958***, *3*, 97.
[336] Schwetlick, K.; Jentzsch, J.; Karl, R.; Wolter, D. *J. Prakt. Chem.* ***1964***, *[4] 25*, 95. See Miyake, Y.; Ashida, Y.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* ***2012***, *48*, 6966.
[337] Boguslavskaya, L.S.; Razuvaev, G.A. *J. Gen. Chem. USSR* ***1963***, *33*, 1967.
[338] Tanko, J.M.; Sadeghipour, M. *Angew. Chem. Int. Ed.* ***1999***, *38*, 159.
[339] Brown, S.H.; Crabtree, R.H. *J. Am. Chem. Soc.* ***1989***, *111*, 2935, 2946; *J. Chem. Educ.* ***1988***, *65*, 290.
[340] Lackner, G.L.; Quasdorf, K.W.; Pratsch, G.; Overman, L.E. *J. Org. Chem.* ***2015***, *80*, 6012; Pratsch, G.; Lackner, G.L.; Overman, L.E. *J. Org. Chem.* ***2015***, *80*, 6025.
[341] Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J.-i. *J. Am. Chem. Soc.* ***2000***, *122*, 10244.
[342] See Siemsen, P.; Livingston, R.C.; Diederich, F. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2632.

in high yields, is called the *Eglinton reaction*.[343] The large-ring annulenes (Sec. 2.K) were prepared by rearrangement and hydrogenation of cyclic polyynes,[344] prepared by the Eglinton reaction with terminal diynes, to give a cyclic trimer of 1,5-hexadiyne (cyclooctadeca-1,3,7,9,13,15-hexayne), and subsequent reaction with K*t*-OBu and then catalytic hydrogenation gave cyclooctadeca-1,3,5,7,9,11,13,15,17-nonaene.[345] The corresponding tetramers (C_{24}), pentamers (C_{30}), and hexamers (C_{36}) were also formed. The Eglinton reaction is of wide scope and many functional groups can be present on the alkyne. The oxidation is usually quite specific for triple-bond hydrogen. 1,4-Diynes have been prepared by the coupling of propargyl alcohols an d terminal alkynes using cupric triflate as a catalyst and MS 4Å.[346]

Another common procedure is the use of catalytic amounts of cuprous salts in the presence of ammonia or ammonium chloride (this method is called the *Glaser reaction*). Atmospheric oxygen or some other oxidizing agent, such as permanganate or hydrogen peroxide, is required in the latter procedure. This method is not satisfactory for cyclic coupling. Hydrogen peroxide, potassium permanganate, potassium ferricyanide, iodine, or Cu(II) can be used as oxidants rather than oxygen.[347] Isolation of copper acetylide during the reaction can be avoided by doing the reaction in pyridine or cyclohexylamine, in the presence of catalytic amount of $CuCl_2$.[348] If the Glaser reaction is done with a *N*,*N*,*N*′,*N*′-tetramethylethylenediamine/CuCl complex, the reaction proceeds in good yield in virtually any organic solvent.[349] A $CuCl_2$-catalyzed Glaser oxidative coupling has been reported.[350] When molecular oxygen is the oxidant, this modification of Glaser condensation is known as the *Hay reaction*. A microwave accelerated Glaser-Hay reaction is known.[351]

Unsymmetrical diynes can be prepared by *Cadiot-Chodkiewic*z coupling,[352] which is the Cu-catalyzed reaction of terminal alkynes with 1-bromoalkynes.

$$R{-}C{\equiv}C{-}H + Br{-}C{\equiv}C{-}R' \xrightarrow{Cu^+} R{-}C{\equiv}C{-}C{\equiv}C{-}R' + HBr$$

This reaction may be regarded as a variation of **10-74**, but it must have a different mechanism since acetylenic halides give the reaction but ordinary alkyl halides do not, which

[343] See Simándi, L.I. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wiley, NY, ***1983***, pp. 529–534; Nigh, W.G. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 11–31; Cadiot, P.; Chodkiewicz, W. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY; ***1969***, pp. 597–647.

[344] See Nakagawa, M. in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 2, Wiley, NY, ***1978***, pp. 635–712. Also see reference 331.

[345] Sondheimer, F.; Wolovsky, R.; Amiel, Y. *J. Am. Chem. Soc.* ***1962***, *84*, 274.

[346] Wang, T.; Chen, X.-l.; Chen, L.; Zhan, Z.-p. *Org. Lett.* ***2011***, *13*, 3324.

[347] Gunter, H.V. *Chemistry of Acetylenes*, Marcel Dekker, NY, ***1969***, pp 597–647 and references cited therein.

[348] Stansbury, H.A.; Proops, W.R. *J. Org. Chem.* ***1962***, *27*, 320.

[349] Hay, A.S. *J. Org. Chem.* ***1960***, *25*, 1275; Hay, A S. *J. Org. Chem.* ***1962***, *27*, 3320.

[350] Li, Y.-N.; Wang, J.-L.; He, L.-N. *Tetrahedron Lett.* ***2011***, *52*, 3485. See Chen, X.; Zhang, H.; Chen, J.; Gong, H. *Chem. Lett.* ***2015***, *44*, 129. For a CuI-catalyzed reaction, see Fan, X.; Li, N.; Shen, T.; Cui, X.-M.; Lv, H.; Zhu, H.-B.; Guan, Y.-H. *Tetrahedron* ***2014***, *70*, 256.

[351] Bédard, A.-C.; Collins, S.K. *Chem. Commun.* ***2012***, *48*, 6420.

[352] Chodkiewicz, W. *Ann. Chim. (Paris)* ***1957***, *[13] 2*, 819; Sindhu, K.S.; Thankachan, A.P.; Sajitha, P.S.; Anilkumar, G. *Org. Biomol. Chem.* ***2015***, *13*, 6891.

is hardly compatible with a nucleophilic mechanism. However, the mechanism is not fully understood. Alkynes have also been coupled using CuI and a Pd catalyst.[353] A variation of the Cadiot-Chodkiewicz method consists of treating a haloalkyne ($R'C{\equiv}CX$) with a copper acetylide ($RC{\equiv}CCu$).[354] The Cadiot-Chodkiewicz procedure can be adapted to the preparation of diynes in which $R' = H$ by the use of $BrC{\equiv}CSiEt_3$ and subsequent cleavage of the $SiEt_3$ group.[355] This protecting group can also be used in the Eglinton or Glaser methods.[356] The Au-catalyzed reaction was reported.[357]

The mechanism of the Eglinton and Glaser reactions probably begins with loss of a proton to give the alkyne anion since there is a base present and acetylenic protons are acidic. It is known, of course, that cuprous ion can form complexes with triple bonds. The final step is probably the coupling of two radicals that are formed *in situ*, but just how the carbanion becomes oxidized to the radical and what part the cuprous ion plays (other than forming the acetylide salt) are matters of considerable speculation,[358] and depend on the oxidizing agent. One proposed mechanism postulated Cu(II) as the oxidant.[359] It has been shown that molecular oxygen forms adducts with Cu(I) supported by tertiary amines, which might be the intermediates in the Glaser reaction where molecular oxygen is the oxidant.[360] For the *Hay reaction*, the mechanism involves a Cu(I)/Cu(III)/Cu(II)/Cu(I) catalytic cycle, and the key step for this reaction is the dioxygen activation during complexation of two molecules of acetylide with molecular oxygen, giving a Cu(III) complex.[361] This mechanism is supported by isolation and characterization of Cu(III) complexes formed under the conditions of the Glaser coupling.

A variation in the Glaser reaction couples terminal alkynes using $CuCl_2$ in supercritical CO_2 (Sec. 9.D.ii)[362] and in ionic liquids.[363] Coupling was also achieved using $CuCl_2$ on KF/Al_2O_3 with microwave irradiation.[364] A transition metal-free coupling reaction is known.[365] Coupling has been achieved under ambient conditions using cupric acetate.[366] Another variation is a Ni-catalyzed cross coupling.[367] Terminal alkynes give 1,3-diynes upon treatment with Cu/iodine.[368]

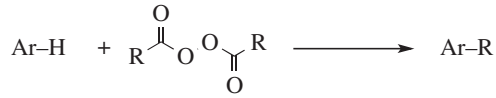
[353] Liu, Q.; Burton, D.J. *Tetrahedron Lett.* ***1997***, *38*, 4371.
[354] Curtis, R.F.; Taylor, J.A. *J. Chem. Soc. C* ***1971***, 186.
[355] Ghose, B.N.; Walton, D.R.M. *Synthesis* ***1974***, 890.
[356] Johnson, T.R.; Walton, D.R.M. *Tetrahedron* ***1972***, *28*, 5221.
[357] Li, X.; Xie, X.; Sun, N.; Liu, Y. *Angew. Chem. Int. Ed.* ***2017***, *56*, 6994.
[358] See Nigh, W.G. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 27–31; Fedenok, L.G.; Berdnikov, V.M.; Shvartsberg, M.S. *J. Org. Chem. USSR* ***1973***, *9*, 1806; Clifford, A.A.; Waters, W.A. *J. Chem. Soc.* ***1963***, 3056.
[359] Bohlmann, F.; Schönowsky, H.; Inhoffen, E.; Grau, G. *Chem. Ber.* ***1964***, *97*, 794.
[360] Wieghardt, K.; Chaudhuri, P. *Prog. Inorg. Chem.* ***1987***, *37*, 329.
[361] Fomina, L.; Vazquez, B.; Tkatchouk, E.; Fomine, S. *Tetrahedron* ***2002***, *58*, 6741.
[362] See Jiang, H.-F.; Tang, J.Y.; Wang, A.-Z.; Deng, G.-H.; Yang, S.-R. *Synthesis* ***2006***, 1155.
[363] Yadav, J.S.; Reddy, B.V.S.; Reddy, K.B.; Gayathri, K.U.; Prasad, A.R. *Tetrahedron Lett.* ***2003***, *44*, 6493.
[364] Kabalka, G.W.; Wang, L.; Pagni, R.M. *Synlett* ***2001***, 108.
[365] Yan, J.; Wang, L. *Synth. Commun.* ***2005***, *35*, 2333.
[366] Balaraman, K.; Kesavan, V. *Synthesis* ***2010***, 3461.
[367] Yin, W.; He, C.; Chen, M.; Zhang, H.; Lei, A. *Org. Lett.* ***2009***, *11*, 709.
[368] Li, D.; Yin, K.; Li, J.; Jia, X. *Tetrahedron Lett.* ***2008***, *49*, 5918.

Recent variations in coupling reactions include the Au,[369] Cu,[370] Rh,[371] Fe,[372] Ni/Ag,[373] or Pd[374]-catalyzed cross coupling of terminal alkynes to give 1,3-diynes. The Cu/porphyrin-catalyzed reaction has been reported.[375] The $CuBr_2$-catalyzed coupling reactions of terminal alkynes using an enaminone as the effective ligand gave symmetrical or unsymmetrical 1,3-diynes.[376] A ball mill has been used for the Cu-catalyzed coupling of terminal alkynes.[377] The homocoupling of terminal alkynes was reported, on highly oriented pyrolitic graphite.[378] Terminal alkynes reacted with butyllithium in the presence of acetoxybenziodoxole to give the 1,3-diyne.[379]

In related reactions, the Cu-catalyzed homocoupling of alkynyl trifluoroborates led to 1,3-diynes.[380] Alkynyl trifluoroborates reacted with vinylic tellurides to give 1,3-enynes.[381] The Pd-catalyzed reaction of vinyl bromides and terminal alkynes gives enynes.[382] 1,3-Dienes are prepared by the Pd-catalyzed homocoupling of alkenyl trifluoroborates.[383]

OS **V**, 517; **VI**, 68, 925; **VIII**, 63.

14-16 Alkylation and Arylation of Aromatic Compounds by Peroxides



This reaction is most often carried out with R = aryl, so the net result is the same as in **13-27**, but the reagent is different.[384] It is used less often than **13-28**, but the scope is similar. When

[369] Peng, H.; Xi, Y.; Ronaghi, N.; Dong, B.; Akhmedov, N.G.; Shi, X. *J. Am. Chem. Soc.* ***2014***, *136*, 13174; Sun, S.; Kroll, J.; Luo, Y.; Zhang, L. *Synlett* ***2012***, *23*, 54. See Mader, L.; Molinari, L.; Rudolph, M.; Rominger, F.; Hashmi, S.K. *Chem. Eur. J.* ***2015***, *21*, 3910.

[370] Su, L.; Dong, J.; Liu, L.; Sun, M.; Qiu, R.; Zhou, Y.; Yin, S.-F. *J. Am. Chem. Soc.* ***2016***, *138*, 12348; Liu, D.-X.; Li, F.-L.; Li, H.-X.; Gao, J.; Lang,, J.-P. *Tetrahedron* ***2014***, *70*, 2416; Trostyanskaya, I.G.; Beletskaya, I.P. *Tetrahedron* ***2017***, *73*, 148; Yan, S.; Pan, S.; Osako, T.; Uozumi, Y. *Synlett* ***2016***, *27*, 1232; Alonso, F.; Melkonian, T.; Moglie, Y.; Yus, M. *Eur. J. Org. Chem.* ***2011***, 2524; Balamurugan, R.; Naveen, N.; Manojveer, S.; Nama, M.V. *Aust. J. Chem.* ***2011***, *64*, 567. For an ionic liquid-promoted reaction, see Li, S.; Chen, X.; Chen, J.; Gong, H. *Bull. Chem. Soc. Jpn.* ***2016***, *89*, 794.

[371] Xu, H.-D.; Zhang, R.-W.; Li, X.; Huang, S.; Tang, W.; Hu, W.-H. *Org. Lett.* ***2013***, *15*, 840.

[372] Liang, Q.; Osten, K.M.; Song, D. *Angew. Chem. Int. Ed.* ***2017***, *56*, 6317; Midya, G.C.; Paladhi, S.; Dhara, K.; Sash, J. *Chem. Commun.* ***2011***, *47*, 6698.

[373] Chen, Q.; Fan, X.-H.; Zhang, L.-P.; Yang, L.-M. *Synth. Commun.* ***2015***, *45*, 824; Mohanty, A.; Roy, S. *Chem. Commun.* ***2017***, *54*, 10796.

[374] Jahier, C.; Zatolochnaya, O.V.; Zvyagintsev, N.V.; Ananikov, V.P.; Gevorgyan, V. *Org. Lett.* ***2012***, *14*, 2846.

[375] Sheng, W.-B.; Chen, T.-Q.; Zhang, M.-Z.; Tian, M.; Jiang, G.-F.; Guo, C.-C. *Tetrahedron Lett.* ***2016***, *57*, 1641.

[376] Liu, Y.; Wang, C.; Wang, X.; Wan, J.-P. *Tetrahedron Lett.* ***2013***, *54*, 3953.

[377] Schmidt, R.; Thorwirth, R.; Szuppa, T.; Stolle, A.; Ondruschka, B.; Hopf, H. *Chem. Eur. J.* ***2011***, *17*, 8129.

[378] Colazzo, L.; Sedona, F.; Moretto, A.; Casarin, M.; Sambi, M. *J. Am. Chem. Soc.* ***2016***, *138*, 10151.

[379] Schörgenhumer, J.; Waser, M. *Tetrahedron Lett.* ***2016***, *57*, 1678.

[380] Paixão, M.W.; Weber, M.; Braga, A.L; de Azeredo, J.B.; Deobald, A.M.; Stefani, H.A. *Tetrahedron Lett.* ***2008***, *49*, 2366.

[381] Stefani, H.A.; Cella, R.; Dörr, F.A.; Pereira, C.M.P.; Zeni, G.; Gomes Jr., M. *Tetrahedron Lett.* ***2005***, *46*, 563.

[382] Feuerstein, M.; Chahen, L.; Doucet, H.; Santelli, M. *Tetrahedron* ***2006***, *62*, 112.

[383] Weber, M.; Singh, F.V.; Vieira, A.S.; Stefani, H.A.; Paixão, M.W. *Tetrahedron Lett.* ***2009***, *50*, 4324.

[384] See Bolton, R.; Williams, G.H. *Chem. Soc. Rev.* ***1986***, *15*, 261; Hey, D.H. *Adv. Free Radical Chem.* ***1966***, *2*, 47.

R = alkyl, the scope is more limited.[385] Only certain aromatic compounds, particularly benzene rings with two or more nitro groups, and fused ring systems, can be alkylated by this procedure. 1,4-Quinones can be alkylated with diacyl peroxides or with lead tetraacetate (methylation occurs with this reagent).

The mechanism is as shown in Sec. 14.A.iii and CIDNP has been observed.[386] The radicals are produced by cleavage of the O—O bond of diacyl peroxides (R(CO)O—O(CO)R) to give an acyl radical (RCO_2•) that loses CO_2 to give R•. Since no relatively stable free radical is present, most of the product arises from dimerization and disproportionation.[387] The addition of a small amount of nitrobenzene increases the yield of arylation product because the nitrobenzene is converted to diphenyl nitroxide, which abstracts a hydrogen atom and diminishes the extent of side reactions.[388] The Pd-catalyzed methylation of aromatic rings in the presence of dicumyl peroxide is another variation.[389]

Aromatic compounds are converted to a biaryl by aryllead tricarboxylates such as $ArPb(OAc)_3$.[390] Best yields (~70–85%) are obtained when the substrate contains alkyl groups; an electrophilic mechanism is likely. *O*-Phenylation is a possible side reaction. As with the aryllead tricarboxylate reactions, a free-radical mechanism is unlikely.[391]

OS **V**, 51. See also, OS **V**, 952; **VI**, 890.

14-17 Photochemical Arylation of Aromatic Compounds

$$ArH + Ar'I \xrightarrow{h\nu} ArAr'$$

Another free-radical arylation method consists of the photolysis of aryl iodides in an aromatic solvent.[392] The role of directing substituents has been discussed.[393] Yields are generally higher than in **13-28** or **14-16**. The aryl iodide may contain OH or COOH groups. The coupling reaction of iodobenzene and azulene to give a phenylazulene was reported (41% conversion and 85% yield).[394] The mechanism is similar to that of **13-28**. The aryl radicals are generated by photolytic cleavage:

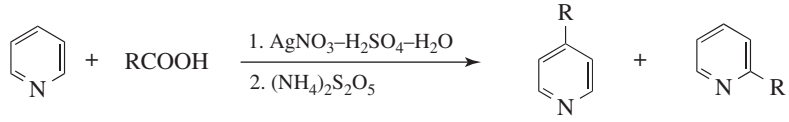
$$ArI \rightarrow AR\bullet + I\bullet$$

The reaction has been applied to intramolecular arylation (analogous to the *Pschorr reaction*).[395]

[385] See Tiecco, M.; Testaferri, L. *React. Intermed. (Plenum)* ***1983***, *3*, 61.
[386] Kaptein, R.; Freeman, R.; Hill, H.D.W.; Bargon, J. *J. Chem. Soc., Chem. Commun.* ***1973***, 953.
[387] The mechanism is actually more complicated. See DeTar, D.F. *J. Am. Chem. Soc.* ***1967***, *89*, 4058. See also, Jandu, K.S.; Nicolopoulou, M.; Perkins, M.J. *J. Chem. Res. (S)* ***1985***, 88.
[388] Chalfont, G.R.; Hey, D.H.; Liang, K.S.Y.; Perkins, M.J. *J. Chem. Soc. B* ***1971***, 233.
[389] Zhang, Y.; Feng, J.; Li, C.-J. *J. Am. Chem. Soc.* ***2008***, *130*, 2900.
[390] Bell, H.C.; Kalman, J.R.; May, G.L.; Pinhey, J.T.; Sternhell, S. *Aust. J. Chem.* ***1979***, *32*, 1531.
[391] Barton, D.H.R.; Finet, J.; Giannotti, C.; Halley, F. *J. Chem. Soc., Perkin Trans. 1* ***1987***, 241.
[392] See Sharma, R.K.; Kharasch, N. *Angew. Chem. Int. Ed.* ***1968***, *7*, 36.
[393] Hofmann, J.; Clark, T.; Heinrich, M.R. *J. Org. Chem.* ***2016***, *81*, 9785.
[394] Ho, T.-I.; Ku, C.-K.; Liu, R.S.H. *Tetrahedron Lett.* ***2001***, *42*, 715.
[395] See Jeffs, P.W.; Hansen, J.F. *J. Am. Chem. Soc.* ***1967***, *89*, 2798; Thyagarajan, B.S.; Kharasch, N.; Lewis, H.B.; Wolf, W. *Chem. Commun.* ***1967***, 614.

Photoirradiation using a Xe lamp, promoted by tetrabutylammonium cyanoborohydride with air, led to radical biaryl coupling of iodoarenes and benzene.[396]

14-18 Alkylation, Acylation, and Carbalkoxylation of Nitrogen Heterocycles[397]



Alkylation of protonated nitrogen heterocycles (e.g., pyridines, quinolines) can be accomplished by treatment with a carboxylic acid, silver nitrate, sulfuric acid, and ammonium peroxydisulfate.[398] The R group can be primary, secondary, or tertiary. The attacking species is R•, formed by[399]

$$2Ag^+ + S_2O_8^{2-} \longrightarrow 2Ag^{2+} + 2SO_4^{2-}$$
$$RCOOH + Ag^{2+} \longrightarrow RCOO\bullet + H^+ + Ag^+$$
$$RCOO\bullet \longrightarrow R\bullet + CO_2$$

A hydroxymethyl group can be introduced (ArH → $ArCH_2OH$) by several variations of this method.[400] Alkylation of these substrates can also be accomplished by generating the alkyl radicals in other ways: from hydroperoxides and $FeSO_4$,[401] from alkyl iodides and H_2O_2/Fe(II),[402] from carboxylic acids and lead tetraacetate, or from the photochemically induced decarboxylation of carboxylic acids by iodosobenzene diacetate.[403] Protonated nitrogen heterocycles can be carbalkoxylated[404] by treatment with esters of α-keto acids and Fenton's reagent.

14.C.ii. Metals as Leaving Groups

14-19 Coupling of Grignard Reagents

$$2RMgX \xrightarrow{M} RR$$

This organometallic coupling reaction is clearly related to the *Wurtz coupling*, discussed in **10-56**, and the coupling of other organometallic compounds is discussed in **14-20**.

[396] Kawamoto, T.; Sato, A.; Ryu, I. *Org. Lett.* ***2014***, *16*, 2111. Also see Kawamoto, T.; Ryu, I. *Org. Biomol. Chem.* ***2014***, *12*, 9733.
[397] See Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* ***1989***, *28*, 489; Vorbrüggen, H.; Maas, M. *Heterocycles* ***1988***, *27*, 2659.
[398] Fontana, F.; Minisci, F.; Barbosa, M.C.N.; Vismara, E. *Tetrahedron* ***1990***, *46*, 2525.
[399] Anderson, J.M.; Kochi, J.K. *J. Am. Chem. Soc.* ***1970***, *92*, 1651.
[400] See Katz, R.B.; Mistry, J.; Mitchell, M.B. *Synth. Commun.* ***1989***, *19*, 317.
[401] Minisci, F.; Selva, A.; Porta, O.; Barilli, P.; Gardini, G.P. *Tetrahedron* ***1972***, *28*, 2415.
[402] Fontana, F.; Minisci, F.; Barbosa, M.C.N.; Vismara, E. *Acta Chem. Scand,* ***1989***, *43*, 995.
[403] Minisci, F.; Vismara, E.; Fontana, F.; Barbosa, M.C.N. *Tetrahedron Lett.* ***1989***, *30*, 4569.
[404] See Heinisch, G.; Lötsch, G. *Angew. Chem. Int. Ed.* ***1985***, *24*, 692.

Grignard reagents can be coupled to give symmetrical dimers[405] by treatment with either thallium(I) bromide[406] or with a transition metal halide such as Fe,[407] Cr, or Cu compounds.[408] The metallic halide is an oxidizing agent and becomes reduced. Both aryl and alkyl Grignard reagents can be dimerized by either procedure, though the TlBr method cannot be applied to R = primary alkyl or to aryl groups with *ortho* substituents. Vinylic and alkynyl Grignard reagents can be coupled (to give 1,3-dienes and 1,3-diynes, respectively) by treatment with $SOCl_2$.[409] Primary alkyl, vinylic, aryl, and benzylic Grignard reagents give symmetrical dimers in high yield (≈90%) when treated with a silver(I) salt in the presence of a nitrogen-containing oxidizing agent such as lithium nitrate, methyl nitrate, or NO_2.[410] This method has been used to close rings of four, five, and six members.[411] The mechanisms of the reactions with metal halides, at least in some cases, probably begin with conversion of RMgX to the corresponding RM (**12-35**), followed by its decomposition to free radicals.[412]

Work continues in this area. The Co-,[413] Cu-,[414] Fe-,[415] and Ni[416]-catalyzed couplings with Grignard reagents are known. The mechanism of the Cu-free asymmetric allylic allylation with Grignard reagents has been explored.[417] The Cu-catalyzed cross coupling of secondary alkyl halides or tosylates with secondary alkyl Grignard reagents, in the presence of TMEDA and LiOMe, has been reported.[418] The Co-catalyzed coupling of alkyl halides with tertiary alkyl Grignard reagents has been reported.[419] The Fe-catalyzed, enantioselective cross coupling of α-chloro esters,[420] and also α-bromo esters,[421] and aryl Grignard reagents has been reported. The *N*-heterocyclic carbene-based, Ni-catalyzed coupling of

[405] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 85–88.

[406] McKillop, A.; Elsom, L.F.; Taylor, E.C. *Tetrahedron* ***1970***, *26*, 4041.

[407] Liu, W.; Lei, A. *Tetrahedron Lett.* ***2008***, *49*, 610.

[408] See Elsom, L.F.; Hunt, J.D.; McKillop, A. *Organomet. Chem. Rev. Sect. A* ***1972***, *8*, 135; Nigh, W.G. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 85–91; Kalkan, M.; Erdik, E.; Pekel, Ö.Ö. *Org. Prep. Proceed. Int.* ***2017***, *49*, 459.

[409] Uchida, A.; Nakazawa, T.; Kondo, I.; Iwata, N.; Matsuda, S. *J. Org. Chem.* ***1972***, *37*, 3749.

[410] Tamura, M.; Kochi, J.K. *Bull. Chem. Soc. Jpn.* ***1972***, *45*, 1120.

[411] Whitesides, G.M.; Gutowski, F.D. *J. Org. Chem.* ***1976***, *41*, 2882.

[412] See Kashin, A.N.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1982***, *51*, 503.

[413] Li, B.; Wu, Z.-H.; Gu, Y.-F.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-S. *Angew. Chem. Int. Ed.* ***2011***, *50*, 1109; Iwasaki, T.; Takagawa, H.; Okamoto, K.; Singh, S.P.; Kuniyasu, H.; Kambe, N. *Synthesis* ***2014***, *46*, 1583.

[414] Ren, P.; Stern, L.-A.; Hu, X. *Angew. Chem. Int. Ed.* ***2012***, *51*, 9110.

[415] Bauer, G.; Cheung, C.W.; Hu, X. *Synthesis* ***2015***, *47*, 1726; Kawamura, S.; Nakamura, M. *Chem. Lett.* ***2013***, *42*, 183.

[416] Vechorkin, O.; Godinat, A.; Scopelliti, R.; Hu, X. *Angew. Chem. Int. Ed.* ***2011***, *50*, 11777; Iwasaki, T.; Tsumura, A.; Omori, T.; Kuniyasu, H.; Terao, J.; Kambe, N. *Chem. Lett.* ***2011***, *40*, 1024; Lohre, C.; Dröge, T.; Wang, C.; Glorius, F. *Chem. Eur. J.* ***2011***, *17*, 6052.

[417] Grassi, D.; Dolka, C.; Jackowski, O.; Alexakis, A. *Chem. Eur. J.* ***2013***, *19*, 1466.

[418] Yang, C.T.; Zhang, Z.-Q.; Liang, J.; Liu, J.-H.; Lu, X.-Y.; Chen, H.-H.; Liu, L. *J. Am. Chem. Soc.* ***2012***, *134*, 11124.

[419] Iwasaki, T.; Takagawa, H.; Singh, S.P.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* ***2013***, *135*, 9604.

[420] Jin, M.; Adak, L.; Nakamura, M. *J. Am. Chem. Soc.* ***2015***, *137*, 7128. For the Fe-catalyzed reaction with chloroalkanes and aryl Grignard reagents, see Ghorai, S.K.; Jin, M.; Hatakeyama, T.; Nakamura, M. *Org. Lett.* ***2012***, *14*, 1066; Perry, M.C.; Gillett, A.N.; Law, T.C. *Tetrahedron Lett.* ***2012***, *53*, 4436.

[421] Liu, F.; Bian, Q.; Mao, J.; Gao, Z.; Liu, D.; Liu, S.; Wang, X.; Wang, Y.; Wang, M.; Zhong, J. *Tetrahedron: Asymmetry* ***2016***, *27*, 663. For a similar Fe-catalyzed reaction with α-bromo acids see Jin, M.; Nakamura, M. *Chem. Lett.* ***2011***, *40*, 1012.

aryl bromide with tertiary alkyl Grignard reagents is known.[422] Pyridinyl Grignard reagents have been coupled with secondary alkyl iodides using $CuLi_2Cl_4$.[423]

OS **VI**, 488.

14-20 Coupling of Other Organometallic Reagents[347]

$$R_2CuLi \xrightarrow[-78\,^\circ C,\ THF]{O_2} RR$$

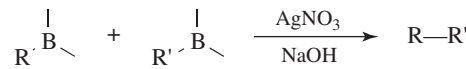
Lithium dialkylcopper reagents can be oxidized to symmetrical dimers by O_2 at −78 °C in THF.[424] The reaction is successful for R = primary and secondary alkyl, vinylic, or aryl groups. Vinylic copper reagents dimerize on treatment with oxygen, or simply on standing at 0 °C for several days or at 25 °C for several hours, to yield 1,3-dienes.[425] Retention of configuration for this reaction has been observed, which demonstrates that free-radical intermediates are not involved.

There are Fe-catalyzed cross-coupling reactions.[426] Coupling products are obtained by treatment of vinylic mercury chlorides[427] with LiCl and a Rh catalyst[428] and by treatment of vinylic tin compounds with a Pd catalyst.[429] Unsymmetrical coupling of vinylic, alkynyl, and arylmercury compounds was achieved in moderate to good yields by treatment with alkyl and vinylic dialkylcopper reagents, for example,[430]

$$PhCH{=}CHHgCl + Me_2CuLi \rightarrow PhCH{=}CHMe$$

The Ni-catalyzed alkyl-alkyl cross-coupling reaction has been reported.[431] The homocoupling of benzylic halides was catalyzed by Ni catalysts.[432] Bromoalkanes were coupled using a Au catalyst.[433] The Pd-catalyzed cross coupling of primary and secondary homoallylic electrophiles is known.[434] The cross coupling of organozinc reagents has been reported.[435]

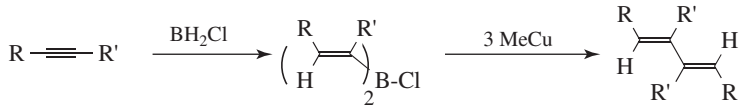
14-21 Coupling of Boranes



[422] Ando, S.; Mawatari, M.; Matsunaga, H.; Ishizuka, T. *Tetrahedron Lett.* ***2016***, *57*, 3287.
[423] Hua, S.-K.; Hu, Q.-P.; Ren, J.; Zeng, B.-B. *Synthesis* ***2013***, *45*, 518.
[424] Whitesides, G.M.; San Filippo Jr., J.; Casey, C.P.; Panek, E.J. *J. Am. Chem. Soc.* ***1967***, *89*, 5302. See also Bertz, S.H.; Gibson, C.P. *J. Am. Chem. Soc.* ***1986***, *108*, 8286.
[425] Rao, S.A.; Periasamy, M. *J. Chem. Soc., Chem. Commun.* ***1987***, 495. See also, Lambert, G.J.; Duffley, R.P.; Dalzell, H.C.; Razdan, R.K. *J. Org. Chem.* ***1982***, *47*, 3350.
[426] Fürstner, A.; Martin, R. *Chem. Lett.* ***2005***, *34*, 624.
[427] See Russell, G.A. *Acc. Chem. Res.* ***1989***, *22*, 1; Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 240–248.
[428] Larock, R.C.; Riefling, B. *J. Org. Chem.* ***1978***, *43*, 1468.
[429] Tolstikov, G.A.; Miftakhov, M.S.; Danilova, N.A.; Vel'der, Ya.L.; Spirikhin, L.V. *Synthesis* ***1989***, 633.
[430] Larock, R.C.; Leach, D.R. *Organometallics* ***1982***, *1*, 74. Also see Larock, R.C.; Hershberger, S.S. *Tetrahedron Lett.* ***1981***, *22*, 2443.
[431] Greene, M.A.; Yonova, I.M.; Williams, F.J.; Jarvo, E.R. *Org. Lett.* ***2012***, *14*, 4293.
[432] Chen, T.; Yang, L.; Li, L.; Huang, K.-W. *Tetrahedron* ***2012***, *68*, 6152.
[433] Tran, H.; McCallum, T.; Morin, M.; Barriault, L. *Org. Lett.* ***2016***, *18*, 4308.
[434] Stokes, B.J.; Opra, S.M.; Sigman, M.S. *J. Am. Chem. Soc.* ***2012***, *134*, 11408.
[435] Pompeo, M.; Froese, R.D.J.; Hadei, N.; Organ, M.G. *Angew. Chem. Int. Ed.* ***2012***, *51*, 11354.

Alkylboranes can be coupled by treatment with silver nitrate and base.[436] Since alkylboranes are easily prepared from alkenes (**15-11**), this is essentially a way of coupling and reducing alkenes; in fact, alkenes can be hydroborated and coupled in the same flask. For symmetrical coupling (R = R′) yields range from 60 to 80% for terminal alkenes and from 35 to 50% for internal ones. Unsymmetrical coupling has also been carried out,[437] but with lower yields. Arylboranes react similarly, yielding biaryls.[438] The mechanism is probably of the free-radical type.

Dimerization of two vinylborane units to give a conjugated diene can be achieved by treatment of divinylchloroboranes (see **15-11**) with methylcopper. (*E*,*E*)-1,3-Dienes are prepared in high yields.[439]



Similarly, symmetrical conjugated diynes RC≡C–C≡CR can be prepared by reaction of lithium dialkyldialkynylborates, $Li^+ [R'_2B(C{\equiv}CR)_2]^-$, with iodine.[440]

The Pd-catalyzed cross coupling of racemic tertiary allylic carbonates and allylboronates gave all-carbon quaternary centers with high regioselectivity and enantioselectivity.[441]

14.C.iii. Halogen as Leaving Group

The conversion of RX to RH can occur by a free-radical mechanism, but this is treated at **19-57**.

14.C.iv. Sulfur as Leaving Group

14-22 Desulfurization

$$RSH \xrightarrow[Ni]{H_2} RH \qquad RSR' \xrightarrow[Ni]{H_2} RH + R'H$$

Thiols and thioethers,[442] both alkyl and aryl, can be desulfurized by hydrogenolysis with Raney nickel.[443] The hydrogen is usually not applied externally, since Raney nickel already contains enough hydrogen for the reaction. Other sulfur compounds can be similarly

[436] Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 306–308.
[437] Brown, H.C.; Verbrugge, C.; Snyder, C.H. *J. Am. Chem. Soc.* ***1961***, *83*, 1001.
[438] Breuer, S.W.; Broster, F.A. *Tetrahedron Lett.* ***1972***, 2193.
[439] See Rao, V.V.R.; Kumar, C.V.; Devaprabhakara, D. *J. Organomet. Chem.* ***1979***, *179*, C7; Campbell Jr.; J.B.; Brown, H.C. *J. Org. Chem.* ***1980***, *45*, 549.
[440] Pelter, A.; Hughes, R.; Smith, K.; Tabata, M. *Tetrahedron Lett.* ***1976***, 4385; Sinclair, J.A.; Brown, H.C. *J. Org. Chem.* ***1976***, *41*, 1078.
[441] Zhang, P.; Le, H.; Kyne, R.E.; Morken, J.P. *J. Am. Chem. Soc.* ***2011***, *133*, 9716.
[442] See Block, E. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, pt. 1, Wiley, NY, ***1980***, pp. 585–600.
[443] See Belen'kii, L.I. in Belen'kii, L.I. *Chemistry of Organosulfur Compounds*, Ellis Horwood, Chichester, ***1990***, pp. 193–228; Pettit, G.R.; van Tamelen, E.E. *Org. React.* ***1962***, *12*, 356; Hauptmann, H.; Walter, W.F. *Chem. Rev.* ***1962***, *62*, 347.

desulfurized,[444] among them disulfides (RSSR), thiono esters (RCSOR′),[445] thioamides (RCDNHR′), sulfoxides, and dithioacetals. The last reaction, which is an indirect way of accomplishing reduction of a carbonyl to a methylene group (see **19-66**), can also give the alkene if a hydrogen atom is present.[446] In most of the examples given, R can also be aryl. Other reagents[447] have also been used,[448] including Sm in acetic acid for desulfurization of vinyl sulfones.[449] A lanthanum-catalyzed desulfurization system has been developed in ionic liquids.[450] The Co-catalyzed desulfurization reaction has been applied to the preparation of isothiocyanates.[451]

An important special case of RSR reduction is desulfurization of thiophene derivatives. This proceeds with concomitant reduction of the double bonds. Many compounds have been made by alkylation of thiophene, followed by catalytic hydrogenation that led to desulfurization and formation of the corresponding alkane. Thiophenes can also be desulfurized to alkenes ($RCH_2CH{=}CHCH_2R'$) with a nickel boride catalyst prepared from $NiCl_2$ and $NaBH_4$ in methanol.[452] It is possible to reduce just one SR group of a dithioacetal by treatment with borane/pyridine in trifluoroacetic acid or in CH_2Cl_2 in the presence of $AlCl_3$.[453] Phenyl selenides RSePh can be reduced to RH with Ph_3SnH[454] or with nickel boride.[455]

It has been shown that reduction of thiophene proceeds through butadiene and butene, not through butane-1-thiol or other sulfur compounds. In other words, the sulfur is removed before the double bonds are reduced, as demonstrated by isolation of the alkenes and the failure to isolate any potential sulfur-containing intermediates.[456]

See Chapter 19 for other reduction reactions involving sulfur compounds.

OS **IV**, 638; **V**, 419; **VI**, 109, 581, 601. See also, OS **VII**, 124, 476.

Sulfides can be cleaved, with a phenylthio group replaced by a lithium,[457] by treatment with Li or lithium naphthalenide in THF.[458] Good yields have been obtained with R = primary, secondary, or tertiary alkyl, or allylic,[459] and containing groups such as double bonds or halogens. Dilithio compounds can be made from compounds containing two separated SPh groups, but it is also possible to replace just one SPh from a compound with two such groups on a single carbon, to give an α-lithio sulfide.[460] The reaction has also been used to prepare α-lithio ethers and α-lithio organosilanes.[457] For some of these compounds

[444] Rentner, J.; Kljajic, M.; Offner, L.; Breinbauer, R. *Tetrahedron* ***2014***, *70*, 8983.
[445] See Baxter, S.L.; Bradshaw, J.S. *J. Org. Chem.* ***1981***, *46*, 831.
[446] Fishman, J.; Torigoe, M.; Guzik, H. *J. Org. Chem.* ***1963***, *28*, 1443.
[447] For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 53-60. See Luh, T.; Ni, Z. *Synthesis* ***1990***, 89; Becker, S.; Fort, Y.; Vanderesse, R.; Caubère, P. *J. Org. Chem.* ***1989***, *54*, 4848.
[448] See Shigemasa, Y.; Ogawa, M.; Sashiwa, H.; Saimoto, H. *Tetrahedron Lett.* ***1989***, *30*, 1277; Ho, K.M.; Lam, C.H.; Luh, T. *J. Org. Chem.* ***1989***, *54*, 4474.
[449] Liu, Y.; Zhang, Y. *Org. Prep. Proceed. Int.* ***2001***, *33*, 376.
[450] Xu, J.; Zhao, S.; Chen, W.; Wang, M.; Song, Y.-F. *Chem. Eur. J.* ***2012***, *18*, 4775.
[451] Seelam, M.; Shaik, B.; Kammela, P.R. *Synth. Commun.* ***2016***, *46*, 1759.
[452] Schut, J.; Engberts, J.B.F.N.; Wynberg, H. *Synth. Commun.* ***1972***, *2*, 415.
[453] Kikugawa, Y. *J. Chem. Soc., Perkin Trans. 1* ***1984***, 609.
[454] Clive, D.L.J.; Chittattu, G.; Wong, C.K. *J. Chem. Soc., Chem. Commun.* ***1978***, 41.
[455] Back, T.G. *J. Chem. Soc., Chem. Commun.* ***1984***, 1417.
[456] Owens, P.J.; Ahmberg, C.H. *Can. J. Chem.* ***1962***, *40*, 941.
[457] See Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* ***1989***, *22*, 152.
[458] Screttas, C.G.; Micha-Screttas, M. *J. Org. Chem.* ***1978***, *43*, 1064; ***1979***, *44*, 713.
[459] See Cohen, T.; Guo, B. *Tetrahedron* ***1986***, *42*, 2803.
[460] See Cohen, T.; Sherbine, J.P.; Matz, J.R.; Hutchins, R.R.; McHenry, B.M.; Willey, P.R. *J. Am. Chem. Soc.* ***1984***, *106*, 3245; Ager, D.J. *J. Chem. Soc., Perkin Trans. 1* ***1986***, 183.

lithium 1-(dimethylamino)naphthalenide is a better reagent than either Li metal or lithium naphthalenide.[461] The mechanism is presumably of the free-radical type.

$$\text{RSPh} \xrightarrow[\text{THF}]{\text{Li Naphthalenide}} \text{RLi}$$

14.C.v. Carbon as Leaving Group

14-23 Decarboxylative Dimerization. The Kolbe Reaction

$$2\text{RCOO}^- \xrightarrow{\text{Electrolysis}} \text{R—R}$$

Electrolysis of carboxylate ions leads to decarboxylation, and combination of the resulting radicals to give the coupling product R—R. This coupling reaction is called the *Kolbe reaction* or the *Kolbe electrosynthesis*.[462] It is used to prepare symmetrical R—R, where R is straight chained, since little or no yield is obtained when there is branching. The reaction is not successful for R = aryl. Many functional groups may be present, though many others inhibit the reaction.[462] Unsymmetrical R—R′ have been made by coupling mixtures of acid salts. The Kolbe reaction has been done using solid-supported bases.[463]

A free-radical mechanism is involved, via formation of RCOO•, loss of CO_2, and formation of R•.

$$\text{RCOO}^- \xrightarrow[\text{oxidation}]{\text{Electrolytic}} \text{RCOO}\bullet \xrightarrow{-\text{CO}_2} \text{R}\bullet \longrightarrow \text{R—R}$$

There is much evidence[464] for this mechanism, including side products (R—H, alkenes) that are characteristic of free-radical intermediates and the fact that electrolysis of acetate ion in the presence of styrene caused some of the styrene to polymerize to polystyrene (such polymerizations can be initiated by free radicals, Sec. 15.B.i). Other side products (ROH, RCO_2R) are sometimes found, stemming from further oxidation of the radical R• to a carbocation R^+.[465]

When the reaction is conducted in the presence of 1,3-dienes, additive dimerization can occur.[466] The radical R• adds to the conjugated system to give $RCH_2CH{=}CHCH_2\bullet$, which dimerizes. Another possible product is $RCH_2CH{=}CHCH_2R$, from coupling of the two kinds of radicals.[467]

[461] See Cohen, T.; Matz, J.R. *Synth. Commun.* ***1980***, *10*, 311.

[462] See Nuding, G.; Vögtle, F.; Danielmeier, K.; Steckhan, E. *Synthesis* ***1996***, 71; Schäfer, H.J. *Top. Curr. Chem.* ***1990***, *152*, 91; *Angew. Chem. Int. Ed.* ***1981***, *20*, 911; Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 238–253; Eberson, L.; Utley, J.H.P. in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, ***1983***, pp. 435–462. Also see Ogawa, K.A.; Boydston, A.J. *Chem. Lett.* ***2015***, *44*, 10.

[463] Kurihara, H.; Fuchigami, T.; Tajima, T. *J. Org. Chem.* ***2008***, *73*, 6888.

[464] See Kraeutler, B.; Jaeger, C.D.; Bard, A.J. *J. Am. Chem. Soc.* ***1978***, *100*, 4903.

[465] See Corey, E.J.; Bauld, N.L.; La Londe, R.T.; Casanova Jr, J.; Kaiser, E.T. *J. Am. Chem. Soc.* ***1960***, *82*, 2645.

[466] Khrizolitova, M.A.; Mirkind, L.A.; Fioshin, M.Ya. *J. Org. Chem. USSR* ***1968***, *4*, 1640; Bruno, F.; Dubois, J.E. *Bull. Soc. Chim. Fr.* ***1973***, 2270.

[467] See Schäfer, H.; Pistorius, R. *Angew. Chem. Int. Ed.* ***1972***, *11*, 841.

The synthesis of terminal allenes was reported using a Cu-catalyzed decarboxylative coupling of carboxylic acids.[468] A silver-catalyzed C—S cross-coupling reaction of aliphatic carboxylic acids has been reported.[469]

In a nonelectrolytic process, aryl acetic acids are converted to *vic*-diaryl compounds

$$2ArCR_2COOH \rightarrow ArCR_2CR_2Ar$$

by treatment with sodium persulfate ($Na_2S_2O_8$) and a catalytic amount of $AgNO_3$.[470] Photolysis of carboxylic acids in the presence of Hg_2F_2 leads to the dimeric alkane via decarboxylation.[471] Both of these reactions involve dimerization of free radicals.

OS **III**, 401; **V**, 445, 463; **VII**, 181.

14-24 The Hunsdiecker Reaction

$$RCOOAg + Br_2 \longrightarrow RBr + CO_2 + AgBr$$

Reaction of a silver salt of a carboxylic acid with bromine is called the *Hunsdiecker reaction*[472] and is a method of decreasing the length of a carbon chain by one unit.[473] The reaction is of wide scope, giving good results for *n*-alkyl R from 2 to 18 carbons and for many branched R too, producing primary, secondary, and tertiary bromides. Many functional groups may be present as long as they are not α substituted. R may also be aryl. However, if R contains unsaturation, the reaction seldom gives good results. Although bromine is the most often used halogen, chlorine and iodine have also been used. Catalytic Hunsdiecker reactions are known,[474] and microwave enhancement has been employed.[475] A transition metal-free Hunsdiecker reaction has been reported.[476]

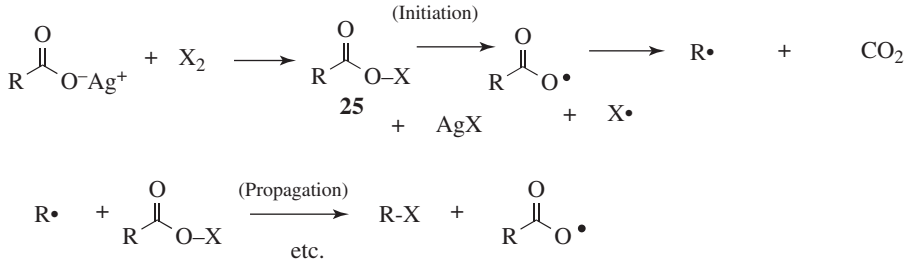
When iodine is the reagent, the ratio between the reactants is very important and determines the products. A 1 : 1 ratio of salt/iodine gives the alkyl halide, as above. A 2 : 1 ratio, however, gives the ester RCOOR. This is called the *Simonini reaction* and is sometimes used to prepare carboxylic esters. The Simonini reaction can also be carried out with lead salts of acids.[477] A more convenient way to perform the *Hunsdiecker reaction* is by use of a mixture of the acid and mercuric oxide instead of the silver salt, since the silver salt must be very pure and dry and such pure silver salts are often not easy to prepare.[478]

A catalytic Hunsdiecker reaction of aliphatic carboxylic acids has been reported, catalyzed by $Ag(Phen)_2OTf$, in which the reaction of carboxylic acids with *t*-butyl

[468] Lim, J.; Choi, J.; Kim, H.-S.; Kim, I.S.; Nam, K.C.; Kim, J.; Lee, S. *J. Org. Chem.* ***2016***, *81*, 303.
[469] Wang, P.-F.; Wang, X.-Q.; Dai, J.J.; Feng, Y.-S.; Xu, H.-J. *Org. Lett.* ***2014***, *16*, 4586.
[470] Fristad, W.E.; Klang, J.A. *Tetrahedron Lett.* ***1983***, *24*, 2219.
[471] Habibi, M.H.; Farhadi, S. *Tetrahedron Lett.* ***1999***, *40*, 2821.
[472] This reaction was first reported by the Russian composer-chemist Alexander Borodin: *Liebigs Ann. Chem.* ***1861***, *119*, 121.
[473] See Wilson, C.V. *Org. React.* ***1957***, *9*, 332; Johnson, R.G.; Ingham, R.K. *Chem. Rev.* ***1956***, *56*, 219. Also see, Naskar, D.; Chowdhury, S.; Roy, S. *Tetrahedron Lett.* ***1998***, *39*, 699.
[474] Das, J.P.; Roy, S. *J. Org. Chem.* ***2002***, *67*, 7861.
[475] Kuang, C.; Yang, Q.; Senboku, H.; Tokuda, M. *Synthesis* ***2005***, 1319.
[476] Li, Z.; Wang, K.; Liu, Z.-Q. *Synlett* ***2014***, *25*, 2508.
[477] Bachman, G.B.; Kite, G.F.; Tuccarbasu, S.; Tullman, G.M. *J. Org. Chem.* ***1970***, *35*, 3167.
[478] Cristol, S.J.; Firth, W.C. *J. Org. Chem.* ***1961***, *26*, 280. See also, Meyers, A.I.; Fleming, M.P. *J. Org. Chem.* ***1979***, *44*, 3405, and references cited therein.

hypochlorite gave the corresponding alkyl chloride.[479] Using $AgNO_3$ as a catalyst, aliphatic carboxylic acids gave decarboxylative fluorination with Selectfluor in aqueous solution, leading to alkyl fluorides.[480]

The mechanism of the Hunsdiecker reaction is believed to involve formation of R•. The first step is not a free-radical process, and its actual mechanism is not known.[481] Compound **25** is an acyl hypohalite and is presumed to be an intermediate, although it has never been isolated from the reaction mixture.



Among the evidence for the mechanism is that optical activity at R is lost (except when a neighboring bromine atom is present, Sec. 14.A.iv); if R is neopentyl, there is no rearrangement, which would certainly happen with a carbocation; and the side products, notably R—R, are consistent with a free-radical mechanism. There is evidence that the Simonini reaction involves the same mechanism as the Hunsdiecker reaction, but that the alkyl halide formed then reacts with excess RCOOAg (**10-17**) to give the ester[482] (see also, **19-12**).

Other methods for accomplishing the conversion RCOOH → RX are[483] (i) treatment of thallium(I) carboxylates with bromine;[484] (ii) treatment of carboxylic acids with lead tetraacetate and halide *ions* (Cl^-, Br^-, or I^-);[485] (iii) reaction of the acids with lead tetraacetate and NCS, which gives tertiary and secondary chlorides in good yields but is not good for R = primary alkyl or phenyl;[486] (iv) treatment of thiohydroxamic esters with CCl_4, $BrCCl_3$ (which gives bromination), CHI_3, or CH_2I_2 in the presence of a radical initiator;[487] (v) photolysis of benzophenone oxime esters of carboxylic acids in CCl_4 ($RCON{=}CPh_2 \rightarrow RCl$).[488] Alkyl fluorides can be prepared in moderate to good yields by treating carboxylic acids RCOOH with XeF_2.[489] This method works best for R = primary and tertiary alkyl, and benzylic. Aromatic and vinylic acids do not react.

[479] Wang, Z.; Zhu, L.; Yin, F.; Su, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* ***2012***, *134*, 4258.
[480] Yin, F.; Wang, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* ***2012***, *134*, 10401.
[481] When Br2 reacts with aryl R, at low temperature in inert solvents, it is possible to isolate a complex containing both Br2 and the silver carboxylate: see Bryce-Smith, D.; Isaacs, N.S.; Tumi, S.O. *Chem. Lett.* ***1984***, 1471.
[482] Bunce, N.J.; Murray, N.G. *Tetrahedron* ***1971***, *27*, 5323.
[483] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 741–744.
[484] Cambie, R.C.; Hayward, R.C.; Jurlina, J.L.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc., Perkin Trans. 1* ***1981***, 2608.
[485] See Sheldon, R.A.; Kochi, J.K. *Org. React.* ***1972***, *19*, 279, pp. 326–334, 390–399.
[486] Becker, K.B.; Geisel, M.; Grob, C.A.; Kuhnen, F. *Synthesis* ***1973***, 493.
[487] Barton, D.H.R.; Lacher, B.; Zard, S.Z. *Tetrahedron* ***1987***, *43*, 4321; Stofer, E.; Lion, C. *Bull. Soc. Chim. Belg.* ***1987***, *96*, 623; Della, E.W.; Tsanaktsidis, J. *Aust. J. Chem.* ***1989***, *42*, 61.
[488] Hasebe, M.; Tsuchiya, T. *Tetrahedron Lett.* ***1988***, *29*, 6287.
[489] Patrick, T.B.; Johri, K.K.; White, D.H.; Bertrand, W.S.; Mokhtar, R.; Kilbourn, M.R.; Welch, M.J. *Can. J. Chem.* ***1986***, *64*, 138. For another method, see Grakauskas, V. *J. Org. Chem.* ***1969***, *34*, 2446.

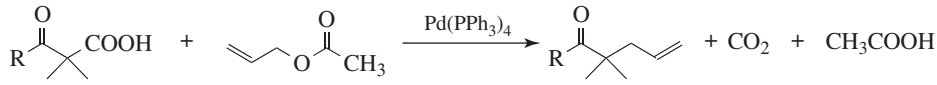
Vinyl carboxylic acids (conjugated acids) were shown to react with NBS and lithium acetate in aqueous acetonitrile, to give the corresponding vinyl bromide:

$$C{=}C{-}CO_2H \rightarrow C{=}C{-}Br$$

using microwave irradiation.[490] A similar reaction was reported using Na_2MoO_4, KBr, and aqueous hydrogen peroxide.[491]

OS **III**, 578; **V**, 126; **VI**, 179; **75**, 124; **X**, 237. See also, OS **VI**, 403.

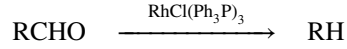
14-25 Decarboxylative Alkylation, Alkenylation, or Alkynylation



The COOH group of a β-keto acid is replaced by an allylic group when the acid is treated with an allylic acetate and a palladium catalyst at room temperature.[492] The reaction is successful for various substituted allylic groups. The less highly substituted end of the allylic group forms the new bond. Thus, both $CH_2{=}CHCHMeOAc$ and $MeCH{=}CHCH_2OAc$ gave $O{=}C(R){-}C{-}CH_2CH{=}CHMe$ as the product.

The transition metal decarboxylative allylation and benzylation are well known.[493] Using $AgNO_3$ as the catalyst and $K_2S_2O_8$ as the oxidant, aliphatic carboxylic acids gave decarboxylative alkynylation to give alkylated alkynes using commercially available ethynylbenziodoxolones in aqueous solution.[494] The Ni-catalyzed decarboxylative coupling of alkynyl carboxylic acids and allylic acetates has been reported.[495] The I_2O_5-promoted decarboxylative trifluoromethylation of cinnamic acids has been reported.[496] A cationic [Ru—H] complex catalyzes selective coupling of α- and β-amino acids with ketones via decarboxylation and deamination to form α-alkylated ketone products.[497] Aromatic and heteroaromatic carboxylic acids have been used for decarboxylative coupling.[498] The Ir-catalyzed decarboxylative allylation of β-keto acids gave γ,δ-unsaturated ketones.[499]

14-26 Decarbonylation of Aldehydes and Acyl Halides



[490] Kuang, C.; Senboku, H.; Tokuda, M. *Synlett* ***2000***, 1439.
[491] Sinha, J.; Layek, S.; Bhattacharjee, M.; Mandal, G.C. *Chem. Commun.* ***2001***, 1916.
[492] Tsuda, T.; Okada, M.; Nishi, S.; Saegusa, T. *J. Org. Chem.* ***1986***, *51*, 421. Also see, Konev, M.O.; Jarvo, E.R. *Angew. Chem. Int. Ed.* ***2016***, *55*, 11340.
[493] Weaver, J.D.; Recio III, A.; Grenning, J.; Tunge, J.A. *Chem. Rev.* ***2011***, *111*, 1846; Wei, Y.; Hu, P.; Zhang, M.; Su, W. *Chem. Rev.* ***2017***, *117*, 8864.
[494] Liu, X.; Wang, Z.; Cheng, X.; Li, C. *J. Am. Chem. Soc.* ***2012***, *134*, 14330.
[495] Choe, J.; Yang, J.; Park, K.; Palani, T.; Lee, S. *Tetrahedron Lett.* ***2012***, *53*, 6908.
[496] Shang, X.-J.; Li, Z.; Liu, Z.-Q. *Tetrahedron Lett.* ***2015***, *56*, 233.
[497] Kalutharage, N.; Yi, C.S. *Angew. Chem. Int. Ed.* ***2013***, *52*, 13651.
[498] Cornella, J.; Larrosa, I. *Synthesis* ***2012***, *44*, 653.
[499] Chen, S.-J.; Lu, G.-P.; Cai, C. *Chem. Commun.* ***2015***, *51*, 11512.

Aldehydes, both aliphatic and aromatic, can be decarbonylated[500] by heating with a Rh,[501] Pd,[502] or other catalysts such as $RhCl(Ph_3P)_3$, which is often called *Wilkinson's catalyst*.[503] In an older reaction aliphatic (but not aromatic) aldehydes are decarbonylated by heating with di-*tert*-butyl peroxide or other peroxides,[504] usually in a solution containing a hydrogen donor, such as a thiol. The reaction has also been initiated with light, and thermally (without an initiator) by heating at ~500 °C.

Wilkinson's catalyst has also been reported to decarbonylate aromatic acyl halides at 180 °C (ArCOX → ArX).[505] This reaction has been carried out with acyl iodides,[506] bromides, and chlorides. Aliphatic acyl halides that lack a hydrogen also give this reaction,[507] but if an α hydrogen is present, elimination takes place instead (**17-15**).

A cyanobacterial aldehyde decarbonylase was used to convert fatty aldehydes to alkanes.[508] The reaction of fatty aldehydes with cyanobacterial aldehyde decarbonylase gave the alkane and formate via decarbonylation.[509] The Ni/*N*-heterocyclic carbene-mediated decarbonylation of simple diaryl ketones gave biaryl compounds.[510] The Ru-catalyzed decarbonylation of alkynyl α-diones gave conjugated ynones and disubstituted alkynes.[511] The decarbonylation of tertiary aldehydes occurs "on-water" at room temperature in the presence of BHT (butylated hydroxytoluene) or in the absence of air, while no reaction takes place in organic solvents.[512] A Pd-catalyzed aldehyde decarbonylation has been reported.[513] Decarbonylation reactions have been done under flow conditions (Sec.7.D).[514]

It is possible to decarbonylate acyl halides in another way, to give alkanes (RCOCl → RH) by heating the substrate with tripropylsilane Pr_3SiH in the presence of *tert*-butyl peroxide.[515] Yields are good for R = primary or secondary alkyl and poor for R = tertiary alkyl or benzylic. There is no reaction when R = aryl.

[500] See Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA, ***1987***, pp. 768–775; Baird, M.C. in Patai, S. *The Chemistry of Functional Groups, Supplement B*, pt. 2, Wiley, NY, ***1979***, pp. 825–857; Tsuji, J. in Wender, I.; Pino, P. *Organic Syntheses Via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 595–654.

[501] Ohno, K.; Tsuji, J. *J. Am. Chem. Soc.* ***1968***, *90*, 99; Baird, C.W.; Nyman, C.J.; Wilkinson, G. *J. Chem. Soc. A* ***1968***, 348.

[502] Rylander, P.N. *Organic Synthesis with Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 260–267.

[503] For a review of this catalyst, see Jardine, F.H. *Prog. Inorg. Chem.* ***1981***, *28*, 63.

[504] See Vinogradov, M.G.; Nikishin, G.I. *Russ. Chem. Rev.* ***1971***, *40*, 916; Schubert, W.M.; Kintner, R.R. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 711–735.

[505] Kampmeier, J.A.; Rodehorst, R.; Philip Jr., J.B. *J. Am. Chem. Soc.* ***1981***, *103*, 1847.

[506] Blum, J.; Rosenman, H.; Bergmann, E.D. *J. Org. Chem.* ***1968***, *33*, 1928.

[507] Tsuji, J.; Ohno, K. *Tetrahedron Lett.* ***1966***, 4713; *J. Am. Chem. Soc.* ***1966***, *88*, 3452.

[508] Warui, D.M.; Li, N.; Nørgaard, H.; Krebs, C.; Bollinger Jr., J.M.; Booker, S.J. *J. Am. Chem. Soc.* ***2011***, *133*, 3316.

[509] Li, N.; Nørgaard, H.; Warui, D.M.; Booker, S.J.; Krebs, C.; Bollinger Jr., J.M. *J. Am. Chem. Soc.* ***2011***, *133*, 6158.

[510] Morioka, T.; Nishizawa, A.; Furukawa, T.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* ***2017***, *139*, 1416.

[511] Whittaker, R.E.; Dong, G. *Org. Lett.* ***2015***, *17*, 5504.

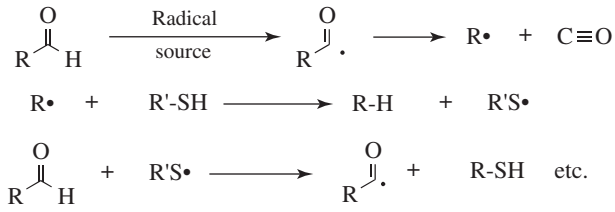
[512] Rodrigues, C.A.B.; de Matos, M.N.; Guerreiro, B.M.H.; Gonçalves, A.M.L.; Romão, C.C.; Afonso, C.A.M. *Tetrahedron Lett.* ***2011***, *52*, 2803.

[513] Modak, A.; Deb, A.; Patra, T.; Rana, S.; Maity, S.; Maiti, D. *Chem. Commun.* ***2012***, *48*, 4253.

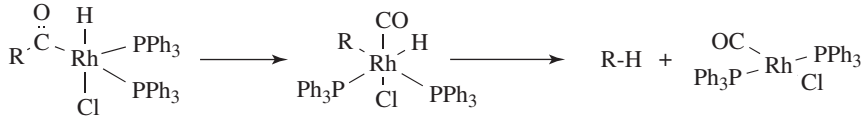
[514] Gutmann, B.; Elsner, P.; Glasnov, T.; Roberge, D.M.; Kappe, C.O. *Angew. Chem. Int. Ed.* ***2014***, *53*, 11557.

[515] Billingham, N.C.; Jackson, R.A.; Malek, F. *J. Chem. Soc., Perkin Trans. 1* ***1979***, 1137.

The mechanism of the peroxide- or light-induced reaction seems to be as shown (in the presence of thiols).[516]



The reaction of aldehydes with Wilkinson's catalyst goes through complexes of the form **26** and **27**, which have been trapped.[517] The reaction has been shown to give retention of configuration at a chiral R;[518] and deuterium labeling demonstrates that the reaction is intramolecular: RCOD gives RD.[519] Free radicals are not involved.[520] The mechanism with acyl halides appears to be more complicated.[521]



26 **27**

For aldehyde decarbonylation by an electrophilic mechanism, see **11-34**.

[516] Berman, J.D.; Stanley, J.H.; Sherman, V.W.; Cohen, S.G. *J. Am. Chem. Soc.* ***1963***, *85*, 4010; Fristrup, P.; Kreis, M.; Palmelund, A.; Norrby, P.-O.; Madsen, R. *J. Am. Chem. Soc.* ***2008***, *130*, 5206.

[517] Kampmeier, J.A.; Harris, S.H.; Mergelsberg, I. *J. Org. Chem.* ***1984***, *49*, 621.

[518] Walborsky, H.M.; Allen, L.E. *J. Am. Chem. Soc.* ***1971***, *93*, 5465. See also, Tsuji, J.; Ohno, K. *Tetrahedron Lett.* ***1967***, 2173.

[519] Walborsky, H.M.; Allen, L.E. *J. Am. Chem. Soc.* ***1971***, *93*, 5465. See, however, Baldwin, J.E.; Bardenm, T.C.; Pugh, R.L.; Widdison, W.C. *J. Org. Chem.* ***1987***, *52*, 3303.

[520] Kampmeier, J.A.; Harris, S.H.; Wedegaertner, D.K. *J. Org. Chem.* ***1980***, *45*, 315.

[521] Kampmeier, J.A.; Liu, T. *Organometallics* ***1989***, *8*, 2742.

CHAPTER 15

Addition to Carbon–Carbon Multiple Bonds

There are four fundamental ways in which addition to a double or triple bond can take place.[1] Three of these are two-step processes, with (i) initial attack by a nucleophile[2] or (ii) attack upon an electrophile or (iii) attack upon a free radical. The second step consists of combination of the resulting intermediate with, respectively, a positive species, a negative species, or a neutral entity. In the fourth type of mechanism, attack at the two carbon atoms of the double or triple bond is simultaneous (concerted). Which of the four mechanisms is operating in any given case is determined by the nature of the substrate, the reagent, and the reaction conditions. Some of the reactions in this chapter can take place by all four mechanistic types. Note that the bond Fukui function has been suggested as a new reactivity index capable of predicting the evolution of bond-breaking and bond-formation processes during an organic reaction involving π conjugated systems.[3] The frontier electron densities proposed by Fukui[4] are local properties that depend on a function $f(r)$ that differentiates one part of a molecule from another and serve as a reactivity index. The density functional expression of this idea is the Fukui function, defined by Parr and Yang.[5] The reactivity of alkenes and alkynes was probed using activation energies, enthalpies of protonation, and carbon 1*s* ionization energies.[6]

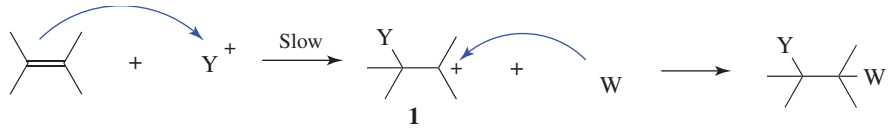
[1] Graulich, N.; Hopf, H.; Schreiner, P.R. *Chem. Eur. J.* ***2011***, *17*, 30.
[2] Ashtekar, K.D.; Vetticatt, M.; Yousefi, R.; Jackson, J.E.; Borhan, B. *J. Am. Chem. Soc.* ***2016***, *138*, 8114.
[3] Gonzalez-Suarez, M.; Aizman, A.; Soto-Delgado, J.; Contreras, R. *J. Org. Chem.* ***2012***, *77*, 90.
[4] Fukui, K. *Theory of Orientation and Stereoselection*, Springer, Berlin, ***1973***; Fukui, K. *Science* ***1982***, *217*, 747.
[5] Parr, R.G,; Yang, W. *J. Am. Chem. Soc.* ***1984***, *106*, 4049; Yang, W.; Parr, R.G.; Pucci, R. *J. Chem. Phys.* ***1984***, *81*, 2862.
[6] Holme, A.; Sæthre, L.J.; Børve, K.J.; Thomas, T.D. *J. Org. Chem.* ***2012***, *77*, 10105.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

15.A. MECHANISMS

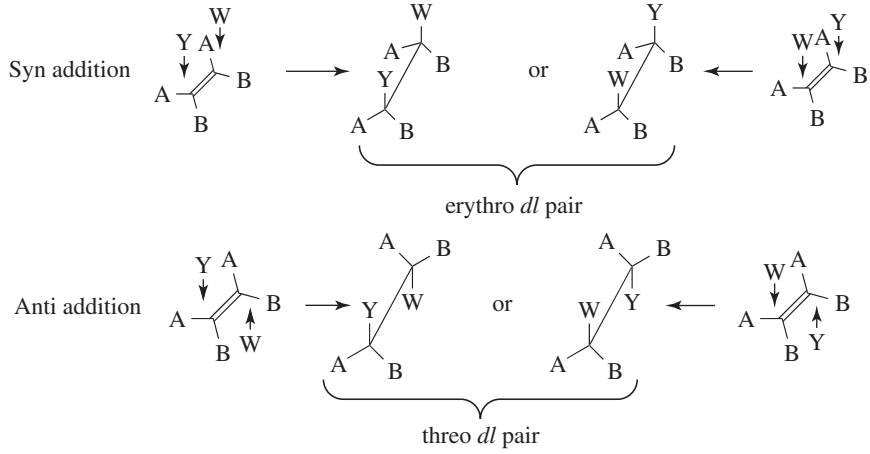
15.A.i. Electrophilic Addition[7]

In the electrophilic addition mechanism, a positive species approaches the double or triple bond and, in the first step, forms a bond by donation of the π pair of electrons[8] to the electrophilic species to form a σ bond:



1

The IUPAC designation for this mechanism is $A_E + A_N$ (or $A_H + A_N$ if $Y^+ = H^+$). As in electrophilic substitution (Sec. 11.A.i), the reactive species need not actually be a positive ion (Y^+) but can be the positive end of a dipole or an induced dipole, but the electron-rich π bond donates two electrons to Y^+. The product of this reaction is a highly reactive intermediate, a carbocation (**1**). In a second step, carbocation **1** reacts with a species that can donate an electron pair and often bears a negative charge, W. This reaction of an electron-rich species with the electron-deficient carbocation is the same as the second step of the S_N1 mechanism. The mechanism is called Ad_E2 (electrophilic addition, bimolecular).



The most useful type of information for investigating the mechanism of addition to a double bond, is perhaps, the stereochemistry of the reaction.[9] The two carbons of the double bond and the four atoms immediately attached to them are all in a plane (Sec. 1.D); there are

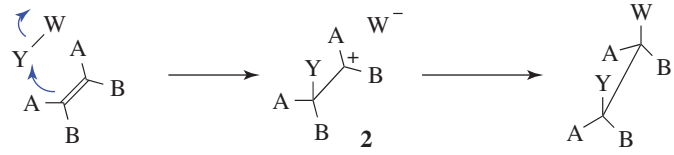
[7] See de la Mare, P.B.D.; Bolton, R. *Electrophilic Additions to Unsaturated Systems*, 2nd ed., Elsevier, NY, ***1982***. For reviews, see Schmid, G.H. in Patai, S. *The Chemistry of Double-Bonded Functional Groups*, *Supplement A*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 679–731; Schmid, G.H.; Garratt, D.G. in Patai, S. *The Chemistry of Double-Bonded Functional Groups*, *Supplement A*, Vol. 1, pt. 2, Wiley, NY, ***1977***, pp. 725–912; Freeman, F. *Chem. Rev.* ***1975***, *75*, 439.

[8] See Mayr, H.; Kempf, B.; Ofial, A.R. *Acc. Chem. Res.* ***2003***, *36*, 66; Meng, B.; Ma, S. *Org. Lett.* ***2012***, *14*, 2674; Zenz, I.; Mayr, H. *J. Org. Chem.* ***2011***, *76*, 9370.

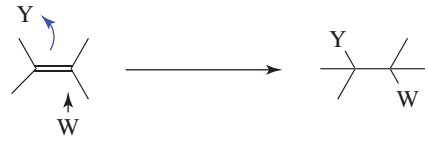
[9] See Fahey, R.C. *Top. Stereochem.* ***1968***, *3*, 237; Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2 (pp. 3–15).

thus three possibilities. The reaction is stereospecific and there are two possible modes of addition. Both Y and W may enter from the same side of the plane (*syn* addition), in which case the *syn* diastereomer will be the major product, or they may enter from opposite sides (*anti* addition) and the *anti* diastereomer will be the major product. Another possibility is that the reaction may be nonstereospecific. In order to determine which of these possibilities is occurring in a given reaction, the following type of experiment is often done: Y—W is added to the *cis* and *trans* isomers of an alkene of the form ABC═CBA. Using the *cis* alkene as an example, if the addition is *syn*, the diastereomer formed will be the *erythro dl* pair, because each carbon has a 50% chance of being attacked by Y. On the other hand, if the addition is *anti*, the diastereomer formed will be the *threo dl* pair.

Of course, the *trans* isomer will give a different result for this stereospecific reaction: the *threo* pair if the addition is *syn* and the *erythro* pair if it is *anti*. The *threo* and *erythro* diastereomers have different physical properties, as expected. In the special case where Y = W (as in the addition of Br_2), the *syn* addition gives only one compound via both modes of addition, and the *erythro* diastereomer is a *meso* compound. In addition to triple bond compounds of the type AC≡CA, *syn* addition results in a *cis* alkene and *anti* addition in a *trans* alkene. By the definition given in Sec. 4.N, addition to triple bonds cannot be stereospecific, although it can be, and often is, stereoselective. This contrasts with a circumstance that would favor *syn* addition: formation of an ion pair **2** after the addition of Y.[10] Since W is already on the same side of the plane as Y, collapse of the ion pair leads to syn addition.



Another possibility is that *anti* addition might, at least in some cases, be caused by the operation of a mechanism in which attack by W and Y are essentially *simultaneous* but from opposite sides:



This mechanism, called the Ad_E3 mechanism (*termolecular addition*, IUPAC A_NA_E),[11] has the disadvantage that three molecules must come together in the transition state. Note that it is the reverse of the E2 mechanism for elimination, for which the transition state is known to possess this geometry (Sec. 17.A.i).

When the electrophile is a proton,[12] the mechanism is the simple $A_H + A_N$ process shown before. This is an A-S_E2 mechanism (see **10-6**). There is a great deal of evidence[13] for

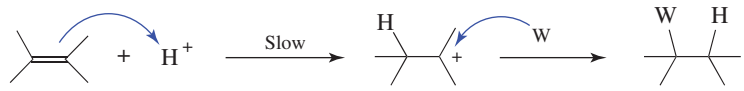
[10] Heasley, G.E.; Bower, T.R.; Dougharty, K.W.; Easdon, J.C.; Heasley, V.L.; Arnold, S.; Carter, T.L.; Yaeger, D.B.; Gipe, B.T.; Shellhamer, D.F. *J. Org. Chem.* ***1980***, *45*, 5150.

[11] See Roberts, R.M.G. *J. Chem. Soc., Perkin Trans. 2* ***1976***, 1374; Pasto, D.J.; Gadberry, J.F. *J. Am. Chem. Soc.* ***1978***, *100*, 1469; Naab, P.; Staab, H.A. *Chem. Ber.* ***1978***, *111*, 2982.

[12] See Sergeev, G.B.; Smirnov, V.V.; Rostovshchikova, T.N. *Russ. Chem. Rev.* ***1983***, *52*, 259.

[13] Also see Hampel, M.; Just, G.; Pisanenko, D.A.; Pritzkow, W. *J. Prakt. Chem.* ***1976***, *318*, 930; Allen, A.D.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1983***, *104*, 3145.

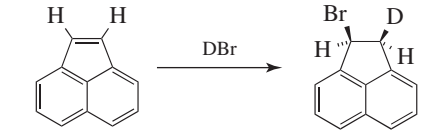
it, including the observation that the reaction is general acid, not specific acid-catalyzed, implying rate-determining proton transfer from the acid to the double bond.[14]



The existence of open carbocation intermediates as the electrophile[15] is supported by the contrast in the pattern of alkyl substituent effects[16] with that found in brominations, where cyclic intermediates are involved (see **15-35**). With respect to the alkene, more-substituted alkenes react with H^+ faster than less-substituted alkenes. An alkyl group on the positively charged carbon atom will stabilize the positive charge due to an inductive effect that leads to a δ− dipole on that carbon.[17] Such inductive effects make a tertiary carbocation more stable than a secondary, which is more stable than a primary, and the rate of reaction of alkenes with H^+ follows the order tetrasubstituted > trisubstituted > disubstituted > monosubstituted > ethene, so formation of a 3° carbocation is faster than formation of a 2°, which is faster than formation of a 1° carbocation.[18]

Carbocations are prone to rearrangement to the more stable carbocation when a less stable carbocation is formed in the initial reaction (Chapter 18). Indeed, many rearrangements have been found to accompany additions of HX and H_2O.[19] It may also be recalled that vinylic ethers react with proton donors in a similar manner (see **10-6**).

The addition of DBr to acenaphthylene as well as to indene and 1-phenylpropene gave predominant *syn* addition, as shown for acenaphthylene.[20]



Acenaphthylene

Changing the reaction conditions can control the stereoselectivity of HCl addition. Addition of HCl to acenapthylene in CH_2Cl_2 at −98 °C gave predominantly *syn* addition, while in ethyl ether at 0 °C, the addition was mostly *anti*.[21]

Addition of HX to triple bonds has the same mechanism, although the intermediate in this case is a vinylic cation, **3**.[22]

[14] Schubert, W.M.; Keeffe, J.R. *J. Am. Chem. Soc.* ***1972***, *94*, 559; Chiang, Y.; Kresge, A.J. *J. Am. Chem. Soc.* ***1985***, *107*, 6363.

[15] See Mayr, H.; Pock, R. *Chem. Ber.* ***1986***, *119*, 2473.

[16] Schmid, G.H.; Garratt, D.G. *Can. J. Chem.* ***1973***, *51*, 2463.

[17] See Anantakrishnan, S.V.; Ingold, C.K. *J. Chem. Soc.* ***1935***, 1396; Swern, D. in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1971***, pp. 451–454; Nowlan, V.J.; Tidwell, T.T. *Acc. Chem. Res.* ***1977***, *10*, 252.

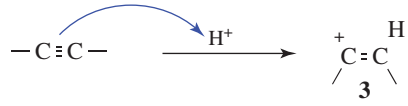
[18] See Bartlett, P.D.; Sargent, G.D. *J. Am. Chem. Soc.* ***1965***, *87*, 1297 and references cited therein.

[19] See Stammann, G.; Griesbaum, K. *Chem. Ber.* ***1980***, *113*, 598.

[20] See Heasley, G.E.; Bower, T.R.; Dougharty, K.W.; Easdon, J.C.; Heasley, V.L.; Arnold, S.; Carter, T.L.; Yaeger, D.B.; Gipe, B.T.; Shellhamer, D.F. *J. Org. Chem.* ***1980***, *45*, 5150.

[21] Becker, K.B.; Grob, C.A. *Synthesis* ***1973***, 789. See also, Naab, P.; Staab, H.A. *Chem. Ber.* ***1978***, *111*, 2982.

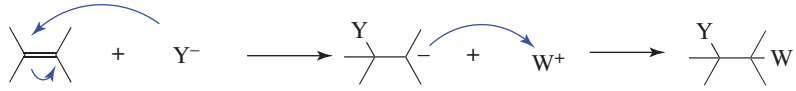
[22] See Rappoport, Z. *React. Intermed. (Plenum)* ***1983***, *3*, 427 (pp. 428–440); Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*, Academic Press, NY, ***1979***, pp. 24–151; Stang, P.J. *Prog. Phys. Org. Chem.* ***1973***, *10*, 205; Modena, G.; Tonellato, U. *Adv. Phys. Org. Chem.* ***1971***, *9*, 185 (pp. 187–231).



In all these cases (except for the Ad_E3 mechanism), it was assumed that formation of the carbocation intermediate is the slow step, and therefore rate determining, and attack by the nucleophile on the intermediate is rapid, and this is probably true in most cases. However, some additions have been found in which the second step is rate determining.[23]

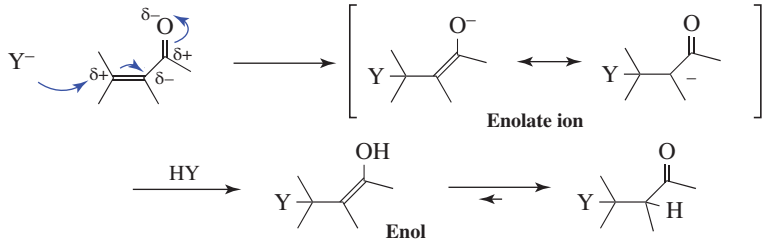
15.A.ii. Nucleophilic Addition[24]

In the first step of nucleophilic addition a nucleophile donates a pair of electrons to one carbon atom of the double or triple bond, creating a carbanion, which reacts with a positive species, W^+, in the second step. The IUPAC label for this mechanism is $A_N + A_E$ or $A_N + A_H$.



When the alkene contains a good leaving group (as defined for nucleophilic substitution), substitution is a side reaction (this is nucleophilic substitution at a vinylic substrate, Sec. 10.F).

In the case of addition of HY to a substrate of the form —C=C—Z, where Z = CHO, COR[25] (including quinones[26]), CO_2R, $CONH_2$, CN, NO_2, SOR, 2R,[27] and so on, addition nearly always follows a nucleophilic mechanism,[28] with the nucleophile (Y^-) bonding with the carbon β to the carbonyl carbon to give a resonance-stabilized enolate anion. Subsequent protonation of the enolate ion is probably at the oxygen to give an enol, which tautomerizes to the ketone (Sec. 2.N.i).



[23] See Bellucci, G.; Berti, G.; Ingrosso, G.; Mastrorilli, E. *Tetrahedron Lett.* ***1973***, 3911.
[24] Patai, S.; Rappoport, Z. in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 469–584.
[25] See in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, ***1989***, the articles by Boyd, G.V. pp. 281–315; and by Duval, D.; Géribaldi, S. pp. 355–469.
[26] See Kutyrev, A.A.; Moskva, V.V. *Russ. Chem. Rev.* ***1991***, *60*, 72; Finley, K.T. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 1, Wiley, NY, ***1988***, pp. 537–717 (see pp. 539–589); Finley, K.T. in Patai, S. *The Chemistry of the Quinonoid Compounds*, pt. 2, Wiley, NY, ***1974***, pp. 877–1144.
[27] See Simpkins, N.S. *Tetrahedron* ***1990***, *46*, 6951; Fuchs, P.L.; Braish, T.F. *Chem. Rev.* ***1986***, *86*, 903.
[28] See Bernasconi, C.F. *Tetrahedron* ***1989***, *45*, 4017.

The mechanism is 1,4-nucleophilic addition to the C=C–C=O (or similar) system and is essentially that of the *Michael reaction* discussed in **15-20**. Indeed, such reactions are often called *Michael reactions* or Michael-type reactions, and this is also known as *conjugate addition*. It is noted that 1,2-addition is the attack of the nucleophile at the carbonyl carbon, which is the normal mode of attack when there is no conjugating C=C unit (see Chapter 16).

The bond polarization that is induced in adjacent atoms by the carbonyl oxygen is shown, and leads to a δ+ dipole on the β carbon. This extension of polarization, called vinylogy (Sec. 6.B), accounts for the attraction of the negatively charged nucleophile for the β carbon and 1,4-addition. Attack of the Y^- ion at the α position is very difficult due to the δ– polarization and repulsion of the like charges, and the resulting carbanion would have no resonance stabilization.[29] Systems of the type C=C–C=C–Z can give 1,2-, 1,4-, or 1,6-addition.[30] *Michael-type reaction*s are reversible, and compounds of the type YCH_2CH_2Z can often be decomposed to Y–H and CH_2=CHZ by heating, either with or without alkali.

Except for *Michael-type substrates*, the stereochemistry of nucleophilic addition to double bonds has been studied only in cyclic systems, where only the *cis* isomer exists. In these cases the reaction has been shown to be stereoselective, with *syn* addition reported in some cases[31] and *anti* addition in others.[32] When the reaction is performed on a Michael-type substrate, C=C–Z, the hydrogen does not arrive at the carbon directly but only through a tautomeric equilibrium. The product naturally assumes the most thermodynamically stable configuration, without relation to the direction of original attack of Y. In one such case (the addition of EtOD and of Me_3CSD to *trans*-MeCH=CHCOOEt) predominant *anti* addition was found; there is evidence that the stereoselectivity here results from the final protonation of the enolate, and not from the initial attack.[33] For obvious reasons, additions to triple bonds cannot be stereospecific. As with electrophilic additions, nucleophilic additions to triple bonds are usually stereoselective and *anti*,[34] although *syn* addition[35] and nonstereoselective addition[36] have also been reported.

15.A.iii. Free-Radical Addition

The mechanism of free-radical addition[37] follows the pattern discussed in Sec. 14.A.i. Principal-component analysis was used to analyze polar and enthalpic effect in radical addition reactions.[38] A radical is generated by photolysis or spontaneous dissociation:

$$Y{-}W \rightarrow Y\bullet + W\bullet$$

[29] See Barbot, F.; Kadib-Elban, A.; Miginiac, P. *J. Organomet. Chem.* ***1988***, *345*, 239.

[30] See, however, Klumpp, G.W.; Mierop, A.J.C.; Vrielink, J.J.; Brugman, A.; Schakel, M. *J. Am. Chem. Soc.* ***1985***, *107*, 6740.

[31] Truce, W.E.; Levy, A.J. *J. Org. Chem.* ***1963***, *28*, 679.

[32] Truce, W.E.; Levy, A.J. *J. Am. Chem. Soc.* ***1961***, *83*, 4641; Zefirov, N.S.; Yur'ev, Yu.K.; Prikazchikova, L.P.; Bykhovskaya, M.Sh. *J. Gen. Chem. USSR* ***1963***, *33*, 2100.

[33] Mohrig, J.R.; Fu, S.S.; King, R.W.; Warnet, R.; Gustafson, G. *J. Am. Chem. Soc.* ***1990***, *112*, 3665.

[34] See Truce, W.E.; Tichenor, G.J.W. *J. Org. Chem.* ***1972***, *37*, 2391.

[35] Hayakawa, K.; Kamikawaji, Y.; Wakita, A.; Kanematsu, K. *J. Org. Chem.* ***1984***, *49*, 1985.

[36] Truce, W.E.; Brady, D.G. *J. Org. Chem.* ***1966***, *31*, 3543; Prilezhaeva, E.N.; Vasil'ev, G.S.; Mikhaleshvili, I.L.; Bogdanov, V.S. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1970***, 1820.

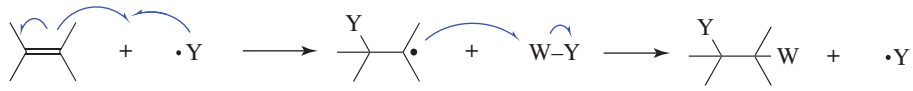
[37] Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, London, ***1974***; Pyor, W.A. *Free Radicals*, McGraw-Hill, NY, ***1965***. See Giese, B. *Rev. Chem. Intermed.* ***1986***, *7*, 3; *Angew. Chem. Int. Ed.* ***1983***, *22*, 753; Abell, P.I. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 63–112; Minisci, F. *Acc. Chem. Res.* ***1975***, *8*, 165.

[38] Héberger, K.; Lopata, A. *J. Chem. Soc., Perkin Trans. 2* ***1995***, 91.

Alternatively, Y—W reacts with R•, generated from another source, so that

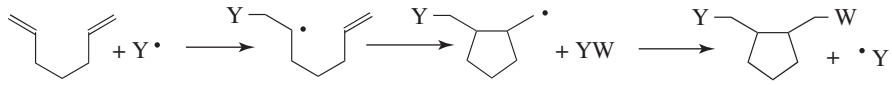
$$R\bullet + Y{-}W \rightarrow R{-}W + Y\bullet$$

For subsequent reaction with an alkene, propagation occurs by (i) addition of the radical Y• to give a carbon radical as the product and (ii) abstraction (an atom transfer), where W is nearly always either hydrogen or halogen (Sec. 14.B.i) then leads to the product (addition of Y and W to C═C) and the radical carrier Y•, in a propagation step.



Termination of the chain can occur in any of the ways discussed in Sec. 14.A.i. If the carbon radical adds to another alkene molecule, a dimer is formed, which can add to still another alkene unit, and chains, long or short, may be built up via free-radical polymerization. Short polymeric molecules (called *telomers*), formed in this manner, are often troublesome side products in free-radical addition reactions.

When free radicals are added to 1,5- or 1,6-dienes, the initially formed radical (**4**) can add intramolecularly to the other bond, leading to a cyclic product (**5**) in a process known a radical cyclization (**15-26**).[39] Radicals of the type **4**, generated in other ways, also undergo these cyclizations. Both five- and six-membered rings can be formed (Sec. 15.B.i; **15-26**).



4 **5**

The free-radical addition mechanism just outlined predicts that the addition should be nonstereospecific, at least if a carbon radical has anything but an extremely short lifetime. However, the reactions may be stereoselective, for reasons similar to those discussed above for nucleophilic addition to alkenes. A few free-radical additions are selective. For example, propyne (at −78 to −60 °C) gave only *cis*-1-bromopropene (*anti* addition), making it stereospecific.[40] Selectivity was observed in radical cyclization reactions of functionalized alkenes, which proceeded via a *trans* ring closure.[41] An important case is probably addition of HBr to 2-bromobut-2-ene under free-radical conditions at −80 °C. Under these conditions, the *cis* isomer gave 92% of the *meso* product, while the *trans* isomer gave mostly the *dl* pair.[42] This stereospecificity disappeared at room temperature, where both alkenes gave the same mixture of products (~78% of the *dl* pair and 22% of the *meso* compound), so the addition was still stereoselective but no longer stereospecific. The stereospecificity at low temperatures is probably caused by a stabilization of the intermediate radical through

[39] RajanBabu, T.V. *Acc. Chem. Res.* ***1991***, *24*, 139; Beckwith, A.L.J. *Rev. Chem. Intermed.* ***1986***, *7*, 143; Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***, pp. 141–209.

[40] Skell, P.S.; Allen, R.G. *J. Am. Chem. Soc.* ***1958***, *80*, 5997.

[41] Ogura, K.; Kayano, A.; Fujino, T.; Sumitani, N.; Fujita, M. *Tetrahedron Lett.* ***1993***, *34*, 8313.

[42] Goering, H.L.; Larsen, D.W. *J. Am. Chem. Soc.* ***1959***, *81*, 5937. Also see, Skell, P.S.; Freeman, P.K. *J. Org. Chem.* ***1964***, *29*, 2524.

the formation of a three-membered ring-bridged bromine radical (see the bromonium ion in **15-35**) rather than Br—C—C•, which would normally be expected. Further evidence for the existence of such bridged radicals was obtained by addition of Br• to alkenes at 77 K. The ESR spectra of the resulting species were consistent with bridged structures.[43]

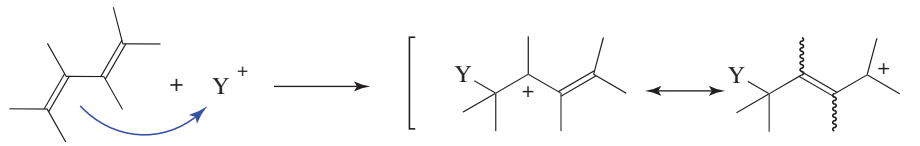
For many radicals, step 1 (C═C + Y• → •C—C—Y) is reversible. In such cases free radicals can cause *cis* → *trans* isomerization of a double bond by reversible formation of a carbon radical, which allows rotation about C—C bonds.[44]

15.A.iv. Cyclic Mechanisms

There are some addition reactions where the initial reaction is not at one carbon of the double bond, but both carbons react simultaneously. Some of these are four-center mechanisms (**15-59**). In others, there is a five- or a six-membered transition state. In these cases the addition to the double or triple bond must be *syn*. The most important reaction of this type is the *Diels-Alder reaction* (**15-56**).

15.A.v. Addition to Conjugated Systems

Michael addition, discussed in Sec. 15.A.ii and **15-20**, is one example of a reaction with a conjugated system, in that case a nucleophile reacted with the C═C unit of the conjugated ketone or other system. Conjugated systems such as buta-1-,3-dienes also react with electrophilic reagents such as HX or X_2. When electrophilic addition is carried out on a compound with two double bonds in conjugation, a 1,2-addition product is often obtained, but a 1,4-addition product is often formed in larger yield:[45] If the diene is unsymmetrical, there may be two 1,2-addition products. The competition between two types of addition product comes about because the carbocation resulting from attack of a C═C unit on Y^+ is a resonance hybrid, with partial positive charges at C-2 (**6**) and C-4 (**7**). Nucleophilic reaction with **6** leads to the 1,2-addition product whereas nucleophilic reaction with **7** leads to the 1,4-addition product. The original reaction with Y^+ is always at the end of the conjugated system because reaction at a middle carbon would give a cation unstabilized by resonance.



6 **7**

An example is the reaction of HBr with penta-1,3-diene to give 3-bromopent-2-ene via a symmetrical allylic carbocation.[46] For reaction with unsymmetrical dienes, more 1,4- than 1,2-addition product is obtained in most cases. This may be a consequence of thermodynamic control of products, as against kinetic, and is usually temperature dependent. It

[43] Abell, P.I.; Piette, L.H. *J. Am. Chem. Soc.* ***1962***, *84*, 916. See also, Leggett, T.L.; Kennerly, R.E.; Kohl, D.A. *J. Chem. Phys.* ***1974***, *60*, 3264.
[44] Golden, D.M.; Furuyama, S.; Benson, S.W. *Int. J. Chem. Kinet.* ***1969***, *1*, 57.
[45] Khristov, V.Kh.; Angelov, Kh.M.; Petrov, A.A. *Russ. Chem. Rev.* ***1991***, *60*, 39.
[46] Lehmkuhl, H.; Reinehr, D.; Henneberg, D.; Schomburg, G.; Schroth, G. *Eur. J. Org. Chem.* ***1975***, 119.

TABLE 15.1 Relative reactivity of some alkenes toward bromine in acetic acid at 24 °C[53a]

Alkene	Relative rate
$PhCH{=}CH_2$	Very fast
$PhCH{=}CHPh$	18
$CH_2{=}CHCH_2Cl$	1.6
$CH_2{=}CHCH_2Br$	1.0
$PhCH{=}CHBr$	0.11
$CH_2{=}CHBr$	0.0011

Reproduced from de la Mare, P.B.D. *Q. Rev. Chem. Soc.* ***1949***, *3*, 126, with permission from the Royal Society of Chemistry.

was found that at low temperatures, buta-1,3-diene and HCl gave only 20–25% 1,4-adduct, while at high temperatures, where attainment of equilibrium is more likely, the mixture contained 75% 1,4-product.[47] 1,2-addition predominated over 1,4- in the reaction between DCl and penta-1,3-diene, where the intermediate was symmetrical (except for the D label).[48] Ion pairs were invoked to explain this result, since Cl^- would attack a free ion equally well at both positions, except for the very small isotope effect.

Addition to conjugated systems can also be accomplished by any of the other three mechanisms. In each case, there is competition between 1,2- and 1,4-addition. In the case of nucleophilic or free-radical attack,[49] the intermediates are resonance hybrids and behave like the intermediate from electrophilic attack. Dienes can similarly give 1,4-addition by a cyclic mechanism. Other conjugated systems, including trienes, enynes, diynes, and so on, have been studied much less but behave similarly. 1,4-Addition to enynes is an important way of making allenes.

Radical addition to conjugated systems is an important part of chain propagation reactions. The rate constants for addition of cyclohexyl radical to conjugated amides have been measured, and shown to be faster than addition to styrene.[50] In additions to $RCH{=}C(CN)_2$ systems, where the R group has a stereogenic center, the Felkin-Anh model (Sec. 4.H, category 1) applies and the reaction proceeds with high selectivity.[51] Addition of some radicals, such as $(Me_3Si)_3Si\bullet$, is reversible and this can lead to poor selectivity or isomerization.[52]

15.B. ORIENTATION AND REACTIVITY

15.B.i. Reactivity

As with electrophilic aromatic substitution (Chapter 11), electron-donating groups increase the reactivity of a double bond toward electrophilic addition and electron-withdrawing groups decrease it. This is illustrated in Tables 15.1[53a] and 15.2.[53b]

[47] Kharasch, M.S.; Kritchevsky, J.; Mayo, F.R. *J. Org. Chem.* ***1938***, *2*, 489.
[48] Nordlander, J.E.; Owuor, P.O.; Haky, J.E. *J. Am. Chem. Soc.* ***1979***, *101*, 1288.
[49] Afanas'ev, I.B.; Samokhvalov, G.I. *Russ. Chem. Rev.* ***1969***, *38*, 318.
[50] Curran, D.P.; Qi, H.; Porter, N.A.; Su, Q.; Wu, W.-X. *Tetrahedron Lett.* ***1993***, *34*, 4489.
[51] Giese, B.; Damm, W.; Roth, M.; Zehnder, M. *Synlett* ***1992***, 441.
[52] Ferreri, C.; Ballestri, M.; Chatgilialoglu, C. *Tetrahedron Lett.* ***1993***, *34*, 5147.
[53] (a) Table 15.1 is from de la Mare, P.B.D. *Q. Rev. Chem. Soc.* ***1949***, *3*, 126, p. 145. (b) Table 15.2 is from Dubois, J.E.; Mouvier, G. *Tetrahedron Lett.* ***1963***, 1325. See also, Grosjean, D.; Mouvier, G.; Dubois, J.E. *J. Org. Chem.* ***1976***, *41*, 3869, 3872.

TABLE 15.2 Relative reactivity of some alkenes toward bromine in methanol[53b]

Alkene	Relative rate
$CH_2{=}CH_2$	3.0×10^1
$CH_3CH_2CH{=}CH_2$	2.9×10^3
cis-$CH_3CH_2CH{=}CHCH_3$	1.3×10^5
$(CH_3)_2C{=}C(CH_3)_2$	2.8×10^7

Reprinted with permission from Dubois, J.E.; Mouvier, G. *Tetrahedron Lett.* ***1963***, 1325, copyright 1963, with permission from Elsevier Science.

As a further illustration, the reactivity toward electrophilic addition of a group of alkenes increased in the order $CCl_3CH{=}CH_2 < Cl_2CHCH{=}CH_2 < ClCH_2CH{=}CH_2 < CH_3CH_2{=}CH_2$.[54] For nucleophilic addition the situation is reversed. These reactions are best carried out on substrates containing three or four electron-withdrawing groups, two of the most common being $F_2C{=}CF_2$[55] and $(NC)_2C{=}C(CN)_2$.[56] The effect of substituents is so great that it is possible to make the statement that *simple alkenes do not react by the nucleophilic mechanism*, *and polyhalo or polycyano alkenes do not generally react by the electrophilic mechanism*.[57] There are some reagents that attack only as nucleophiles (e.g., ammonia) that add only to substrates susceptible to nucleophilic attack. Other reagents react only as electrophiles (e.g., $F_2C{=}CF_2$) that do not react with other alkenes. In still other cases, the same reagent reacts with a simple alkene by the electrophilic mechanism and with a polyhalo alkene by a nucleophilic mechanism. For example, Cl_2 and HF are normally electrophilic reagents, but it has been shown that Cl_2 adds to $(N{\equiv}C)_2C{=}CHC{\equiv}N$ with initial attack by Cl^-[58] and that HF adds to $F_2C{=}CClF$ with initial attack by F^-.[59] Compounds that have a double bond conjugated with a Z group (as defined in Sec. 15.A.ii) nearly always react by a nucleophilic mechanism.[60] These are actually 1,4-additions, also discussed in Sec. 15.A.ii. A number of studies have been made of the relative activating abilities of various Z groups.[61] On the basis of these studies, the following order of decreasing activating ability has been suggested for Z: $NO_2 > COAr > CHO > COR > SO_2Ar > CN > CO_2R > SOAr > CONH_2 > CONHR$.[62]

It seems obvious that electron-withdrawing groups enhance nucleophilic addition and inhibit electrophilic addition because they lower the electron density of the double bond. Addition of electrophilic radicals to electron-rich alkenes has been reported,[63] so the

[54] Shelton, J.R.; Lee, L. *J. Org. Chem.* ***1960***, *25*, 428.
[55] See Chambers, R.D.; Mobbs, R.H. *Adv. Fluorine Chem.* ***1965***, *4*, 51.
[56] See Fatiadi, A.J. *Synthesis* ***1987***, 249, 749; Dhar, D.N. *Chem. Rev.* ***1967***, *67*, 611.
[57] See Olah, G.A.; Mo, Y.K. *J. Org. Chem.* ***1972***, *37*, 1028; Belen'kii, G.G.; German, L.S. *Sov. Sci. Rev. Sect. B* ***1984***, *5*, 183; Dyatkin, B.L.; Mochalina, E.P.; Knunyants, I.L. *Fluorine Chem. Rev.* ***1969***, *3*, 45.
[58] Dickinson, C.L.; Wiley, D.W.; McKusick, B.C. *J. Am. Chem. Soc.* ***1960***, *82*, 6132. For another example, see Atkinson, R.C.; de la Mare, P.B.D.; Larsen, D.S. *J. Chem. Soc., Perkin Trans. 2* ***1983***, 271.
[59] Miller Jr., W.T.; Fried, J.H.; Goldwhite, H. *J. Am. Chem. Soc.* ***1960***, *82*, 3091.
[60] Müllen, K.; Wolf, P. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, ***1989***, pp. 513–558.
[61] See Ring, R.N.; Tesoro, G.C.; Moore, D.R. *J. Org. Chem.* ***1967***, *32*, 1091.
[62] Shenhav, H.; Rappoport, Z.; Patai, S. *J. Chem. Soc. B* ***1970***, 469.
[63] Curran, D.P.; Ko, S.-B. *Tetrahedron Lett.* ***1998***, *39*, 6629.

reaction is possible in some cases. This is probably true, and yet similar reasoning does not always apply to a comparison between double and triple bonds.[64] There is a higher concentration of electrons between the carbons of a triple bond than in a double bond, and yet triple bonds are *less* subject to attack at an electrophilic site and *more* subject to nucleophilic attack than double bonds.[65] This statement is not universally true, but it does hold in most cases. In compounds containing both double and triple bonds (nonconjugated), bromine, an electrophilic reagent, always adds to the double bond.[66] Addition of electrophilic H^+ (acid-catalyzed hydration, **15-3**; addition of hydrogen halides, **15-2**) takes place at about the same rates for alkenes as for corresponding alkynes.[67] Furthermore, the presence of electron-withdrawing groups lowers the alkene/alkyne rate ratio. For example, while styrene $PhCH{=}CH_2$ was brominated 3000 times faster than PhC≡CH, the addition of a second phenyl group (PhCH=CHPh versus PhC≡CPh) lowered the rate ratio to about 250.[68] In the case of *trans*-MeOOCCH=CHCOOMe versus MeOOCC≡CCOOMe, the triple bond compound was actually brominated faster.[69]

As mentioned earlier, it is true that in general triple bonds are more susceptible to nucleophilic attack and less prone to reaction at an electrophilic site than double bonds, in spite of their higher electron density. One explanation is that the electrons in the triple bond are held more tightly because of the smaller carbon–carbon distance; it is thus harder to donate an electron pair to an electrophile. There is evidence from far-UV spectra to support this conclusion.[70] Another possible explanation has to do with the availability of the unfilled orbital in the alkyne. It has been shown that a π^* orbital of bent alkynes (e.g., cyclooctyne) has a lower energy than the π^* orbital of alkenes, and it has been suggested[71] that linear alkynes can achieve a bent structure in their transition states when reacting with an electrophile.

Although alkyl groups in general increase the rates of electrophilic addition, as mentioned in Sec. 15.A.i, category 1, there is a different pattern depending on whether the intermediate is a bridged ion or an open carbocation. For brominations and other electrophilic additions in which the first step of the mechanism is rate determining, the rates for substituted alkenes correlate well with the ionization potentials of the alkenes, which means that steric effects are not important.[72] Where the second step is rate determining [e.g., oxymercuration (**15-3**), hydroboration (**15-12**)], steric effects are important.[73]

Free-radical additions can occur with any type of substrate. The determining factor is the presence of a reactive free-radical species. Some reagents, e.g., HBr, RSH, attack by ionic mechanisms if no initiator is present, but in the presence of a free-radical initiator,

[64] In Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, Wiley, NY, ***1978***, see the articles by Schmid, G.H. pt. 1, pp. 275–341, and by Dickstein, J.I.; Miller, S.I. pt. 2, pp. 813–955; Miller, S.I.; Winterfeldt, E. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 267–334. For comparisons of double and triple bond reactivity, see Melloni, G.; Modena, G.; Tonellato, U. *Acc. Chem. Res.* ***1981***, *14*, 227; Allen, A.D.; Chiang, Y.; Kresge, A.J.; Tidwell, T.T. *J. Org. Chem.* ***1982***, *47*, 775.

[65] See Strozier, R.W.; Caramella, P.; Houk, K.N. *J. Am. Chem. Soc.* ***1979***, *101*, 1340.

[66] Petrov, A.A. *Russ. Chem. Rev.* ***1960***, *29*, 489.

[67] Melloni, G.; Modena, G.; Tonellato, U. *Acc. Chem. Res.* ***1981***, *14*, 227 (p. 228).

[68] Robertson, P.W.; Dasent, W.E.; Milburn, R.M.; Oliver, W.H. *J. Chem. Soc.* ***1950***, 1628.

[69] Wolf, S.A.; Ganguly, S.; Berliner, E. *J. Am. Chem. Soc.* ***1985***, *50*, 1053.

[70] Walsh, A.D. *Q. Rev. Chem. Soc.* ***1948***, *2*, 73.

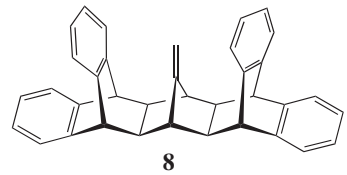
[71] Ng, L.; Jordan, K.D.; Krebs, A.; Rüger, W. *J. Am. Chem. Soc.* ***1982***, *104*, 7414.

[72] Nelson, D.J.; Cooper, P.J.; Soundararajan, R. *J. Am. Chem. Soc.* ***1989***, *111*, 1414.

[73] See Winterfeldt, E. *Angew. Chem. Int. Ed.* ***1967***, *6*, 423; *Newer Methods Prep. Org. Chem.* ***1971***, *6*, 243.

the mechanism changes and the addition is of the free-radical type. Nucleophilic radicals (Sec. 14.A.ii) behave like nucleophiles in that the rate is increased by the presence of electron-withdrawing groups in the substrate. The reverse is true for electrophilic radicals.[74] However, nucleophilic radicals react with alkynes more slowly than with the corresponding alkenes,[75] which is contrary to what might have been expected.[76]

Steric influences are important in some cases. In catalytic hydrogenation, where the substrate must be adsorbed onto the catalyst surface, the reaction becomes more difficult with increasing substitution. The hydrocarbon **8**, in which the double bond is entombed between the benzene rings, does not react with Br_2, H_2SO_4, O_3, BH_3,:CBr_2, or other reagents that react with most double bonds.[77]

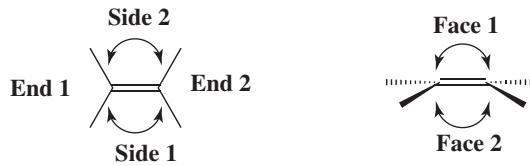


8

A similarly inactive compound is tetra-*tert*-butylallene $(t\text{-Bu})_2C{=}C{=}C(t\text{-Bu})_2$, which is inert to Br_2, Cl_2, O_3, and catalytic hydrogenation.[78]

15.B.ii. Orientation

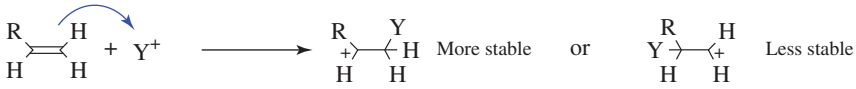
When an unsymmetrical reagent is added to an unsymmetrical substrate, the question arises is "Which side of the reagent goes to which side of the double or triple bond?" In other words, what is the *regioselectivity* of the reaction? *Regioselectivity is defined as one direction of bond making or breaking that occurs preferentially over all other possible directions.* The terms side and face are arbitrary, and a simple guide is shown to help understand the arguments used here.



For reaction with an electrophile, the traditional answer is given by *Markovnikov's rule: The positive portion of the reagent goes to the side of the double or triple bond that has more hydrogen atoms*.[79] Mechanistically, regioselectivity is predicted by attack of the π

[74] See Tedder, J.M. *Angew. Chem. Int. Ed.* ***1982***, *21*, 401.
[75] Giese, B.; Lachhein, S. *Angew. Chem. Int. Ed.* ***1982***, *21*, 768.
[76] See Volovik, S.V.; Dyadyusha, G.G.; Staninets, V.I. *J. Org. Chem. USSR* ***1986***, *22*, 1224.
[77] Butler, D.N.; Gupt, I.; Ng, W.W.; Nyburg, S.C. *J. Chem. Soc., Chem. Commun.* ***1980***, 596.
[78] Bolze, R.; Eierdanz, H.; Schlüter, K.; Massa, W.; Grahn, W.; Berndt, A. *Angew. Chem. Int. Ed.* ***1982***, *21*, 924.
[79] See Isenberg, N.; Grdinic, M. *J. Chem. Educ.* ***1969***, *46*, 601; Grdinic, M.; Isenberg, N. *Intra-Sci. Chem. Rep.,* ***1970***, *4*, 145–162.

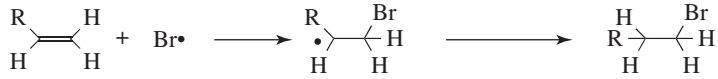
bond on Y^+, *forming a bond to the carbon that will give the more stable carbocation*. In this example, the secondary carbocation is more stable than the primary.



This mechanism is supported by evidence from core electron spectroscopy and by theoretical analysis.[80] The *Hammond postulate* is invoked to say that the lower energy carbocation is preceded by the lower energy transition state. *Markovnikov's rule* also applies for halogen substituents, and the mechanistic rationale is that the halogen stabilizes the carbocation by resonance, so the intermediate with the positive charge on the Cl-bearing carbon is more stable.

Alkenes containing strong electron-withdrawing groups may violate *Markovnikov's rule*, but formation of the more stable carbocation still controls the reaction. For example, attack at the Markovnikov position of $Me_3N^+{-}CH{=}CH_2$ would give an ion with positive charges on adjacent atoms. The compound $CF_3CH{=}CH_2$ has been reported to give electrophilic addition with acids in an *anti-Markovnikov* direction, but it has been shown[81] that, when treated with acids, this compound does not give simple electrophilic addition at all; the apparently anti-Markovnikov products are formed by other pathways. Molecular electrostatic potentials for the π region of substituted alkenes were studied, with electron-donating and electron-withdrawing substituents (based on the increase or decrease in the negative character of V_{min}, the most negative-value point), and plots of V_{min} shows a good linear correlation with the Hammett σ_ρ constants, suggesting similar substituent electronic effects for substituted ethylenes and substituted benzenes.[82]

In free-radical addition[83] the main effect seems to be steric.[84] All substrates $CH_2{=}CHX$ preferentially react at the CH_2, regardless of the identity of X or of the radical. With a reagent such as HBr, which generates Br• *in situ* via hydrogen atom exchange, this means that the addition is anti-Markovnikov:



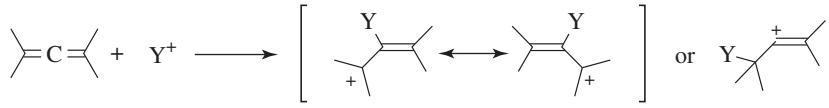
Thus the observed orientation in both kinds of HBr addition (Markovnikov electrophilic and anti-Markovnikov free radical) is caused by formation of the more stable secondary intermediate.

For conjugated dienes, attack at a positive ion, by a negative ion, or reaction with a free radical is almost always at the *end* of the conjugated system, since in each case this gives an intermediate stabilized by resonance. In the case of an unsymmetrical diene, the more

[80] Sæthre, L.J.; Thomas, T.D.; Svensson, S. *J. Chem. Soc., Perkin Trans. 2* ***1997***, 749.
[81] Myhre, P.C.; Andrews, G.D. *J. Am. Chem. Soc.* ***1970***, *92*, 7595, 7596. See also, Newton, T.A. *J. Chem. Educ.* ***1987***, *64*, 531.
[82] Suresh, C.H.; Koga, N.; Gadre, S.R. *J. Org. Chem.* ***2001***, *66*, 6883.
[83] Tedder, J.M.; Walton, J.C. *Tetrahedron* ***1980***, *36*, 701; *Acc. Chem. Res.* ***1976***, *9*, 183. See also, Giese, B. *Rev. Chem. Intermed.* ***1986***, *7*, 3; Tedder, J.M. *J. Chem. Educ.* ***1984***, *61*, 237.
[84] See, however, Gleicher, G.J.; Mahiou, B.; Aretakis, A.J. *J. Org. Chem.* ***1989***, *54*, 308.

stable ion is formed. For example, isoprene (CH_2=CMeCH=CH_2) treated with HCl gives only Me_2CClCH=CH_2 and Me_2C=CHCH_2Cl, with none of the product arising from attack at the other end. PhCH=CHCH=CH_2 gives only PhCH=CHCHClCH_3 since it is the only one of the eight possible products that has a double bond in conjugation with the ring and that results from attack that places the proton at an end of the conjugated system.

When allenes attack electrophilic reagents,[85] Markovnikov's rule would predict that the formation of the new bond should be at the end of the system, since there are no hydrogen atoms in the middle.



Reaction at the center gives a carbocation stabilized by resonance, but not immediately. In order for such stabilization to be in effect, the three *p* orbitals must be parallel, and it requires a rotation about the C—C bond.[86] Therefore, the stability of the allylic cation has no effect on the transition state, which still has a geometry similar to that of the original allene (Sec. 4.C, category 5). Probably because of this, reaction of the unsubstituted CH_2=C=CH_2 is most often at the end carbon, to give a vinylic cation, although reaction at the center carbon has also been reported. However, as alkyl or aryl groups are substituted on the allene carbons, reaction at the middle carbon becomes more favorable because the resulting cation is stabilized by the alkyl or aryl groups (it is now a secondary, tertiary, or benzylic cation). For example, allenes of the form RCH=C=CH_2 react most often at the end, but RCH=C=CHR′ usually gives reaction at the center carbon.[87] Free radicals[88] react with allenes most often at the end,[89] although reaction at the middle carbon has also been reported.[90] As with reactions that proceed via electrophilic intermediates, and for the same reason, the stability of the allylic radical has no effect on the transition state of the reaction between a free radical and an allene. Again, the presence of alkyl groups increases the extent of reaction by a radical at the middle carbon.[91]

15.B.iii. Stereochemical Orientation

It has already been pointed out that some additions are *syn*, with both groups approaching from the same side, and that others are *anti*, with the groups approaching from opposite sides of the double or triple bond. Steric orientation must be considered for cyclic compounds. In *syn* addition to an unsymmetrical cyclic alkene, the two groups can come in from the more-hindered face or from the less-hindered face of the double bond. The rule is that *syn* addition

[85] See Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***; Pasto, D.J. *Tetrahedron* ***1984***, *40*, 2805; Smadja, W. *Chem. Rev.* ***1983***, *83*, 263. In Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, see the articles by Landor, S.R., Jacobs, T.L.; Hopf, H. pp. 351–577. Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*, Academic Press, NY, ***1979***, pp. 152–167. See Ma, S. *Pure Appl. Chem.* ***2006***, *78*,197.

[86] See Okuyama, T.; Izawa, K.; Fueno, T. *J. Am. Chem. Soc.* ***1973***, *95*, 6749.

[87] Also see Poutsma, M.L.; Ibarbia, P.A. *J. Am. Chem. Soc.* ***1971***, *93*, 440.

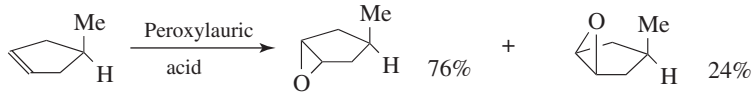
[88] Jacobs, T.L. in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, pp. 399–415.

[89] Griesbaum, K.; Oswald, A.A.; Quiram, E.R.; Naegele, W. *J. Org. Chem.* ***1963***, *28*, 1952.

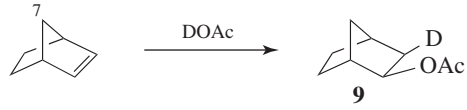
[90] See Pasto, D.J.; L'Hermine, G. *J. Org. Chem.* ***1990***, *55*, 685.

[91] See Pasto, D.J.; Warren, S.E.; Morrison, M.A. *J. Org. Chem.* ***1981***, *46*, 2837. See, however, Bartels, H.M.; Boldt, P. *Liebigs Ann. Chem.* ***1981***, 40.

is usually, although not always, from the less-hindered face. For example, epoxidation of 4-methylcyclopentene gave 76% addition from the less-hindered face and 24% from the more-hindered face.[92]



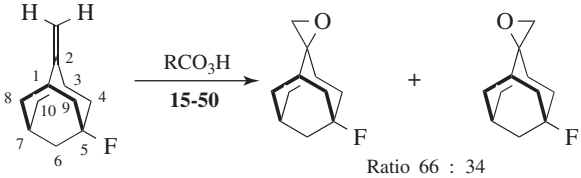
In *anti* addition to a cyclic substrate, the initial reaction with the electrophile is also from the less-hindered face. Many (but not all) electrophilic additions to norbornene and similar strained bicycloalkenes are *syn* additions,[93] where reaction is always from the *exo* side, as in formation of **9**,[94] unless the *exo* side is blocked by substituents in the 7 position, in which case *endo* attack may predominate; for example, 7,7-dimethylnorbornene undergoes syn-*endo* epoxidation (**15-46**) and hydroboration[95] (**15-11**).



9

However, addition of DCl and F_3CCO_2D to 7,7-dimethylnorbornene and oxymercuration (**15-2**) of 7,7-dimethylnorbornene proceeds *syn-exo* in spite of the methyl groups in the 7 position.[96] Similarly, free-radical additions to norbornene and similar molecules are often *syn-exo*, although *anti* additions and *endo* attacks are also known.[97]

Electronic effects can also play a part in determining which face reacts preferentially with the electrophilic species. In the adamantane derivative **10**, steric effects are about the same for each face of the double bond. Yet epoxidation, dibromocarbene reactions (**15-60**), and hydroboration (**15-11**) all take place predominantly from the face that is *syn* to the electron-withdrawing fluorine.[98] In the case shown, about twice as much **11** was formed, compared to **12**.



10 **11** **12**

Similar results have been obtained on other substrates:[99] groups that are electron withdrawing by the field effect (*−I*) direct attack from the *syn* face; *+I* groups from the *anti* face,

[92] Henbest, H.B.; McCullough, J.J. *Proc. Chem. Soc.* ***1962***, 74.
[93] See Traylor, T.G. *Acc. Chem. Res.* ***1969***, *2*, 152.
[94] Koga, N.; Ozawa, T.; Morokuma, K. *J. Phys. Org. Chem.* ***1990***, *3*, 519.
[95] Brown, H.C.; Kawakami, J.H.; Liu, K. *J. Am. Chem. Soc.* ***1973***, *95*, 2209.
[96] Brown, H.C.; Liu, K. *J. Am. Chem. Soc.* ***1975***, *97*, 600, 2469.
[97] See Azovskaya, V.A.; Prilezhaeva, E.N. *Russ. Chem. Rev.* ***1972***, *41*, 516.
[98] Srivastava, S.; le Noble, W.J. *J. Am. Chem. Soc.* ***1987***, *109*, 5874. See also, Bodepudi, V.R.; le Noble, W.J. *J. Org. Chem.* ***1991***, *56*, 2001.
[99] Cieplak, A.S.; Tait, B.D.; Johnson, C.R. *J. Am. Chem. Soc.* ***1989***, *111*, 8447.

for both electrophilic and nucleophilic attack. These results are attributed[100] to hyperconjugation (Sec. 2.M). For the adamantane case, there is overlap between the σ* orbital of the newly forming bond (between the attacking species and C-2 in **10**) and the filled σ orbitals of the C_α—C_β bonds on the opposite side. This is called the *Cieplak effect*. The $LiAlH_4$ reduction of 2-axial methyl or methoxy cyclohexanones supports Cieplak's proposal.[101] In addition reactions of methanol to norbornanones, however, little evidence was found to support the Cieplak effect.[102] The four possible bonds are C-3—C-4 and C-1—C-9 on the *syn* side and C-3—C-10 and C-1—C-8 on the *anti* side. The preferred pathway is the one where the incoming group has the more electron-rich bonds on the side *opposite* to it (these are the ones it overlaps with). Since the electron-withdrawing F has its greatest effect on the bonds closest to it, the C-1—C-8 and C-3—C-10 bonds are more electron rich, and the group comes in on the face *syn* to the F.

In the reaction of Br_2 and HOBr with a cyclohexene, the initially formed product is conformationally specific too, being mostly diaxial.[103] This is so because diaxial opening of the three-membered ring intermediate in these cases (reaction **15-35**) preserves a maximum co-planarity of the participating centers in the transition state; indeed, on opening, epoxides also give diaxial products.[104] However, the initial diaxial product may then pass over to the diequatorial conformer unless other groups on the ring render the latter less stable than the former. In free-radical additions to cyclohexenes in which cyclic intermediates are not involved, the initial reaction with the radical is also usually from the axial direction,[105] resulting in a diaxial initial product if the overall addition is *anti*. The direction from which unsymmetrical radicals react has also been studied.[106]

15.B.iv. Addition to Cyclopropane Rings[107]

It was shown in Sec. 4.Q.iv that cyclopropane rings resemble double bonds in some aspects of their reactivity.[108] It is not surprising, therefore, that cyclopropanes undergo addition reactions analogous to those undergone by double bond compounds, resulting in the opening of the cyclopropane ring. The reaction

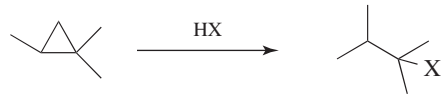
$$\text{cyclopropane} + HBr \rightarrow CH_3CH_2CH_2Br$$

illustrates the relationship to the alkene reaction.

Additions to cyclopropanes can take place by any of the four mechanisms already discussed in this chapter, but the most important type involves reaction with an electrophile.[109] For substituted cyclopropanes, these reactions usually follow *Markovnikov's rule*, although exceptions are known and the degree of regioselectivity is often small.

[100] Cieplak, A.S. *J. Am. Chem. Soc.* ***1981***, *103*, 4540. See also, Jorgensen, W.L. *Chemtracts: Org. Chem.* ***1988***, *1*, 71.
[101] Senda, Y.; Nakano, S.; Kunii, H.; Itoh, H. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 1009.
[102] Coxon, J.M.; McDonald, D.Q. *Tetrahedron* ***1992***, *48*, 3353.
[103] Readio, P.D.; Skell, P.S. *J. Org. Chem.* ***1966***, *31*, 753, 759.
[104] See Anselmi, C.; Berti, G.; Catelani, G.; Lecce, L.; Monti, L. *Tetrahedron* ***1977***, *33*, 2771.
[105] LeBel, N.A.; Czaja, R.F.; DeBoer, A. *J. Org. Chem.* ***1969***, *34*, 3112.
[106] See Giese, B. *Angew. Chem. Int. Ed.* ***1989***, *28*, 969.
[107] Charton, M. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 569–592; Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165.
[108] See, however, Gordon, A.J. *J. Chem. Educ.* ***1967***, *44*, 461.
[109] See DePuy, C.H. *Top. Curr. Chem.* ***1973***, *40*, 73–101. For a list of references to pertinent mechanistic studies, see Wiberg, K.B.; Kass, S.R. *J. Am. Chem. Soc.* ***1985***, *107*, 988.

The application of Markovnikov's rule to these substrates can be illustrated by the reaction of 1,1,2-trimethylcyclopropane with HX.[110] The rule predicts that the electrophile (in this case H^+) goes to the carbon with the most hydrogen atoms and the nucleophile (X) goes to the carbon that can best stabilize a positive charge (in this case the tertiary rather than the secondary carbon).



The stereochemistry of the reaction can be investigated at two positions – the one that becomes connected to the electrophile and the one that becomes connected to the nucleophile. The results at the former position are mixed. Additions have been found to take place with 100% retention,[111] 100% inversion,[112] and with mixtures of retention and inversion.[113] At the carbon that becomes connected to the nucleophile the result is usually inversion, although retention has also been found,[114] and elimination, rearrangement, and racemization processes often compete, indicating that in many cases a positively charged carbon is generated at this position.

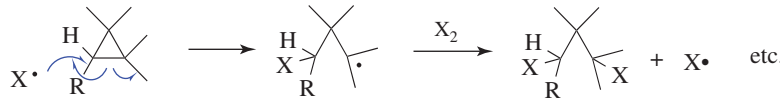
At least three mechanisms have been proposed for electrophilic addition (these mechanisms are shown for reaction with HX, but analogous mechanisms can be written for other electrophiles).

- The first mechanism involves a corner-protonated cyclopropane;[115] examples of such ions were seen in the 2-norbornyl and 7-norbornenyl cations (Sec. 10.C.i).
- The second mechanism involves an edge-protonated cyclopropane, in which a proton bridges two carbon atoms of the three-membered ring.
- A third mechanism is a one-step S_E2-type attack on H^+ to give the classical carbocation that reacts with the nucleophile.

Although the three mechanisms show retention of configuration at the carbon that becomes attached to the proton, the first and third mechanisms can also result in inversion at this carbon. Unfortunately, the evidence on hand at present does not allow unequivocal selection of any of these as the exclusive mechanism in all cases. Matters are complicated by the possibility that more than one edge-protonated cyclopropane is involved, at least in some cases. There is strong evidence for the edge-protonated mechanism with the electrophiles Br^+ and Cl^+.[116] There is evidence for the corner-protonated pathway for mechanism with D^+ and Hg^{2+}.[117] *Ab initio* studies show that the corner-protonated pathway is slightly more stable (~1.4 kcal mol^{-1}, 6 kJ mol^{-1}) than the edge-protonated pathway.[118] There is some evidence against formation of a carbocation as suggest by the third mechanism.[119]

[110] Kramer, G.M. *J. Am. Chem. Soc.* ***1970***, *92*, 4344.
[111] See Hendrickson, J.B.; Boeckman Jr., R.K. *J. Am. Chem. Soc.* ***1969***, *91*, 3269.
[112] See Hogeveen, H.; Roobeek, C.F.; Volger, H.C. *Tetrahedron Lett.* ***1972***, 221; Battiste, M.A.; Mackiernan, J. *Tetrahedron Lett.* ***1972***, 4095. See also, Coxon, J.M.; Steel, P.J.; Whittington, B.I. *J. Org. Chem.* ***1990***, *55*, 4136.
[113] DePuy, C.H.; Fünfschilling, P.C.; Andrist, A.H.; Olson, J.M. *J. Am. Chem. Soc.* ***1977***, *99*, 6297.
[114] Hendrickson, J.B.; Boeckman Jr., R.K. *J. Am. Chem. Soc.* ***1971***, *93*, 4491.
[115] Collins, C.J. *Chem. Rev.* ***1969***, *69*, 543; Lee, C.C. *Prog. Phys. Org. Chem.* ***1970***, *7*, 129.
[116] Coxon, J.M.; Steel, P.J.; Whittington, B.I. *J. Org. Chem.* ***1989***, *54*, 3702.
[117] Lambert, J.B.; Chelius, E.C.; Bible Jr., R.H.; Hadju, E. *J. Am. Chem. Soc.* ***1991***, *113*, 1331.
[118] Koch, W.; Liu, B.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1989***, *111*, 3479, and references cited therein.
[119] Wiberg, K.B.; Kass, S.R. *J. Am. Chem. Soc.* ***1985***, *107*, 988.

Free-radical additions to cyclopropanes have been much less studied, but it is known that Br_2 and Cl_2 add to cyclopropanes by a free-radical mechanism in the presence of UV light. The addition follows *Markovnikov's rule*, with the initial radical reacting at the least-substituted carbon and the second group going to the most-substituted position. Several investigations have shown that the reaction is stereospecific at one carbon, taking place with inversion there, but nonstereospecific at the other carbon.[120] A mechanism that accounts for this behavior is[121]

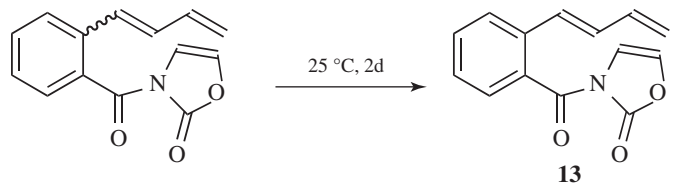


15.C. REACTIONS

15.C.i. Isomerization of Double and Triple Bonds

15-1 Isomerization

Without a transition metal catalyst, there is usually a rather high energy barrier for the excited state required for *E*/*Z* isomerization.[122] However, double bonds that are conjugated to aromatic rings are known to isomerize from *Z* to *E*, sometimes spontaneously. An example is the conjugated diene isolated as a 2:1 *E:Z* mixture, but completely isomerized to the *E* isomer (**13**) upon standing at ambient temperature.[123]



13

The transition metal-catalyzed isomerization of an alkene from *E* to *Z* or *Z* to *E* is a well-studied reaction.[124] Among the metals examined, Pt is widely used, and rather selective.[125] A 1:1 mixture of *cis*/*trans*-styrene derivatives was isomerized to a 90% yield of the *trans*-styrene derivatives using a Pd catalyst.[126] Isomerization of cyclic alkenes is

[120] Maynes, G.G.; Applequist, D.E. *J. Am. Chem. Soc.* ***1973***, *95*, 856; Incremona, J.H.; Shea, K.J.; Skell, P.S. *J. Am. Chem. Soc.* ***1973***, *95*, 6728; Upton, C.J.; Incremona, J.H. *J. Org. Chem.* ***1976***, *41*, 523.

[121] See Wiberg, K.B.; Waddell, S.T.; Laidig, K. *Tetrahedron Lett.* ***1986***, *27*, 1553.

[122] Arai, T.; Takahashi, O. *J. Chem. Soc., Chem. Commun.* ***1995***, 1837.

[123] Gaenzler, F.C.; Guo, C.; Zhang, Y.-W.; Azab, M.E.; Salem, M.A.I; Fan, D.P. Smith, M.B. *Tetrahedron* ***2009***, *65*, 8781.

[124] See Dugave, C.; Demange, L. *Chem. Rev.* ***2003***, *103*, 2475. See Bond, G.C.; Wells, P.B. *Adv. Catal.* ***1964***, *15*, 91; Anderson, J.R.; Baker, B.G. in *Chemisorption and Reactions on Metallic Films*, Vol. 2, Anderson, J.R. (ed.), Academic Press, London, ***1971***, p. 63; Zaera, F. *Langmuir* ***1996***, *12*, 88.

[125] Lee, I.; Zaera, F. *J. Am. Chem. Soc.* ***2005***, *127*, 12174.

[126] Yu, J.; Gaunt, M.J.; Spencer, J.B. *J. Org. Chem.* ***2002***, *67*, 4627. See also Kim, I.S.; Dong, G.R.; Jung, Y.H. *J. Org. Chem.* ***2007***, *72*, 5424.

difficult for rings of seven members and less, but *cis*/*trans* isomerization of cyclooctene is induced photochemically.[127] Radical-induced *E*/*Z* isomerization is known.[128] Isomerization of the C=C units in dienes is also induced photochemically.[129] (−)-Riboflavin has been used for the (*E*)- to (*Z*)-alkene isomerization.[130]

In general, there is an energetic preference of an α,β versus β,γ double bond.[131] Allylic arenes ($Ar{-}CH_2CH{=}CH_2$) have been converted to the corresponding (*Z*)-1-propenyl arene ($Ar{-}CH{=}CHMe$) using a Ru catalyst[132] or a polymer-supported Ir catalyst.[133] The isomerization of allylbenzenes to 1-propenylbenzenes has been reviewed.[134] A computational study of the asymmetric alkene isomerization of β,γ- to α,β-unsaturated butenolides, catalyzed by novel cinchona alkaloid derivatives, was reported.[135] Ruthenium hydrides promoted the positional isomerization of 1,3-dienes into more highly substituted 1,3-dienes.[136] A co-catalyst and organosilane led to irreversible isomerization of terminal alkenes by one position.[137] The synthesis of (*Z*)-alkenes has been reported, by the Rh-catalyzed isomerization of the alkene moiety of β,γ-unsaturated ketones to the conjugated ketone.[138] Using a Pd catalyst, the *exo* methylenes of 2,6-disubstituted bicyclo[3.3.1]nonan-9-ones were isomerized, under an atmosphere of hydrogen, to predominantly form the bis-endocyclic isomer with C_2 symmetry.[139] The La-catalyzed isomerization of allylic alcohols to homoallylic alcohols has been reported.[140] The isomerization of 1,3-dienes using [$CoBr_2$(py-imine)] gave the (*Z*)-1,3-diene whereas [$CoBr_2$(dpppMe$_2$)] gave the (2*Z*),(4*E*)-configured 2,4-dienes.[141] The Rh-catalyzed isomerization of 4-pentenals into 3-pentenals has been reported.[142]

Propargylic systems were isomerized to 1,3-dienes using a Au complex,[143] and the 1,3-transposition of ynones used a Au catalyst.[144] The stereoselective rearrangement of allenic alcohols to (*E,E*)-1,3-dien-2-yl triflates and chlorides was reported using TMSOTf or TMSCl.[145] The cesium hydroxide-catalyzed isomerization of terminal alkynes to the corresponding allene has been reported.[146]

For conjugated carbonyl compounds that have a hydrogen atom at the γ position (C-4), it is possible to move a double bond *out* of conjugation. Photolysis of conjugated esters, at −40 °C in the presence of *N*,*N*-dimethylaminoethanol, gave the nonconjugated

[127] Royzen, M.; Yap, G.P.A.; Fox, J.M. *J. Am. Chem. Soc.* ***2008***, *130*, 3760.
[128] Baag, Md.M.; Kar, A.; Argade, N.P. *Tetrahedron* ***2003***, *59*, 6489.
[129] Wakamatsu, K.; Takahashi, Y.; Kikuchi, K.; Miyashi, T. *J. Chem. Soc., Perkin Trans. 2* ***1996***, 2105.
[130] Metternich, J.B.; Gilmour, R. *J. Am. Chem. Soc.* ***2015***, *137*, 11254.
[131] Lee, P.S.; Du, W.; Boger, D.L.; Jorgensen, W.L. *J. Org. Chem.* ***2004***, *69*, 5448.
[132] Sato, T.; Komine, N.; Hirano, M.; Komiya, S. *Chem. Lett.* ***1999***, 441.
[133] Baxendale, I.R.; Lee, A.-L.; Ley, S.V. *Synlett* ***2002***, 516.
[134] Hassam, M.; Taher, A.; Arnott, G.E.; Green, I.R.; van Otterlo, W.A.L. *Chem. Rev.* ***2015***, *115*, 5462.
[135] Xue, X.-S.; Li, X.; Yu, A.; Yang, C.; Song, C.; Cheng, J.-P. *J. Am. Chem. Soc.* ***2013***, *135*, 7462.
[136] Clark, J.R.; Griffiths, J.R.; Diver, S.T. *J. Am. Chem. Soc.* ***2013***, *135*, 3327.
[137] Crossley, S.W.M.; Barabé, F.; Shenvi, R.A. *J. Am. Chem. Soc.* ***2014***, *136*, 16788.
[138] Zhuo, L.-G.; Yao, Z.-K.; Yu, Z.-X. *Org. Lett.* ***2013***, *15*, 4634.
[139] Jung, M.E.; Lee, G.S.; Pham, H.V.; Houk, K.N. *Org. Lett.* ***2014***, *16*, 2382.
[140] Seo, S.Y.; Yu, X.; Marks, T.J. *Tetrahedron Lett.* ***2013***, *54*, 1828.
[141] Pünner, F.; Schmidt, A.; Hilt, G. *Angew. Chem. Int. Ed.* ***2012***, *51*, 1270.
[142] Yip, S.Y.Y.; Aïssa, C. *Angew. Chem. Int. Ed.* ***2015***, *54*, 6870.
[143] Wang, Z.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* ***2014***, *136*, 8887.
[144] Shiroodi, R.K.; Soltani, M.; Gevorgyan, V. *J. Am. Chem. Soc.* ***2014***, *136*, 9882.
[145] Sabbasani, V.R.; Mamidipalli, P.; Lu, H.; Xia, Y.; Lee, D. *Org. Lett.* ***2013***, *15*, 1552.
[146] Li, Y.; Chen, J.; Qiu, R.; Wang, X.; Long, J.; Zhu, L.; Au, C.-T.; Xu, X. *Tetrahedron Lett.* ***2015***, *56*, 5504. For an organomagnesium-catalyzed isomerization, see Rochat, R.; Yamamoto, K.; Lopez, M.J.; Nagae, H.; Tsurugi, H.; Mashima, K. *Chem. Eur. J.* ***2015***, *21*, 8112.

ester.[147] Heating an *N*-allylic amide (N—C—C=C) with $Fe(CO)_5$, neat, gave the enamide (N—C=C—C).[148] Conjugated aldehydes have been isomerized using thiourea in DMF.[149] Double bonds of atoms other than carbon are subject to isomerization. Azobenzenes (Ar—N=N—Ar) exist as *E* and *Z* isomers, and photochemical isomerization is possible.[150]

15.C.ii. Reactions in Which Hydrogen Adds to One Side

A. Halogen on the Other Side

15-2 Addition of Hydrogen Halides

Any of the four hydrogen halides can be added to double bonds.[151] Alkenes react as Brønsted-Lowry bases with HI, HBr, and HF[152] at room temperature, but reaction with HCl is more difficult and usually requires heat.[12] HCl adds easily in the presence of silica gel, however.[153] HF is difficult to handle, but a convenient method for the addition of HF involves the use of a poly(HF)/pyridine solution in THF.[154] An aprotic solution of HBr has been reported, HBr•DMPU.[155]

The addition of hydrogen halides to simple alkenes, in the absence of peroxides, takes place by an electrophilic mechanism, and the orientation is in accord with *Markovnikov's rule*.[156] In other words, the π bond of the alkene donates two electrons to the acidic proton of H—X such that a new C—H bond is formed that generates the more stable carbocation. The addition follows second-order kinetics.[157] Alkenes react with HBr in dioxane to give the alkyl bromide.[158] Hex-1-ene reacts with Me_3SiCl in water to give 2-chlorohexane.[159]

When peroxides are added, the addition of HBr occurs by a free-radical mechanism in which Br• is generated and reacts with the C=C moiety to form the more stable radical, which reacts with H—Br to give the final product with an *anti-Markovnikov* orientation (Sec. 15.B.i).[160] It must be emphasized that this is true *only* for HBr. Free-radical addition

[147] Bargiggia, F.; Piva, O. *Tetrahedron: Asymmetry* ***2001***, *12*, 1389.
[148] Sergeyev, S.; Hesse, M. *Synlett* ***2002***, 1313.
[149] Phillips, O.A.; Eby, P.; Maiti, S.N. *Synth. Commun.* ***1995***, *25*, 87.
[150] Carreño, M.C.; García, I.; Ribagorda, M.; Merino, E.; Pieraccini, S.; Spada, G.P. *Org. Lett.* ***2005***, *7*, 2869.
[151] For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 633–636.
[152] See Sharts, C.M.; Sheppard, W.A. *Org. React.* ***1974***, *21*, 125 (pp. 192–198, 212–214); Hudlicky, M. *The Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, ***1976***, pp. 36–41.
[153] Kropp, P.J.; Daus, K.A.; Tubergen, M.W.; Kepler, K.D.; Wilson, V.P.; Craig, S.L.; Baillargeon, M.M.; Breton, G.W. *J. Am. Chem. Soc.* ***1993***, *115*, 3071.
[154] Olah, G.A.; Welch, J.T.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979***, *44*, 3872. For a related method, see Olah, G.A.; Li, X. *Synlett* ***1990***, 267.
[155] Li, Z.; Ebule, R.; Kostyo, J.; Hammond, G.B.; Xu, B. *Chem. Eur. J.* ***2017***, *23*, 12739.
[156] See Ref. 12; Dewar, M.J.S. *Angew. Chem. Int. Ed.* ***1964***, *3*, 245.
[157] Boregeaud, R.; Newman, H.; Schelpe, A.; Vasco, V.; Hughes, D.E.P. *J. Chem. Soc., Perkin Trans. 2* ***2002***, 810.
[158] Nishio, Y.; Mifune, R.; Sato, T.; Ishikawa, S.; Matsubara, H. *Tetrahedron Lett.* ***2017***, *58*, 1190.
[159] Boudjouk, P.; Kim, B.-K.; Han, B.-H. *Synth. Commun.* ***1996***, *26*, 3479.
[160] See Thaler, W.A. *Methods Free-Radical Chem.* ***1969***, *2*, 121 (pp. 182–195).

of HF and HI has never been observed, even in the presence of peroxides; free-radical addition of HCl has been observed only rarely. In the rare cases where free-radical addition of HCl was noted, the orientation was still Markovnikov, presumably because the more stable product was formed.[161] Free-radical addition of HF, HI, and HCl is energetically unfavorable (Sec. 14.B.i and Sec. 14.C.i).

It is known that under some conditions anti-Markovnikov addition of HBr takes place even when peroxides have not been added. This reaction happens because the substrate alkenes absorb oxygen from the air, forming small amounts of peroxides (**14-6**). Markovnikov addition can be ensured by rigorous purification of the substrate, but in practice this is not easy to achieve, and it is more common to add inhibitors, for example phenols or quinones, which suppress the free-radical pathway. The presence of free-radical precursors such as peroxides in the reaction of HBr does not inhibit the ionic mechanism. Markovnikov addition of HBr, HCl, and HI has also been accomplished, in high yields, by the use of phase-transfer catalysis.[162] Anti-Markovnikov bromides were prepared by the reaction of alkenes and HBr in acetic acid.[163]

Fluorination of alkenes is possible. Alkenes reacted with $KHSO_4$-13HF to give the corresponding Markovnikov alkyl fluoride.[164] The reaction of alkenes with Selectfluor, mediated by Fe(III)/$NaBH_4$, led to free-radical hydrofluorination of unactivated alkenes with exclusive Markovnikov addition.[165] The Co-catalyzed hydrofluorination of alkenes using $(Me_2SiH)_2O$ and *N*-fluoropyridinium salts gave the alkyl fluoride with Markovnikov selectivity.[166] Aryl alkenes reacted with 2 equivalents of Selectfluor in the presence of a Pd catalyst to give the α-fluoro arene.[167] Treatment of an alkene with KHF_2 and SiF_4 leads to the alkyl fluoride.[168]

Alkynes also react as bases with acids such as HX. It is possible to add 1[169] or 2 equivalents of any of the four hydrogen halides to triple bonds:

$$-C\equiv C- + H-X \rightarrow -CH=CX-$$
$$-CH=CX- + H-X \rightarrow -CH_2-CX_2-$$

Markovnikov's rule ensures that *gem*-dihalides and not *vic*-dihalides are the products of the addition of 2 equivalents. Alkynes were converted to vinyl bromides with anti-Markovnikov regioselectivity using $(CCl_2B)_2$, with both *i*-PrCuCl and 2-*tert*-butyl potassium phenoxide in catalytic amounts, in the presence of Ph_2SiH_2. A halosilane was formed and generated HX *in situ*.[170] Heating alkynes with dibromomethane in the presence of *N*,*N*-dimethylaniline and air gave the corresponding vinyl bromide.[171] Alkynes reacted with

[161] Mayo, F.R. *J. Am. Chem. Soc.* ***1962***, *84*, 3964.
[162] Landini, D.; Rolla, F. *J. Org. Chem.* ***1980***, *45*, 3527.
[163] Galli, M.; Fletcher, C.J.; de Pozo, M.; Goldup, S.M. *Org. Biomol. Chem.* ***2016***, *14*, 5622.
[164] Lu, Z.; Zeng, X.; Hammond, G.B.; Xu, B. *J. Am. Chem. Soc.* ***2017***, *139*, 18202.
[165] Barker T.J.; Boger, D.L. *J. Am. Chem. Soc.* ***2012***, *134*, 13588.
[166] Shigehisa, H.; Nishi, E.; Fujisawa, M.; Hiroya, K. *Org. Lett.* ***2013***, *15*, 5158.
[167] Emer, E.; Pfeifer, L.; Brown, J.M.; Gouverneur, V. *Angew. Chem. Int. Ed.* ***2014***, *53*, 4181.
[168] Tamura, M.; Shibakami, M.; Kurosawa, S.; Arimura, T.; Sekiya, A. *J. Chem. Soc., Chem. Commun.* ***1995***, 1891.
[169] See Cousseau, J. *Synthesis* ***1980***, 805; Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* ***1990***, 675.
[170] Uehling, M.R.; Rucker, R.P.; Lalic, G. *J. Am. Chem. Soc.* ***2014***, *136*, 8799.
[171] Chen, X.; Chen, T.; Xiang, Y.; Zhou, Y.; Han, D.; Han, L.-B.; Yin, S.-F. *Tetrahedron Lett.* ***2014***, *55*, 4572.

phosphorus reagents and iodine to give the corresponding vinyl iodide.[172] Terminal alkynes reacted with excess LiCl in the presence of a Pd catalyst and a catalytic amount of $CuCl_2$ to give the vinyl chloride.[173] Phenylacetylene reacted with HCl in the presence of a Ru catalyst to give the 1-chloro-1-phenylethene.[174] 2-Bromo-1-alkenes were prepared from 1-alkynes using a microwave-assisted reaction with LiBr, TMSCl, and tetraethylammonium bromide in acetonitrile.[175] Bromotrimethylsilane adds to alkynes to give the vinyl bromide.[176]

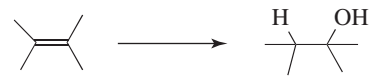
Brønsted-Lowry acids such as HX are electrophilic reagents, and many polyhalo or polycyano alkenes do not react with them in the absence of free-radical conditions. A nucleophilic addition mechanism is possible, and occurs with *Michael-type substrates* C═C─Z,[177] where the nucleophile add to the β carbon, even in the presence of free-radical initiators. Vinylcyclopropanes, however, react with opening of the cyclopropane ring to give a homoallylic chloride.[178]

The reaction with HX has been carried out with conjugated dienes, where both 1,2- and 1,4-addition are possible. Hydrogen iodide adds 1,4 to conjugated dienes in the gas phase by a pericyclic mechanism.[179] Ketenes reacted with HX to give acyl halides.[180]

OS **I**, 166; **II**, 137, 336; **III**, 576; **IV**, 238, 543; **VI**, 273; **VII**, 59; **80**, 129.

B. Oxygen on the Other Side

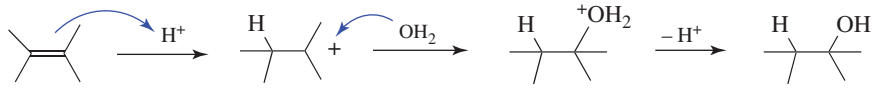
15-3 Hydration of Double Bonds



Double bonds can be hydrated by treatment with water and an acid catalyst. Sulfuric acid is a common catalyst, but other acids that have relatively nonnucleophilic counterions, such as nitric, perchloric, or, more commonly, sulfonic acids (*p*-toluenesulfonic acid, methanesulfonic acid, etc.) can also be used. The mechanism is electrophilic and begins with attack of the π bond on an acidic proton (Sec. 15.A.i). The resulting carbocation is then attacked by negative species, such as HSO_4^- (or similar counterion in the case of other acids), to give the initial product, an alkyl hydrogensulfate (H─C─C─OSO_2OH), which can be isolated in some cases. However, such compounds are rather unstable, and under the reaction conditions and are usually hydrolyzed to the alcohol (**10-4**).

Other nucleophiles are present in the reaction under some reaction conditions, either from the solvent or from added compounds. In an aqueous medium, water is a competitive nucleophile, and attack by water forms oxonium ion **14**.

[172] Kawaguchi, S.; Masuno, H.; Sonoda, M.; Nomoto, A.; Ogawa, A. *Tetrahedron* ***2012***, *68*, 9818.
[173] Derosa, J.; Cantu, A.L.; Boulous, M.N.; O'Duill, M.L.; Turnbull, J.L.; Liu, Z.; De La Torre, D.M.; Engle, K.M. *J. Am. Chem. Soc.* ***2017***, *139*, 5183.
[174] Dérien, S.; Klein, H.; Bruneau, C. *Angew. Chem. Int. Ed.* ***2015***, *54*, 12112.
[175] Bunrit, A.; Ruchirawat, S.; Thongsornkleeb, C. *Tetrahedron Lett.* ***2011***, *52*, 3124.
[176] Su, M.; Yu, W.; Jin, Z. *Tetrahedron Lett.* ***2001***, *42*, 3771.
[177] For an example, see Marx, J.N. *Tetrahedron* ***1983***, *39*, 1529.
[178] Siriwardana, A.I.; Nakamura, I.; Yamamoto, Y. *Tetrahedron Lett.* ***2003***, *44*, 985.
[179] Gorton, P.J.; Walsh, R. *J. Chem. Soc., Chem. Commun.* ***1972***, 782. See Sergeev, G.B.; Stepanov, N.F.; Leenson, I.A.; Smirnov, V.V.; Pupyshev, V.I.; Tyurina, L.A.; Mashyanov, M.N. *Tetrahedron* ***1982***, *38*, 2585.
[180] Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975***, *4*, 231. See Allen, A.D.; Tidwell, T.T. *Chem. Rev.* ***2013***, *113*, 7287.



14

Products such as the alkyl hydrogensulfate are not involved when other nucleophiles react with the carbocation, and the mechanism is exactly (by the principle of microscopic reversibility) the reverse of El elimination of alcohols (**17-1**).[181] *The initial carbocation occasionally rearranges to a more stable one.* For example, hydration of $CH_2{=}CHCH(CH_3)_2$ gives $CH_3CH_2COH(CH_3)_2$. Hydration of simple alkenes leads to alcohols predicted by *Markovnikov's rule*.

Oxymercuration[182] (addition of oxygen and mercury) of alkenes followed by *in situ* treatment with sodium borohydride[183] (**12-24**), gives an alcohol under mild conditions, in high yields, and *without rearrangement products*. In oxymercuration *the mercury stabilizes the initially formed carbocation by back-donation of the mercury d orbitals such that rearrangement does not occur*.[184] For example, treatment of 2-methylbut-1-ene with aqueous mercuric acetate,[185] followed by reaction with $NaBH_4$, gave 2-methylbutan-2-ol. This method, which is applicable to mono-, di-, tri-, and tetraalkyl- as well as phenyl-substituted alkenes, gives almost complete Markovnikov addition. Hydroxy, methoxy, acetoxy, halo, and other groups may be present in the substrate, and generally do not cause difficulties.[186] Oxymercuration of alkenes has been reported in water, using cyclodextrins as phase-transfer catalysts.[187] When two double bonds are present in the same molecule, changing the carboxylic acid ligand of the mercuric salt allows oxymercuration of the less-substituted one without affecting the other, using ultrasound.[188]

Indirect hydration, with anti-Markovnikov orientation, was achieved using hydroboration (**15-11**). Alkenes react with PhO_2BH and a Nb catalyst, followed by oxidation with $NaOO^-$, to give the alcohol,[189] and Cp_2TiCl_4 can also be used.[190] Ketenes add water to give carboxylic acids ($R_2C{=}C{=}O \rightarrow R_2CO_2H$) in a reaction catalyzed by acids:[191] The hydration of the allene moiety of electron-deficient allenic esters and ketones, promoted by

[181] See Vinnik, M.I.; Obraztsov, P.A. *Russ. Chem. Rev.* ***1990***, *59*, 63; Liler, M. *Reaction Mechanisms in Sulphuric Acid*, Academic Press, NY, ***1971***, pp. 210–225.

[182] See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***; Kitching, W. *Organomet. React.* ***1972***, *3*, 319; Oullette, R.J. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 140–166; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 387–396.

[183] Brown, H.C.; Geoghegan Jr., P.J.; Lynch, G.J.; Kurek, J.T. *J. Org. Chem.* ***1972***, *37*, 1941; Barrelle, M.; Apparu, M. *Bull. Soc. Chim. Fr.* ***1972***, 2016.

[184] See Chatt, J. *Chem. Rev.* ***1951***, *48*, 7; Rodgman, A.; Wright, G.F. *J. Org. Chem.* ***1953***, *18*, 1617; Allen, E.R.; Cartlidge, J.; Taylor, M.M.; Tipper, C.F.H. *J. Phys. Chem.* ***1959***, *63*, 1437.

[185] See Butler, R.N. in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, ***1981***, pp. 1–145.

[186] See the extensive tables in Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 4–71.

[187] Abreu, A.R.; Costa, I.; Rosa, C.; Ferreira, L.M.; Lourenço, A.; Santos, P.P. *Tetrahedron* ***2005***, *61*, 11986.

[188] Einhorn, J.; Einhorn, C.; Luche, J.L. *J. Org. Chem.* ***1989***, *54*, 4479.

[189] Burgess, K.; Jaspars, M. *Tetrahedron Lett.* ***1993***, *34*, 6813.

[190] Burgess, K.; van der Donk, W.A. *Tetrahedron Lett.* ***1993***, *34*, 6817.

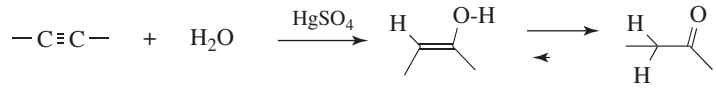
[191] See Tidwell, T.T. *Acc. Chem. Res.* ***1990***, *23*, 273; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975***, *4*, 231.

Oxone in DMF, gave 1,3-dicarbonyl compounds.[192] Cycloisomerization of α-allenols with $Hg(ClO_4)_2 \cdot 3H_2O$, gave 2,5-dihydrofurans.[193]

A preparation of alcohols involved the reaction of alkenes with water and a Pd catalyst, a Ru catalyst *(Shvo's catalyst)*, and benzoquinone.[194] The Pd-catalyzed hydration of terminal alkenes gave primary allylic alcohols,[195] while terminal alkenes gave the corresponding secondary alcohol using Cr and Cu complexes.[196]

OS **IV**, 555, 560; **VI**, 766. Also see, OS **V**, 818.

15-4 Hydration of Triple Bonds



Alkynes react with water and a Brønsted acid catalyst[197] to give an enol, which tautomerizes to the carbonyl. The hydration of terminal alkynes leads to a methyl ketone and internal alkynes can lead to two different ketones. Only acetylene gives an aldehyde. Metal-free reactions are known, often using strong acids. Terminal aryl alkynes reacted with water in the presence of 20% triflic acid, in 2,2,2-trifluroethanol, to give the acetophenone.[198] Phenyl acetylene was converted to acetophenone, for example, in water at 100 °C with a catalytic amount of Tf_2NH (trifluoromethanesulfonimide), which is a very powerful acid.[199] Simple alkynes can also be converted to ketones by heating with formic acid, without a catalyst.[200] Allenes can be hydrolyzed to ketones using an acid catalyst.[201]

The hydration of triple bonds can be carried out with aqueous mercuric ion salts (often the sulfate or acetate or even mercuric oxide) as catalysts,[202] and always gave the more stable vinyl carbocation, and reaction with water gives the hydroxy/mercury intermediate via a vinyl/mercury complex. In contrast to oxymercuration of alkenes, the hydroxy/organomercury intermediate from this reaction (Hg^+—C═C—OH) is unstable and loss of mercury *in situ* leads to an enol product, which tautomerizes to the ketone. It is noted that a spectrum of the enol was detected by flash photolysis when phenylacetylene was hydrated photolytically.[203] The reaction can be conveniently carried out with a catalyst prepared by impregnating mercuric oxide onto Nafion-H (a superacidic perfluorinated resin/sulfonic acid; Sec. 5.A.ii).[204] Note that another possibility for a vinyl/mercury

[192] Yi, Y.P.; Zheng, Y.; Nie, J.; Ma, J.-A. *Tetrahedron Lett.* ***2015***, *56*, 4523.
[193] Alcaide, B.; Almendros, P.; Luna, A.; Soriano, E. *J. Org. Chem.* ***2015***, *80*, 7050.
[194] Yang, Y.; Guo, J.; Ng, H.; Chen, Z.; Teo, P. *Chem. Commun.* ***2012***, *48*, 5497.
[195] Tomita, R.; Mantani, K.; Hamasaki, A.; Ishida, T.; Tokunaga, M. *Chem. Eur. J.* ***2014***, *20*, 9914.
[196] Khusnutdinov, R.I.; Oshnyakova, T.M.; Shchadneva, N.A. *Russ. J. Org. Chem.* ***2013***, *49*, 1428.
[197] Liang, S.; Hammond, G.B.; Xu, B. *Chem. Commun.* ***2015***, *51*, 903.
[198] Liu, W.; Wang, H.; Li, C.J. *Org. Lett.* ***2016***, *18*, 2184.
[199] Tsuchimoto, T.; Joya, T.; Shirakawa, E.; Kawakami, Y. *Synlett* ***2000***, 1777.
[200] Menashe, N.; Reshef, D.; Shvo, Y. *J. Org. Chem.* ***1991***, *56*, 2912.
[201] See Cramer, P.; Tidwell, T.T. *J. Org. Chem.* ***1981***, *46*, 2683.
[202] See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 123–148; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Vol. 2, Academic Press, NY, ***1974***, pp. 91–95. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1217–1219. Also see Adcock, H.V.; Davies, P.W. *Synthesis* ***2012***, *44*, 3401.
[203] Chiang, Y.; Kresge, A.J.; Capponi, M.; Wirz, J. *Helv. Chim. Acta* ***1986***, *69*, 1331.
[204] Olah, G.A.; Meidar, D. *Synthesis* ***1978***, 671.

complex is a mercury-stabilized carbocation rather than a formal three-membered ring complex.

Other catalysts used to convert alkynes to the ketone include Cu,[205] Fe,[206] Pd,[207] Ru,[208] Rh,[209] In,[210] Mn,[211] Co,[212] Ag,[213] or Au.[214] Gold(I) catalysts have also been used in the hydration of allenes.[215] The aerobic hydration of aryl acetylenes gave acetophenone derivatives in the presence of an Fe catalyst in acetic acid.[216] The microwave-assisted, Cu-catalyzed hydration of aryl acetylenes has been reported.[217] The Pd-catalyzed reaction of aryl terminal alkynes with aqueous HCl gave the acetophenone derivative.[218] Alkynes were converted to methyl ketones by reaction with cobaloxime with methanol in air.[219] The reaction of alkynes and water in the presence of an In catalyst and PTSA gave the corresponding ketone.[220]

Terminal alkynes reacted with water, in the presence of a Au/Ru catalyst, to give the Markovnikov alcohol, whereas reaction with water in the presence of a diruthenium catalyst gave the anti-Markovnikov alcohol, both in isopropanol.[221] Catalysts have been developed for the *anti-Markovnikov* hydration of alkynes.[222] When oct-1-yne was heated with water, isopropyl alcohol, and a Ru catalyst, for example, the product was octanal.[223] The presence of certain functionality can influence the regioselectivity of hydration. Terminal alkynes reacted with aqueous THF and a Ru catalyst, and with a bipyridyl ligand, to give the corresponding aldehyde.[224] An Fe catalyst has been used to convert terminal alkynes to aldehydes.[225]

When a carboxylic acid that contains a double bond in the chain is treated with a strong acid, the intramolecular hydration reaction gives a γ- and/or a δ-lactone, regardless of the original position of the double bond in the chain, since strong acids catalyze double bond

[205] Hassam, M.; Li, W.-S. *Tetrahedron* ***2015***, *71*, 2719.
[206] Cabrero-Antonino, J.R.; Leyva-Pérez, A.; Corma, A. *Chem. Eur. J.* ***2012***, *18*, 11107.
[207] Zhang, Z.; Wu, L.; Liao, J.; Wu, W.; Jiang, H.; Li, J.; Li, J. *J. Org. Chem.* ***2015***, *80*, 7494.
[208] Mainkar, P.S.; Chippala, V.; Chegondi, R.; Chandrasekhar, S. *Synlett* ***2016***, *27*, 1968.
[209] Liu, X.; Li, L.; Wang, Z.; Fu, X. *Chem. Commun.* ***2015***, *51*, 11896.
[210] Hirabayashi, T.; Okimoto, Y.; Saito, A.; Morita, M.; Sakaguchi, S.; Ishii, Y. *Tetrahedron* ***2006***, *62*, 2231.
[211] Zhou, B.; Chen, H.; Wang, C. *J. Am. Chem. Soc.* ***2013***, *135*, 1264.
[212] Hou, S.; Yang, H.; Cheng, B.; Zhai, H.; Li, Y. *Chem. Commun.* ***2015***, *51*, 11896; Tachinami, T.; Nishimura, T.; Ushimaru, R.; Noyori, R.; Naka, H. *J. Am. Chem. Soc.* ***2013***, *135*, 50.
[213] Thuong, M.B.T.; Mann, A.; Wagner, A. *Chem. Commun.* ***2012***, *48*, 434; Chen, Z.-W.; Ye, D.-N.; Qian, Y.-P.; Ye, M.; Liu, L.-X. *Tetrahedron* ***2013***, *69*, 6116.
[214] Brenzovich Jr., W.E. *Angew. Chem. Int. Ed.* ***2012***, *51*, 8933; Xie, L.; Liang, Z.; Yan, D.; He, W.; Xiang, J. *Synlett* ***2013***, *24*, 1809; Das, A.K.; Park, S.; Muthaiah, S.; Hong, S.H. *Synlett* ***2015***, *26*, 2517.
[215] Zhang, Z.; Lee, S.D.; Fisher, A.S.; Widenhoefer, R.A. *Tetrahedron* ***2009***, *65*, 1794.
[216] Bassetti, M.; Ciceri, S.; Lancia, F.; Pasquini, C. *Tetrahedron Lett.* ***2014***, *55*, 1608. See Tanemura, K.; Suzuki, T. *Tetrahedron Lett.* ***2017***, *58*, 955; Niu, T.-f.; Jiang, D.-y.; Li, S.-y.; Shu, X.-g.; Li, H.; Zhang, A.-l.; Xu, J.-y.; Ni, B.-q. *Tetrahedron Lett.* ***2017***, *58*, 1156.
[217] Jha, M.; Shelke, G.M.; Pericherla, K.; Kumar, A. *Tetrahedron Lett.* ***2014***, *55*, 4814.
[218] Xu, C.; Du, W.; Zeng, Y.; Dai, B.; Guo, H. *Org. Lett.* ***2014***, *16*, 948.
[219] Hou, S.; Yang, H.; Cheng, B.; Zhai, H.; Li, T. *Chem. Commun.* ***2017***, *53*, 6926.
[220] Gao, Q.; Li, S.; Pan, Y.; Xu, Y.; Wang, H. *Tetrahedron* ***2013***, *69*, 3775.
[221] Li, L.; Herzon, S.B. *J. Am. Chem. Soc.* ***2012***, *134*, 17376.
[222] Labonne, A.; Kribber, T.; Hintermann, L. *Org. Lett.* ***2006***, *8*, 5853.
[223] Suzuki, T.; Tokunaga, M.; Wakatsuki, Y. *Org. Lett.* ***2001***, *3*, 735. Also see Grotjahn, D.B.; Lev, D.A. *J. Am. Chem. Soc.* ***2004***, *126*, 12232.
[224] Li, L.; Zeng, M.; Herzon, S.B. *Angew. Chem. Int. Ed.* ***2014***, *53*, 7892.
[225] Chowdhury, A.D.; Ray, R.; Lahiri, G.K. *Chem. Commun.* ***2012***, *48*, 5497.

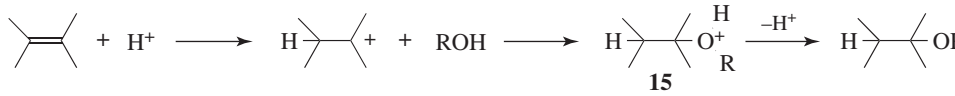
shifts (**15-1**; and see **12-2**).[226] The double bond always migrates to a position favorable for the reaction, whether this has to be toward or away from the carboxyl group. The use of a chiral *Cinchonidine* alkaloid additive leads to lactone formation with modest enantioselectivity.[227]

Carboxylic esters, thiol esters, and amides can be made, respectively, by acid-catalyzed hydration of acetylenic ethers, thioethers,[228] and ynamines, without a mercuric catalyst.[229] This reaction is ordinary electrophilic addition, with rate-determining protonation as the first step.[230] The trifluoroacetic acid (TFA)-mediated hydration of ynamides to give amides was reported.[231] Certain other alkynes have also been hydrated to ketones with strong acids in the absence of mercuric salts.[232]

OS **III**, 22; **IV**, 13; **V**, 1024.

15-5 Addition of Alcohols and Phenols to Give Ethers

Just as water adds to an alkene via hydration to form an alcohol, alcohols can also add to form an ether.[233] The addition of alcohols and phenols to double bonds is catalyzed by acids or bases. When the reactions are acid catalyzed, the mechanism is electrophilic, where H^+ from the acid catalyst is attacked by the π bond. The more stable carbocation is formed and subsequently attacked by a molecule of alcohol to give an oxonium ion, **15**.



The addition, therefore, follows *Markovnikov's rule*. Primary alcohols give better results than secondary, and tertiary alcohols are relatively inactive. Addition of alcohols to allylic systems can proceed with rearrangement, and the use of chiral additive can lead to asymmetric induction.[234] The uncatalyzed addition of alcohols occurs in supercritical alcohols.[235]

Metal-catalyzed addition to alkenes is a useful variation. The Au(III)/$CuCl_2$-catalyzed reaction of alcohols and alkenes gave the ether.[236] The Pd-catalyzed addition of alcohols to aryl alkenes gives the ether,[237] and the Au-catalyzed intermolecular addition of phenols

[226] See Ansell, M.F.; Palmer, M.H. *Q. Rev. Chem. Soc.* ***1964***, *18*, 211. For a Rh(I)-catalyzed reaction in ionic liquids, see Oonishi, Y.; Ogura, J.; Sato, Y. *Tetrahedron Lett.* ***2007***, *48*, 7505.

[227] Wang, M.; Gao, L.X.; Mai, W.P.; Xia, A.X.; Wang, F.; Zhang, S.B. *J. Org. Chem.* ***2004***, *69*, 2874.

[228] Braga, A.L.; Martins, T.L.C.; Silveira, C.C.; Rodrigues, O.E.D. *Tetrahedron* ***2001***, *57*, 3297. Also see Brandsma, L.; Bos, H.J.T.; Arens, J.F. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 751–860.

[229] Arens, J.F. *Adv. Org. Chem.* ***1960***, *2*, 163; Brandsma, L.; Bos, H.J.T.; Arens, J.F. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 774–775.

[230] Banait, N.; Hojatti, M.; Findlay, P.; Kresge, A.J. *Can. J. Chem.* ***1987***, *65*, 441.

[231] Huang, H.; Tang, L.; Xi, Y.; He, G.; Zhu, H. *Tetrahedron Lett.* ***2016***, *57*, 1873.

[232] Noyce, D.S.; Schiavelli, M.D. *J. Am. Chem. Soc.* ***1968***, *90*, 1020, 1023.

[233] Ondet, P.; Lemière, G.; Duñach, E. *Eur. J. Org. Chem.* ***2017***, 761.

[234] See Nakamura, H.; Ishihara, K.; Yamamoto, H. *J. Org. Chem.* ***2002***, *67*, 5124.

[235] Kamitanaka, T.; Hikida, T.; Hayashi, S.; Kishida, N.; Matsuda, T.; Harada, T. *Tetrahedron Lett.* ***2007***, *48*, 8460.

[236] Zhang, X.; Corma, A. *Chem. Commun.* ***2007***, 3080.

[237] Gligorich, K.M.; Schultz, M.J.; Sigman, M.S. *J. Am. Chem. Soc.* ***2006***, *128*, 2794.

leads to aryl ethers.[238] Aryl ethers were prepared by the Ir-[239] or Pd-catalyzed[240] reaction of terminal alkenes with phenols. 2-Alkenyl cyclic ethers were prepared from dienes that have a distal hydroxyl group when heated with catalytic Au and catalytic Ag compounds.[241]

The oxymercuration-demercuration procedure mentioned in **15-3** can be adapted to the preparation of ethers in what is known as *alkoxymercuration-demercuration* (with Markovnikov orientation), if the reaction is carried out in an alcohol (ROH) solvent.[242] Primary alcohols give good yields when mercuric acetate is used, but for secondary and tertiary alcohols it is necessary to use mercuric trifluoroacetate.[243] However, even this reagent fails where the product would be a ditertiary ether. It is possible to combine the alcohol reactant with another reagent. If the oxymercuration is carried out in the presence of a hydroperoxide instead of an alcohol, the product (after demercuration with $NaBH_4$) is an alkyl peroxide (*peroxy-mercuration*).[244] This reaction can be done intramolecularly.[245]

Alcohols add intramolecularly to alkenes to generate cyclic ethers, and the product often bears a hydroxyl unit,[246] but not always.[247] A transition metal-free synthesis of tetrahydrofurans from alkene alcohols used a catalytic amount of iodine and a catalytic amount of $PhSiH_3$.[248] Cyclization is facilitated by Re,[249] Ti,[250] or Pt compounds,[251] leading to functionalized tetrahydrofurans[252] or tetrahydropyans. Furan derivatives are available from alkene ketones using $CuCl_2$ and a Pd catalyst[253] or a Cr,[254] Ag(I),[255] or lanthanide catalyst.[256] A Au catalyst was used with conjugated ketones bearing an alkyne substituent to give fused-ring furans.[257] Intramolecular addition of alcohols to alkenes can be promoted by a Pd catalyst, but migration of the double bond in the final product can be a problem.[258] Tetrahydrofurans were prepared from alkene alcohols by using a Cu,[259] No,[260]

[238] Yang, C.-G.; He, C. *J. Am. Chem. Soc.* ***2005***, *127*, 6966.
[239] Sevov, C.S.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2013***, *135*, 9303. See Haibach, M.C.; Guan, C.; Wang, D.Y.; Li, B.; Lease, N.; Steffens, A.M.; Krogh-Jespersen, K.; Goldman, A.S. *J. Am. Chem. Soc.* ***2013***, *135*, 15062.
[240] Race, N.J.; Schwalm, C.S.; Nakamuro, T.; Sigman, M.S. *J. Am. Chem. Soc.* ***2016***, *138*, 15881.
[241] Chandrasekhar, B.; Ryu, J.-S. *Tetrahedron* ***2012***, *68*, 4805.
[242] See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 162–345.
[243] See Brown, H.C.; Kurek, J.T.; Rei, M.; Thompson, K.L. ***1985***, *50*, 1171.
[244] See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 346–366.
[245] Garavelas, A.; Mavropoulos, I.; Perlmutter, P.; Westman, F. *Tetrahedron Lett.* ***1995***, *36*, 463.
[246] Gruttadauric, M.; Aprile, C.; Riela, S.; Noto, R. *Tetrahedron Lett.* ***2001***, *42*, 2213; Huang, D.; Wang, H.; Xue, F.; Guan, H.; Li, L.; Peng, X.; Shi, Y. *Org. Lett.* ***2011***, *13*, 6350. See Ghebreghiorgis, T.; Kirk, B.H.; Aponick, A.; Ess, D.H. *J. Org. Chem.* ***2013***, *78*, 7664; Aponick, A.; Biannic, B. *Org. Lett.* ***2011***, *13*, 1330.
[247] Miura, K.; Hondo, T.; Okajima, S.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *J. Org. Chem.* ***2002***, *67*, 6082; Marotta, E.; Foresti, E.; Marcelli, T.; Peri, F.; Righi, P.; Scardovi, N.; Rosini, G. *Org. Lett.* ***2002***, *4*, 4451.
[248] Fujita, S.; Abe, M.; Shibuya, M.; Yamamoto, Y. *Org. Lett.* ***2015***, *17*, 3822.
[249] McDonald, F.E.; Towne, T.B. *J. Org. Chem.* ***1995***, *60*, 5750.
[250] Lattanzi, A.; Della Sala, G.D.; Russo, M.; Screttri, A. *Synlett* ***2001***, 1479.
[251] Qian, H.; Han, X.; Widenhoefer, R.A. *J. Am. Chem. Soc.* ***2004***, *126*, 9536.
[252] de la Torre, A.; Cuyamendous, C.; Bultel-Poncé, V.; Durand, T.; Galano, J.-M.; Oger, C. *Tetrahedron* ***2016***, *72*, 5003.
[253] Han, X.; Widenhoefer, R.A. *J. Org. Chem.* ***2004***, *69*, 1738.
[254] Miki, K.; Nishino, F.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* ***2002***, *124*, 5260.
[255] Yang, C.-G.; Reich, N.W.; Shi, Z.; He, C. *Org. Lett.* ***2005***, *7*, 4553.
[256] Yu, X.; Seo, S.Y.; Marks, T.J. *J. Am. Chem. Soc.* ***2007***, *129*, 7244.
[257] Yao, T.; Zhang, X.; Larock, R.C. *J. Am. Chem. Soc.* ***2004***, *126*, 11164.
[258] Rönn, M.; Bäckvall, J.-E.; Andersson, P.G. *Tetrahedron Lett.* ***1995***, *36*, 7749. See Tiecco, M.; Testaferri, L.; Santi, C. *Eur. J. Org. Chem.* ***1999***, 797.
[259] Murayama, H.; Nagao, K.; Ohmiya, H.; Sawamura, M. *Org. Lett.* ***2015***, *17*, 2039.
[260] Ferrand, L.; Tang, Y.; Aubert, C.; Fensterbank, L.; Mouriès-Mansuy, V.; Petit, M.; Amatore, M. *Org. Lett.* ***2017***, *19*, 2062.

or an Fe catalyst.[261] Substituted tetrahydropyrans were prepared from allylic alcohols that have a distal hydroxyl group using an Fe catalyst.[262] Tetrahydropyrans or tetrahydrofurans were prepared from alkenes that have a distal hydroxyl group by treatment with $Ca(NTf)_2/Bu_4NPF_6$.[263] The intramolecular reaction of unsaturated alcohols to form cyclic ethers was catalyzed by self-assembled resorcin[4]arene hexamer.[264] The asymmetric synthesis of THF derivatives from ε-hydroxy-α,β-unsaturated ketones was mediated by cinchona/alkaloid/thiourea-based bifunctional organocatalysts.[265]

Alcohols add to alkynes under certain conditions to give vinyl ethers. In an excess of alcohol, and in the presence of a Pt[266] or a Au catalyst,[267] internal alkynes are converted to ketals. The alcohol to alkyne addition reaction is quite useful for the preparation of heterocycles, and dihydrofurans,[268] furans,[269] benzofurans,[270] and pyran derivatives[271] have been prepared using this approach. The alkoxymercuration of alkynes generally gives an acetal. Allenes or alkynes react to form a Rh complex, generated by a Rh compound and HX, and subsequent reaction with an alcohol gives a chiral allylic ether.[272] Allenes reacted with alcohols in the presence of a Au catalyst and MS 3Å to give allylic ethers.[273] The reaction of ethanol with 1,1-diphenylethene and a Co catalyst and a photocatalyst gave the vinyl ether.[274] The Au-catalyzed reaction of alcohols and alkynes to give vinyl ethers has been reported with good regioselectivity.[275] The Rh-catalyzed anti-Markovnikov hydroalkoxylation of terminal alkynes gave the vinyl ether.[276]

Enol ethers are more susceptible than triple bonds to electrophilic attack, and the addition of alcohols to enol ethers can also be catalyzed by acids.[277] One utilization of this is the reaction of dihydropyran (a vinyl ether) with an alcohol to give the 2-alkoxytetrahydropyran, which is often used to protect the OH groups of primary and secondary alcohols[278] and phenols.[279] For deprotection, the 2-alkoxytetrahydropyran is easily cleaved back to the alcohol and dihydropyran by treatment with dilute acids (**10-6**).

Allenes react with alcohols and so allenic alcohols have been converted to tetrahydrofuran derivatives bearing a vinyl group at the α position, using diphenyliodonium salts.[280] In

[261] Ke, F.; Li, Z.; Xiang, H.; Zhou, X. *Tetrahedron Lett.* ***2011***, *52*, 318.
[262] Bosset, C.; Stanfield, P.A.; Meerpoel, L.; Berthelot, D.; Guérinot, A.; Cossy, J. *J. Org. Chem.* ***2015***, *80*, 12509.
[263] Diba, A.K.; Begouin, J.-M.; Niggemann, M. *Tetrahedron Lett.* ***2012***, *53*, 6629.
[264] Catti, L.; Tiefenbacher, K. *Chem. Commun.* ***2015***, *51*, 892.
[265] Asano, K.; Matsubara, S. *J. Am. Chem. Soc.* ***2011***, *133*, 16711. See Guérinot, A.; Serra-Muns, A.; Bensoussan, C.; Reymond, S.; Cossy, J. *Tetrahedron* ***2011***, *67*, 5024.
[266] Hartman, J.W.; Sperry, L. *Tetrahedron Lett.* ***2004***, *45*, 3787.
[267] Santos, L.L.; Ruiz, V.R.; Sabater, M.J.; Corma, A. *Tetrahedron* ***2008***, *64*, 7902.
[268] Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* ***1999***, *64*, 7687.
[269] Qing, F.L.; Gao, W.-Z.; Ying, J. *J. Org. Chem.* ***2000***, *65*, 2003. See Kel'in, A.V.; Gevorgyan, V. *J. Org. Chem.* ***2002***, *67*, 95.
[270] Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* ***2000***, *2*, 297. See also, Arcadi, A.; Cacchi, S.; DiGiuseppe, S.; Fabrizi, G.; Marinelli, F. *Synlett* ***2002***, 453.
[271] Davidson, M.H.; McDonald, F.E. *Org. Lett.* ***2004***, *6*, 1601.
[272] Liu, Z.; Breit, B. *Angew. Chem. Int. Ed.* ***2016***, *55*, 8440.
[273] Webster, S.; Sutherland, D.R.; Lee, A.-L. *Chem. Eur. J.* ***2016***, *22*, 18593.
[274] Yi, H.; Niu, L.; Song, C.; Li, Y.; Dou, B.; Singh, A.K.; Lei, A. *Angew. Chem. Int. Ed.* ***2017***, *56*, 1120.
[275] Goodwin, J.A.; Aponick, A. *Chem. Commun.* ***2015***, *51*, 8730.
[276] Kondo, M.; Kochi, T.; Kakiuchi, F. *J. Am. Chem. Soc.* ***2011***, *133*, 32.
[277] See Kresge, A.J.; Yin, Y. *J. Phys. Org. Chem.* ***1989***, *2*, 43.
[278] See Bolitt, V.; Mioskowski, C.; Shin, D.; Falck, J.R. *Tetrahedron Lett.* ***1988***, *29*, 4583.
[279] See Johnston, R.D.; Marston, C.R.; Krieger, P.E.; Goem G.L. *Synthesis* ***1988***, 393.
[280] Kang, S.-K.; Baik, T.-G.; Kulak, A.N. *Synlett* ***1999***, 324.

the presence of allylic bromide and a Pd catalyst, allenic alcohols lead to allylically substituted dihydrofurans.[281] The intramolecular Au-catalyzed reaction of alcohols and allenes has been reported.[282] Intramolecular addition of alcohols to allenes leads to cyclic vinyl ethers.[283]

Base-catalyzed reactions are known. For those substrates more susceptible to nucleophilic attack, for example, polyhalo alkenes and alkenes of the type C═C─Z (Z is an electron-withdrawing group), it is better to carry out the reaction in basic solution, where the attacking species is RO^-.[284] Since triple bonds are more susceptible to nucleophilic attack than double bonds, it might be expected that bases would catalyze addition to triple bonds particularly well. This is the case, and enol ethers and acetals can be produced by this reaction.[285] In base-catalyzed addition to triple bonds, the rate falls in going from a primary to a tertiary alcohol, and phenols require more severe conditions. Phenyl acetylenes were converted to the corresponding methoxy alkene (vinyl ether) by treatment with KOMe in DMF, with improved yields by the addition of DMEDA (*N*,*N*′-dimethylethylenediamine).[286]

Photochemical addition of alcohols to certain double bond compounds (cyclohexenes, cycloheptenes) is possible[287] in the presence of a photosensitizer such as benzene. The mechanism is electrophilic and *Markovnikov* orientation is found. The alkenes react in their first excited triplet states.[288]

Both alcohols and phenols add to ketenes to give carboxylic esters:[289]

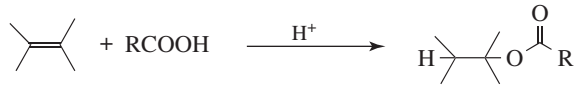
$$R_2C{=}C{=}O + ROH \rightarrow R_2CHCO_2R$$

This reaction has been done intramolecularly (with the ketene end of the molecule generated and used *in situ*) to form medium- and large-ring lactones.[290] In the presence of a strong acid, ketene reacts with aldehydes or ketones (in their enol forms) to give enol acetates. 1,4-Asymmetric induction is possible when chiral alcohols add to ketenes.[291]

In the presence of other reagents, functionalized ethers can be formed. In methanol with an R─Se─Br reagent, alkenes are converted to selenoalkyl ethers (MeO─C─C─SeR).[292]

OS **III**, 371, 774, 813; **IV**, 184, 558; **VI**, 916; **VII**, 66, 160, 304, 334, 381; **VIII**, 204, 254; **IX**, 472.

15-6 Addition of Carboxylic Acids to Form Esters



[281] Ma, S.; Gao, W. *J. Org. Chem.* ***2002***, *67*, 6104.
[282] Zhang, Z.; Widenhoefer, R.A. *Angew. Chem. Int. Ed.* ***2007***, *46*, 283.
[283] Mukai, C.; Ohta, M.; Yamashita, H.; Kitagaki, S. *J. Org. Chem.* ***2004***, *69*, 6867.
[284] See Chambers, R.D.; Mobbs, R.H. *Adv. Fluorine Chem.* ***1965***, *4*, 51 (pp. 53–61).
[285] Shostakovskii, M.F.; Trofimov, B.A.; Atavin, A.S.; Lavrov, V.I. *Russ. Chem. Rev.* ***1968***, *37*, 907.
[286] Cuthbertson, J.; Wilden, J.D. *Tetrahedron* ***2015***, *71*, 4385.
[287] See Wan, P.; Yates, K. *Rev. Chem. Intermed.* ***1984***, *5*, 157.
[288] Marshall, J.A. *Acc. Chem. Res.* ***1969***, *2*, 33.
[289] Quadbeck, G. *Newer Methods Prep. Org. Chem.* ***1963***, *2*, 133–161. See Tidwell, T.T. *Acc. Chem. Res.* ***1990***, *23*, 273; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975***, *4*, 231.
[290] Boeckman Jr., R.K.; Pruitt, J.R. *J. Am. Chem. Soc.* ***1989***, *111*, 8286.
[291] Cannizzaro, C.E.; Strassner, T.; Houk, K.N. *J. Am. Chem. Soc.* ***2001***, *123*, 2668.
[292] Back, T.G.; Moussa, Z.; Parvez, M. *J. Org. Chem.* ***2002***, *67*, 499.

Carboxylic esters are produced by the addition of carboxylic acids to alkenes, a reaction that is usually acid catalyzed (by Brønsted-Lowry or Lewis acids[293]) and similar in mechanism to **15-5**. Since *Markovnikov's rule* is followed, hard-to-get esters of tertiary alcohols can be prepared from alkenes of the form $R_2C{=}CHR$.[294] The reaction of alkenes and carboxylic acids in the presence of an acridinium photooxidant and 20% of thiophenol gave the anti-Markovnikov ester addition product.[295] An alkene reacted with carboxylic acids using a disilane catalyst with a photosensitizer to give the allylic ester.[296] Alkenoic acids were cyclized to γ-lactones using an Ir catalyst.[297]

Carboxylic esters have also been prepared by the acyloxymercuration-demercuration of alkenes (similar to the procedures mentioned in **15-3** and **15-4**).[298] Addition of carboxylic acids to alkenes to form esters or lactones is catalyzed by Pd compounds.[299] Thallium acetate also promotes this cyclization reaction.[300] Diene carboxylic acids have been cyclized using acetic acid and a Pd catalyst to form lactones that have an allylic acetate moiety elsewhere in the molecule.[301]

Imidazole derivatives proved to be effective ligands in the Ru-catalyzed reaction of alkenes and formates to give one-carbon-elongated esters.[302] Terminal alkenes reacted with carboxylic acids using Pd catalyst, in the presence of benzoquinone, to give an allylic ester.[303] Styrene derivatives reacted with formic acid and a Pd catalyst to give the carboxylic acid product, and the regiochemical selectivity was controlled by the choice of phosphine ligand.[304] Carboxylic acids with a distal allene moiety cyclized in the presence of a Rh catalyst to give the corresponding lactone that has an alkenyl unit.[305] Lactones were formed by the intramolecular reaction of acid and an alkene moiety, catalyzed by a Au compound[306] or an Ir catalyst.[307]

Triple bonds can give enol esters[308] or acylals when treated with carboxylic acids. Mercuric salts are typical catalysts[309] and vinylmercury compounds ($RO_2C{-}C{=}C{-}HgX$) are intermediates,[310] but Ru complexes have also been used.[311] Terminal alkynes ($RC{\equiv}CH$)

[293] See Ballantine, J.A.; Davies, M.; Purnell, H.; Rayanakorn, M.; Thomas, J.M.; Williams, K.J. *J. Chem. Soc., Chem. Commun.* ***1981***, 8.
[294] See Peterson, P.E.; Tao, E.V.P. *J. Org. Chem.* ***1964***, *29*, 2322.
[295] Perkowski, A.J.; Nicewicz, D.A. *J. Am. Chem. Soc.* ***2013***, *135*, 10334.
[296] Ortgies, S.; Depken, C.; Breder, A. *Org. Lett.* ***2016***, *18*, 2856.
[297] Nagamoto, M.; Nishimura, T. *Chem. Commun.* ***2015***, *51*, 13466.
[298] See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 367–442.
[299] Larock, R.C.; Hightower, T.R. *J. Org. Chem.* ***1993***, *58*, 5298; Annby, U.; Stenkula, M.; Andersson, C.-M. *Tetrahedron Lett.* ***1993***, *34*, 8545.
[300] Ferraz, H.M.C.; Ribeiro, C.M.R. *Synth. Commun.* ***1992***, *22*, 399.
[301] Verboom, R.C.; Persson, B.A.; Bäckvall, J.-E. *J. Org. Chem.* ***2004***, *69*, 3102.
[302] Konishi, H.; Ueda, T.; Muto, T.; Manabe, K. *Org. Lett.* ***2012***, *14*, 4722.
[303] Kondo, H.; Yu, F.; Yamaguchi, J.; Liu, G.; Itami, K. *Org. Lett.* ***2014***, *16*, 4212.
[304] Liu, W.; Ren, W.; Li, J.; Shi, Y.; Chang, W.; Shi, Y. *Org. Lett.* ***2017***, *19*, 1748.
[305] Ganss, S.; Bernhard Breit, B. *Angew. Chem. Int. Ed.* ***2016***, *55*, 9738.
[306] Handa, S.; Lippincott, D.J.; Aue, D.H.; Lipshutz, B.H. *Angew. Chem. Int. Ed.* ***2014***, *53*, 10658.
[307] Nagamoto, M.; Nishimura, T. *Chem. Commun.* ***2015***, *51*, 13466.
[308] Goossen, L.J.; Paetzold, J.; Koley, D. *Chem. Commun.* ***2003***, 706. See Hua, R.; Tian, X. *J. Org. Chem.* ***2004***, *69*, 5782. See also Quintero-Duque, S.; Marie Dyballa, K.; Fleischer, I. *Tetrahedron Lett.* ***2015***, *56*, 2634.
[309] See Bianchini, C.; Meli, A.; Peruzzini, M.; Zanobini, F.; Bruneau, C.; Dixneuf, P.H. *Organometallics* ***1990***, *9*, 1155.
[310] Bassetti, M.; Floris, B. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 227; Grishin, Yu.K.; Bazhenov, D.V.; Ustynyuk, Yu.A.; Zefirov, N.S.; Kartashov, V.R.; Sokolova, T.N.; Skorobogatova, E.V.; Chernov, A.N. *Tetrahedron Lett.* ***1988***, *29*, 4631.
[311] Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *J. Org. Chem.* ***1987***, *52*, 2230.

react with CO_2, a secondary amine R'_2NH, and a Ru complex catalyst to give enol carbamates RCH=CHOC(=O)NR.[312] This reaction has also been performed intramolecularly, to produce unsaturated lactones.[313] Cyclic unsaturated lactones (internal vinyl esters) have been generated from alkyne carboxylic acids using a Pd[314] or a Ru catalyst.[315]

Enol esters were generated by the reaction of alkynes and carboxylic acids using a Ru catalyst[316] or a Pd catalyst with silver carbonate.[317] Aryl 1-alkynyl-2-aldehyde dimethylacetals gave enantioselective carboalkoxylation to the optically active β-alkoxyindanone derivatives. This was catalyzed by cationic Au complexes and the methodology was extended to the enantioselective synthesis of 3-methoxycyclopentenones.[318] Ynol ethers reacted with carboxylic acids and silver oxide to give the *trans* addition product, a (*Z*)-α-alkoxy enol ester. Subsequent Ni-catalyzed reaction with arylboronic acids (**13-13**) gave the 1-aryl vinyl ether.[319] Carboxylic acids reacted with alkynes to give the vinyl ester with a dinuclear Pd catalyst, with a catalytic amount of tributylborane.[320] A computational study for the mechanism of coinage metal-catalyzed reactions of carboxylic acids with alkynes has been reported.[321] Enynes reacted with carboxylic acids at the alkyne moiety, in the presence of trialkylphosphines, to give the dienyl ester.[322]

Allene carboxylic acids have been cyclized to butenolides with copper(II) chloride.[323] Allene esters were converted to butenolides by treatment with acetic acid and LiBr.[324] Cyclic carbonates can be prepared from allene alcohols using carbon dioxide and a Pd catalyst.[325] A carboxylic acid with a distal alkene unit was cyclized and gave a selenomethyl ester by treatment with $(DHQD)_2PHAL$ and *N*-phenylselenophthalimide.[326]

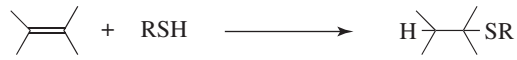
Sulfonic acids add to alkenes and alkynes. The reaction of an alkyne with *para*-toluenesulfonic acid and treatment with silica gives the vinyl sulfonate ($C{=}C{-}OSO_2Tol$).[327] Cyclic sulfonates can be generated by the reaction of an allylic sulfonate salt ($C{=}C{-}C{-}OSO_3^-$) with silver nitrate in acetonitrile containing an excess of bromine and a catalytic amount of water.[328] Sultones are formed when alkenes react with PhIO and 2 equivalents of Me_2SiSO_3Cl.[329]

OS **III**, 853; **IV**, 261, 417, 444; **V**, 852, 863; **VII**, 30, 411. Also see, OS **I**, 317.

[312] Mahé, R.; Sasaki, Y.; Bruneau, C.; Dixneuf, P.H. *J. Org. Chem.* ***1989***, *54*, 1518.
[313] See Sofia, M.J.; Katzenellenbogen, J.A. *J. Org. Chem.* ***1985***, *50*, 2331. For a list of other examples, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 1895.
[314] Liao, H.-Y.; Cheng, C.-H. *J. Org. Chem.* ***1995***, *60*, 3711.
[315] Jiménez-Tenorio, M.; Puerta, M.C.; Valerga, P.; Moreno-Dorado, F.J.; Guerra, F.M.; Massanet, G.M. *Chem. Commun.* ***2001***, 2324.
[316] Jeschke, J.; Gäbler, C.; Lang, H. *J. Org. Chem.* ***2016***, *81*, 476.
[317] Wang, D.; Ding S.; Huang, J.; Zhao, K. *Chem. Commun.* ***2013***, *49*, 1211.
[318] Zi, W.; Toste, F.D. *J. Am. Chem. Soc.* ***2013***, *135*, 12600.
[319] Yin, J.; Bai, Y.; Mao, M.; Zhu, G. *J. Org. Chem.* ***2014***, *79*, 9179.
[320] Tsukada, N.; Takahashi, A.; Inoue, Y. *Tetrahedron Lett.* ***2011***, *52*, 248.
[321] Jover, J.; Maseras, F. *J. Org. Chem.* ***2014***, *79*, 11981.
[322] Li, W.; Zhang, J. *Org. Lett.* ***2014***, *16*, 162.
[323] Ma, S.; Wu, S. *J. Org. Chem.* ***1999***, *64*, 9314.
[324] Ma, S.; Li, L.; Wei, Q.; Xie, H.; Wang, G.; Shi, Z.; Zhang, J. *Pure. Appl. Chem.* ***2000***, *72*, 1739.
[325] Uemura, K.; Shiraishi, D.; Noziri, M.; Inoue, Y. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 1063.
[326] Niu, W.; Yeung, Y.-Y. *Org. Lett.* ***2015***, *17*, 1660.
[327] Braga, A.L.; Emmerich, D.J.; Silveira, C.C.; Martins, T.L.C.; Rodrigues, O.E.D. *Synlett* ***2001***, 371.
[328] Steinmann, J.E.; Phillips, J.H.; Sanders, W.J.; Kiessling, L.L. *Org. Lett.* ***2001***, *3*, 3557.
[329] Bassindale, A.R.; Katampe, I.; Maesano, M.G.; Patel, P.; Taylor, P.G. *Tetrahedron Lett.* ***199***, *40*, 7417.

C. Sulfur on the Other Side

15-7 Addition of H_2S and Thiols to Give Thiols or Thioethers



Hydrogen sulfide (H_2S) and thiols add to alkenes to give alkyl thiols or sulfides by electrophilic, nucleophilic, or free-radical mechanisms.[330] In the absence of initiators, the addition to simple alkenes is by an electrophilic mechanism, similar to that in **15-5**, and *Markovnikov's rule* is followed. However, this reaction is usually very slow and often cannot be done, or it requires very severe conditions unless a Brønsted-Lowry or Lewis acid catalyst is used. For example, the reaction can be performed in concentrated H_2SO_4[331] or with the addition of $AlCl_3$.[332] In the presence of free-radical initiators, H_2S and thiols add to double and triple bonds by a free-radical mechanism and the orientation is *anti-Markovnikov*.[333] Anti-Markovnikov addition of thiols to vinyl ethers occurs under solvent-free and catalyst-free conditions,[334] and is promoted by water.[335]

Additives can influence the regioselectivity. Styrene reacts with thiophenol to give primarily the anti-Markovnikov product, but addition of thiophenol in the presence of Montmorillonite K-10 clay gives primarily the Markovnikov addition product.[336] The addition of thiophenol to an alkene with a zeolite, however, leads to the anti-Markovnikov sulfide.[337] In fact, the orientation can be used as a diagnostic tool to indicate which mechanism is operating. Free-radical addition can be done with H_2S, RSH (R may be primary, secondary, or tertiary), ArSH, or RCOSH.[338] The alkenes may be terminal, internal, contain branching, be cyclic, and have various functional groups including OH, CO_2H, CO_2R, NO_2, RSO_2, and so on. Addition of Ph_3SiSH to terminal alkenes under radical conditions also leads to the primary thiol.[339] Lewis acids have been used for the hydrothiolation of alkenes.[340] Thiols add to alkenes under photochemical conditions to form thioethers, and the reaction can be done intramolecularly to give cyclic thioethers.[341] Diaryl sulfides were added to multiple bond compounds via an electrogenerated acid catalyst.[342] The reaction of aryl alkynoates

[330] Wardell, J.L. in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, ***1974***, pp. 169–178.
[331] Shostakovskii, M.F.; Kul'bovskaya, N.K.; Gracheva, E.P.; Laba, V.I.; Yakushina, L.M. *J. Gen. Chem. USSR* ***1962***, *32*, 707.
[332] Belley, M.; Zamboni, R. *J. Org. Chem.* ***1989***, *54*, 1230.
[333] See Voronkov, M.G.; Martynov, A.V.; Mirskova, A.N. *Sulfur Rep.* ***1986***, *6*, 77; Griesbaum, K. *Angew. Chem. Int. Ed.* ***1970***, *9*, 273; Oswald, A.A.; Griesbaum, K. in Kharasch, N.; Meyers, C.Y. *Organic Sulfur Compounds*, Vol. 2, Pergamon, Elmsford, NY, ***1966***, pp. 233–256; Stacey, F.W.; Harris Jr., J.F. *Org. React.* ***1963***, *13*, 150 (pp. 165–196, 247–324).
[334] Lou, F.-W.; Xu, J.-M.; Liu, B.-K.; Wu, Q.; Pan, Q.; Lin, X.-F. *Tetrahedron Lett.* ***2007***, *48*, 8815. See Silveira, C.C.; Mendes, S.R.; Líbero, F.M. *Synlett* ***2010***, 790.
[335] Ranu, B.C.; Mandal, T. *Synlett* ***2007***, 925; Ranu, B.C. *Can. J. Chem.* ***2009***, *87*, 1605.
[336] Kanagasabapathy, S.; Sudalai, A.; Benicewicz, B.C. *Tetrahedron Lett.* ***2001***, *42*, 3791.
[337] Kumar, P.; Pandey, R.K.; Hegde, V.R. *Synlett* ***1999***, 1921.
[338] Janssen, M.J. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 720–723.
[339] Haché, B.; Gareau, Y. *Tetrahedron Lett.* ***1994***, *35*, 1837.
[340] Mosaferi, E.; Ripsman, D.; Stephan, D.W. *Chem. Commun.* ***2016***, *52*, 8291.
[341] Kirpichenko, S.V.; Tolstikova, L.L.; Suslova, E.N.; Voronkov, M.G. *Tetrahedron Lett.* ***1993***, *34*, 3889.
[342] Matsumoto, K.; Shimazaki, H.; Sanada, T.; Shimada, K.; Hagiwara, S.; Suga, S.; Kashimura, S.; Yoshida, J. *Chem. Lett.* ***2013***, *42*, 843.

with thiols gave the vinyl sulfide via decarboxylative coupling when treated with dicumyl peroxide.[343]

Transition metal catalysts have been used for hydrothiolation reactions. A Cu catalyst has been used with alkenes that bear a heteroatom.[344] Vinyl halides reacted with thiols when heated with KOH in the presence of a catalytic amount of Cu_2O and 1,10-phenanthroline.[345] The Au-catalyzed hydrothiolation of unactivated alkenes with thiols gave vinyl sulfides, with *anti*-Markovnikov selectivity.[346]

Alkynes react with thiols to give vinyl sulfides. With alkynes it is possible to add 1 or 2 molar equivalents of RSH, giving a vinyl sulfide[347] or a dithioketal, respectively. Thiols also add to alkynes with a Pd catalyst to give vinyl sulfides.[348] Sulfonic acids add to alkynes to give vinyl sulfonates in the presence of a Au catalyst.[349] The Rh,[350] In,[351] organoactinide,[352] organozirconium,[353] or Pt-catalyzed[354] reaction of alkynes with thiols gives the corresponding vinyl sulfide. The intramolecular addition of a thiol to an ene-yne, with a Pd catalyst, leads to substituted thiophene derivatives.[355] The reaction of an alkyne with diphenyl disulfide and a Pd catalyst leads to the bis(vinyl)sulfide, PhS—C═C—SPh.[356] Ketenes add thiols to give thiol esters:[357]

$$R_2C{=}C{=}O + RSH \rightarrow R_2CHCOSR$$

(*Z*)-Organothioenynes were prepared by hydrothiolation of buta-1,3-ynes.[358] The Pd and Cu co-catalyzed Markovnikov addition of thiols to alkenes or alkynes gave alkyl sulfides or vinyl sulfides.[359] A Ru complex allowed hydrothiolation of alkynes.[360] 1-Alkenyl sulfides were prepared from alkynes and organic disulfides using organoaluminum reagents.[361] Terminal alkynes reacted with thiols to give the (*E*)-vinyl sulfide in the presence of a Cu catalyst, but gave the *Z* isomer with the Cu catalyst and CO_2.[362] Arylthiols reacted with alkynes to give vinyl sulfides in the presence of potassium phosphate to give (*Z*)-vinyl sulfides, whereas (*E*)-vinyl sulfides were formed under solvent- and base-free conditions.[363] Thiols reacted with alleneols in the presence of an In catalyst to give a

[343] Ni, S.; Zhang, L.; Zhang, W.; Mei, H.; Han, J.; Pan, Y. *J. Org. Chem.* ***2016***, *81*, 9470.
[344] Xi, H.; Ma, E.; Li, Z. *Tetrahedron* ***2016***, *72*, 4111.
[345] Kao, H.-L.; Lee, C.-F. *Org. Lett.* ***2011***, *13*, 5204.
[346] Tamai, T.; Fujiwara, K.; Higashimae, S.; Nomoto, A.; Ogawa, A. *Org. Lett.* ***2016***, *18*, 2114.
[347] See Arjona, O.; Medel, R.; Rojas, J.; Costa, A.M.; Vilarrasa, J. *Tetrahedron Lett.* ***2003***, *44*, 6369.
[348] Kuniyasu, H.; Ogawa, A.; Sato, K.-I.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* ***1992***, *114*, 5902.
[349] Cui, D.-M.; Meng, Q.; Zheng, J.-Z.; Zhang, C. *Chem. Commun.* ***2009***, 1577.
[350] Cao, C.; Fraser, L.R.; Love, J.A. *J. Am. Chem. Soc.* ***2005***, *127*, 17614; Yang, J.; Sabarre, A.; Fraser, L.R.; Patrick, B.O.; Love, J.A. *J. Org. Chem.* ***2009***, *74*, 182.
[351] Yadav, J.S.; Subba Reddy, B.V.; Raju, A.; Ravindar, K.; Baishya, G. *Chem. Lett.* ***2007***, *36*, 1474.
[352] Weiss, C.J.; Wobser, S.D.; Marks, T.J. *J. Am. Chem. Soc.* ***2009***, *131*, 2062.
[353] Weiss, C.J.; Marks, T.J. *J. Am. Chem. Soc.* ***2010***, *132*, 10533.
[354] Yamashita, F.; Kuniyasu, H.; Terao, J.; Kambe, N. *Org. Lett.* ***2008***, *10*, 101.
[355] Gabriele, B.; Salerno, G.; Fazio, A. *Org. Lett.* ***2000***, *2*, 351.
[356] Ananikov, V.P.; Beletskaya, I.P. *Org. Biomol. Chem.* ***2004***, *2*, 284.
[357] See Blake, A.J.; Friend, C.L.; Outram, R.J.; Simpkins, N.S.; Whitehead, A.J. *Tetrahedron Lett.* ***2001***, *42*, 2877.
[358] Santana, A.S.; Carvalho, D.B.; Casemiro, N.S.; Hurtado, G.R.; Viana, L.H.; Kassab, N.A.; Barbosa, S.L.; Marques, F.A.; Guerrero Jr., P.G.; Baroni, A.C.M. *Tetrahedron Lett.* ***2012***, *53*, 5733.
[359] Ma, H.; Ren, X.; Zhou, X.; Ma, C.; He, Y.; Huang, G.-S. *Tetrahedron Lett.* ***2015***, *56*, 6022.
[360] Yang, Y.; Rioux, R.M. *Chem. Commun.* ***2011***, *47*, 6557.
[361] Ramazanov, I.R.; Kadikova, R.N.; Zosim, T.P.; Dzhemilev, U.M. *Synthesis* ***2015***, *47*, 2670.
[362] Riduan, S.N.; Ying, J.Y.; Zhang, Y. *Org. Lett.* ***2012***, *14*, 1780.
[363] Liao, Y.; Chen, S.; Jiang, P.; Qi, H.; Deng, G.-J. *Eur. J. Org. Chem.* ***2013***, 6878.

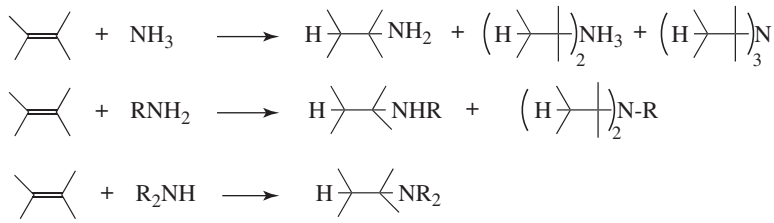
1-alkenyl vinyl sulfide.[364] A Rh-catalyzed addition of thiols to allenes gave branched allylic thioethers.[365]

Selenium compounds (RSeH) add in a similar manner to thiols.[366] Vinyl selenides can be prepared from alkynes using diphenyl diselenide and sodium borohydride.[367] A Pd-catalyzed reaction of PhSeH with alkynes, in pyridine, also gives the corresponding vinyl selenide.[368] The Pd-catalyzed hydroselenation of *N*-vinyl lactams gave the corresponding *N*,*Se*-acetals as Markovnikov adducts.[369]

OS **III**, 458; **IV**, 669; **VIII**, 302. See also, OS **VIII**, 458.

D. Nitrogen or Phosphorus on the Other Side

15-8 Addition of Ammonia and Amines, Phosphines, and Related Compounds[370]



Ammonia and primary and secondary amines add to alkenes *in some cases*.[371] Ammonia and amines are much weaker acids than water, alcohols, and thiols (see **15-3**, **15-5**, **15-7**) and since acids turn NH_3 into the weak acid, the ammonium ion NH_4^+, this reaction does not occur by an electrophilic mechanism. The reaction tends to give very low yields, if any, with ordinary alkenes, unless extreme conditions are used (e.g., 178–200 °C, 800–1000 atm, and the presence of metallic Na, for the reaction between NH_3 and ethylene[372]). There is, however, a proton-catalyzed hydroamination reaction in which aniline derivatives add to alkenes in the presence of anilinium salts, in 20–90% yield depending on the alkene.[373] The hydroamination of terminal alkenes via reaction of *N*-alkylhydroxylamines with allylic amines gave 3-amino-2-*N*-hydroxylamino compounds.[374]

There are many examples of transition metal-catalyzed[375] addition of nitrogen compounds to alkenes, alkynes,[376] and so on. Amines can be added to many alkenes using

[364] Webster, S.; Young, P.C.; Barker, G.; Rosair, G.M.; Lee, A.-L. *J. Org. Chem.* ***2015***, *80*, 1703.
[365] Pritzius, A.B.; Breit, B. *Angew. Chem. Int. Ed.* ***2015***, *54*, 3121; Pritzius, A.B.; Breit, B. *Angew. Chem. Int. Ed.* ***2015***, *54*, 15818.
[366] Kuniyasu, H.; Ogawa, A.; Sato, K.-I.; Ryu, I.; Sonoda, N. *Tetrahedron Lett.* ***1992***, *33*, 5525.
[367] Dabdoub, M.J.; Baroni, A.C.M.; Lenardão, E.J.; Gianeti, T.R.; Hurtado, G.R. *Tetrahedron* ***2001***, *57*, 4271.
[368] Kamiya, I.; Nishinaka, E.; Ogawa, A. *J. Org. Chem.* ***2005***, *70*, 696.
[369] Tamai, T.; Yoshikawa, M.; Higashimae, S.; Nomoto, A.; Ogawa, A. *J. Org. Chem.* ***2016***, *81*, 324.
[370] Müller, T.E.; Hultzsch, K.C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* ***2008***, *108*, 3795.
[371] See Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C.G.; Seayad, J.; Thiel, O.R.; Tillack, A.; Trauthwein, H. *Synlett* ***2002***, 1579. For selectivity, see Tillack, A.; Khedkar, V.; Beller, M. *Tetrahedron Lett.* ***2004***, *45*, 8875.
[372] Howk, B.W.; Little, E.L.; Scott, S.L.; Whitman, G.M. *J. Am. Chem. Soc.* ***1954***, *76*, 1899. See Legnani, L.; Bhawal, B.N.; Morandi, B. *Synthesis* ***2017***, *49*, 776.
[373] Anderson, L.L.; Arnold, J.; Bergman, R.G. *J. Am. Chem. Soc.* ***2005***, *127*, 14542.
[374] Zhao, S.-B.; Bilodeau, E.; Lemieux, V.; Beauchemin, A.M. *Org. Lett.* ***2012***, *14*, 5082.
[375] See Smith, A.R.; Lovick, H.M.; Livinghouse, T. *Tetrahedron Lett.* ***2012***, *53*, 6358; Lepori, C.; Hannedouche, J. *Synthesis* ***2017***, *49*, 1158; Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L.J. *Chem. Rev.* ***2015***, *115*, 2596. For a discussion of asymmetric hydroamination, see Hannedouche, J.; Schulz, E. *Chem. Eur. J.* ***2013***, *19*, 4972.
[376] For a review, see Doye, S. *Synlett* ***2004***, 1653.

Pd,[377] Rh,[378] Cu,[379] In,[380] Ti,[381] Fe,[382] Ta,[383] Zr,[384] Au,[385] Y,[386] Zn,[387] Mo,[388] and various lanthanide catalysts,[389] including Sr.[390] Both Ti- and Zr-catalyzed hydroamination reactions have been reported.[391] Complexation with the metal lowers the electron density of the double bond, facilitating nucleophilic attack.[392] *Markovnikov* orientation is observed and the addition is *anti*.[393] Aniline reacts with dienes and a Pd catalyst to give allylic amines.[394] Diene amines react with Sm catalysts to give 2-alkenyl pyrrolidines.[395] The mechanism of the Au(I)-catalyzed hydroamination reaction of alkenes has been studied.[396] It is believed to involve a ligand substitution reaction in the active Au species followed by nucleophile attack of the N nucleophile on the activated double bond, which is followed by proton transfer from the NH_2 group to the unsaturated carbon atom.

Allylic amines and thiols reacted in the presence of a Rh catalyst to give β-alkylthio or γ-alkylthio amines, depending on the ligand used.[397] The reaction of alkenes and amines, in the presence of CO and a Ru catalyst, gave the anti-Markovnikov aminomethylation product.[398] The reaction of alkenes with diethoxymethylsilane and esters of hydroxylamines

[377] See Bäckvall, J. *Adv. Met.-Org. Chem.* ***1989***, *1*, 135. Also see Gurak Jr., J.A.; Yang, K.S.; Liu, Z.; Engle, K.M. *J. Am. Chem. Soc.* ***2016***, *138*, 5805.

[378] The anti-Markovkinov amine is produced: Utsonomiya, M.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2004***, *126*, 2702; Routaboul, L.; Buch, C.; Klein, H.; Jackstell, R.; Beller, M. *Tetrahedron Lett.* ***2005***, *46*, 7401; Chen, C.; Jin, S.; Zhang, Z.; Wei, B.; Wang, H.; Zhang, K.; Lv, H.; Dong, X.-Q.; Zhang, X. *J. Am. Chem. Soc.* ***2016***, *138*, 9017. For mechansitic studies, see Takaya, J.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2005***, *127*, 5756.

[379] See Pirnot, M.T.; Wang, Y.-M.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***2016***, *55*, 48.

[380] Huang, J.-M.; Wong, C.-M.; Xu, F.-X.; Loh, T.-P. *Tetrahedron Lett* ***2007***, *48*, 3375.

[381] Kaspar, L.T.; Fingerhut, B.; Ackermann, L. *Angew. Chem. Int. Ed.* ***2005***, *44*, 5972; Dörfler, J.; Doye, S. *Angew. Chem. Int. Ed.* ***2013***, *52*, 1806. For a discussion of the mechanism, see Prochnow, I.; Zark, P.; Müller, T.; Doye, S. *Angew. Chem. Int. Ed.* ***2011***, *50*, 6401.

[382] Michaux, J.; Terrasson, V.; Marque, S.; Wehbe, J.; Prim, D.; Campagne, J.-M. *Eur. J. Org. Chem.* ***2007***, 2601; Zhu, K.; Shaver, M.P.; Thomas, S.P. *Chem. Asian J.* ***2016***, *11*, 977.

[383] Herzon, S.B.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2007***, *129*, 6690.

[384] Zhou, X.; Wei, B.; Sun, X.-L.; Tang, Y.; Xie, Z. *Chem. Commun.* ***2015***, *51*, 5751; Sun, Q.; Wang, Y.; Yuanm D.; Yao, Y.; Shen, Q. *Chem. Commun.* ***2015***, *51*, 7633; Payne, P.R.; Bexrud, J.A.; Leitch, D.C.; Schafer, L.L. *Can. J. Chem.* ***2011***, *89*, 1222.

[385] Hesp, K.D.; Stradiotto, M. *J. Am. Chem. Soc.* ***2010***, *132*, 18026; Butler, K.L.; Tragni, M.; Widenhoefer, R.A. *Angew. Chem. Int. Ed.* ***2012***, *51*, 5175.

[386] O'Shaughnessy, P.N.; Scott, P. *Tetrahedron: Asymmetry* ***2003***, *14*, 1979.

[387] Liu, G.-Q.; Li, W.; Wang, Y.-M.; Ding, Z.-Y.; Li, Y.-M. *Tetrahedron Lett.* ***2012***, *53*, 4393. Also see Lühl, A.; Nayek, H.P.; Blechert, S.; Roesky, P.W. *Chem. Commun.* ***2011***, *47*, 8280.

[388] Srivastava, R.S.; Nicholas, K.M. *Chem. Commun.* ***1996***, 2335.

[389] Hultzsch, K.C. *Org. Biomol. Chem.* ***2005***, *3*, 1819; Yin, P.; Loh, T.-P. *Org. Lett.* ***2009***, *11*, 3791. See Reznichenko, A.L.; Nguyen, H.N.; Hultzsch, K.C. *Angew. Chem. Int. Ed.* ***2010***, *49*, 8984.

[390] For both Sr and Ca catalysis, see Brinkmann, C.; Barrett, A.G.M.; Hill, M.S.; Procopiou, P.A. *J. Am. Chem. Soc.* ***2012***, *134*, 2193.

[391] Braun, C.; Bräse, S.; Schafer, L.L. *Eur. J. Org. Chem.* ***2017***, 1760.

[392] Hegedus, L.S.; Åkermark, B.; Zetterberg, K.; Olsson, L.F. *J. Am. Chem. Soc.* ***1984***, *106*, 7122.

[393] See Utsunomiya, M.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2003***, *125*, 14286.

[394] Minami, T.; Okamoto, H.; Ikeda, S.; Tanaka, R.; Ozawa, F.; Yoshifuji, M. *Angew. Chem. Int. Ed.* ***2001***, *40*, 4501.

[395] Hong, S.; Marks, T.J. *J. Am. Chem. Soc.* ***2002***, *124*, 7886.

[396] Kovács, G.; Ujaque, G.; Lledós, A. *J. Am. Chem. Soc.* ***2008***, *130*, 853.

[397] Kennemur, J.L.; Kortman, G.D.; Hull, K.L. *J. Am. Chem. Soc.* ***2016***, *138*, 11914.

[398] Gülak, S.; Wu, L.; Liu, Q.; Franke, R.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed.* ***2014***, *53*, 7320. For the use of a Rh catalyst, see Nairoukh, Z.; Blum, J. *J. Org. Chem.* ***2014***, *79*, 2397; Liu, G.; Huang, K.; Cai, C.; Cao, B.; Chang, M.; Wu, W.; Zhang, X. *Chem. Eur. J.* ***2011***, *17*, 14559.

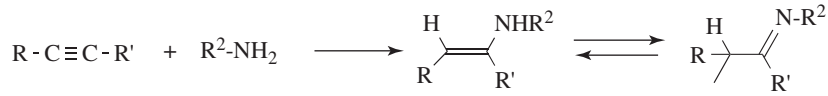
with a Cu catalyst gave α-branched amines, whereas aliphatic alkenes exclusively gave the anti-Markovnikov hydroamination product.[399] An Ir-catalyzed addition of indole to alkenes has been reported.[400] The Cu-catalyzed anti-Markovnikov addition of amines to 1,1-disubstittued alkenes has been reported.[401] Homoallylic amines reacted with amines in the presence of a Rh catalyst to give the corresponding diamine.[402] Ketene silyl acetals reacted with amines in the presence of a Cu catalyst to give the corresponding α-amino ester.[403] The Rh-catalyzed hydroamination of 1,3-dienes by reaction with amines in the presence of BINAP and mandelic acid gave homoallylic amines with anti-Markovnikov selectivity.[404]

Cyclization reactions are useful variations of this reaction. Alkenyl amines give cyclic amines as the major product, in good yield, when treated with *n*-butyllithium.[405] Reaction of a secondary amine with butyllithium generates an amide base, which reacts with alkenes to give alkyl amines,[406] and can add intramolecularly to an alkene to form a pyrrolidine.[407] The trifluoroacetic acid-promoted hydroamination has been reported.[408] Neodymium complexes have been developed for the near-IR luminescence spectroscopic probe that allows monitoring of the cyclization reaction.[409] An intramolecular addition of an amine unit to an alkene to form a cyclic amine was reported using Pd,[410] Rh,[411] Pt,[412] Au,[413] Ca,[414] Sc,[415] Sm,[416] Ti,[417] Fe,[418] Y,[419] Zr,[420] and Lu[421] as well as lanthanide reagents,[422] including a

[399] Zhu, S.; Niljianskul, N.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2013***, *135*, 15746.
[400] Sevov, C.S.; Zhou, J. Hartwig, J.F. *J. Am. Chem. Soc.* ***2014***, *136*, 3200.
[401] Zhu, S.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2014***, *136*, 15913.
[402] Ensign, S.C.; Vanable, E.P.; Kortman, G.D.; Weir, L.J.; Hull, K.L. *J. Am. Chem. Soc.* ***2015***, *137*, 13748.
[403] Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* ***2012***, *51*, 11827.
[404] Yang, X.-H.; Lu, A.; Dong, V.M. *J. Am. Chem. Soc.* ***2017***, *139*, 14049.
[405] Ates, A.; Quinet, C. *Eur. J. Org. Chem.* ***2003***, 1623.
[406] Hartung, C.G.; Breindl, C.; Tillack, A.; Beller, M. *Tetrahedron* ***2000***, *56*, 5157.
[407] Fujita, H.; Tokuda, M.; Nitta, M.; Suginome, H. *Tetrahedron Lett.* ***1992***, *33*, 6359.
[408] Liu, G.-Q.; Cui, B.; Sun, H.; Li, Y.-M. *Tetrahedron* ***2014***, *70*, 5696. For the effect of hydrogen bonds on the reaction, see Li, T.T.; Liu, G.-Q.; Wang, Y.-M.; Cui, B.; Sun, H.; Li, Y.-M. *Tetrahedron* ***2015***, *71*, 7003.
[409] Bennett, S.D.; Pope, S.J.A.; Ward, B.D. *Chem. Commun.* ***2013***, *49*, 6072.
[410] Ney, J.E.; Wolfe, J.P. *J. Am. Chem. Soc.* ***2005***, *127*, 8644. See also, Sakai, N.; Ridder, A.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2006***, *128*, 8134; Lu, Z.; Stahl, S.S. *Org. Lett.* ***2012***, *14*, 1234; Jana, R.; Pathak, T.P.; Jensen, K.H.; Sigman, M.S. *Org. Lett.* ***2012***, *14*, 4074.
[411] Liu, Z.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2008***, *130*, 1570. See Nguyen, T.O.; Man, B.Y.-W.; Hodgson, R.; Messerle, B.A. *Aust. J. Chem.* ***2011***, *64*, 741.
[412] Zhang, R.; Xu, Q.; Mei, L.-y.; Li, S.-k.; Shi, M. *Tetrahedron* ***2012***, *68*, 3172.
[413] Timmerman, J.C.; Laulhé, S.; Widenhoefer, R.A. *Org. Lett.* ***2017***, *19*, 1466; Serrano-Becerra, J.M.; Maier, A.F.G.; González-Gallardo, S.; Moos, E.; Kaub, C.; Gaffga, M.; Niedner-Schatteburg, G.; Roesky, P.W.; Breher, F.; Paradies, J. *Eur. J. Org. Chem.* ***2014***, 4515.
[414] Wixey, J.S.; Ward, B.D. *Chem. Commun.* ***2011***, *47*, 5449. See Nixon, T.D.; Ward, B.D. *Chem. Commun.* ***2012***, *48*, 11790.
[415] Kim, J.Y.; Livinghouse, T. *Org. Lett.* ***2005***, *7*, 4391.
[416] Quinet, C.; Ates, A.; Markó, I.E. *Tetrahedron Lett.* ***2008***, *49*, 5032.
[417] Müller, C.; Loos, C.; Schulenberg, N.; Doye, S. *Eur. J. Org. Chem.* ***2006***, 2499.
[418] Huehls, C.B.; Lin, A.; Yang, J. *Org. Lett.* ***2014***, *16*, 3620.
[419] Chai, Z.; Hua, D.; Li, K.; Chu, J.; Yang, G. *Chem. Commun.* ***2014***, *50*, 177.
[420] See Manna, K.; Eedugurala, N.; Sadow, A.D. *J. Am. Chem. Soc.* ***2015***, *137*, 425; Wang, X.; Chen, Z.; Sun, X.-L.; Tang, Y.; Xie, Z. *Org. Lett.* ***2011***, *13*, 4758.
[421] Gribkov, D.V.; Hultzsch, K.C.; Hampel, F. *J. Am. Chem. Soc.* ***2006***, *128*, 3748.
[422] Ryu, J.-S.; Marks, T.J.; McDonald, F.E. *Org. Lett.* ***2001***, *3*, 3091. See Hong, S.; Tian, S.; Metz, M.V.; Marks, T.J. *J. Am. Chem. Soc.* ***2003***, *125*, 14768.

Y reagent.[423] A Zn/Zr bimetallic catalyst has been used with high enantioselectivity.[424] A Pd/Ir tandem catalyst was reported for the two-step hydroamination of alkenes with an ammonia source that gave branched primary amines.[425] Other nitrogen compounds, among them hydroxylamine and hydroxylamines,[426] *O*-benzoylhydroxylamines with a Cu catalyst,[427] hydrazines,[428] and amides (**15-9**), also add to alkenes.

Amines add to triple bonds[429] to give enamines that have a hydrogen on the nitrogen and (analogously to enols) tautomerize (Sec. 2.N.ii, category 4) to the more stable imine.[430]



When ammonia is used instead of a primary amine, the corresponding $R_2C{=}NH$ imine product is not stable enough for isolation, but polymerizes. The frustrated Lewis acid-catalyzed hydroamination of terminal alkynes has been reported.[431]

Transition metal catalysis for reaction with alkynes is an important area of research, and catalysts include Pd,[432] Rh,[433] Ti,[434] Ta,[435] Ni,[436] Cu,[437] Ag,[438] Ta,[439] Ga,[440] Zr,[441] or Au.[442] Anti-Markovnikov addition of alkynes is possible using a Cu catalyst.[443] The intramolecular addition of amines to alkynes has been reported using a Pd catalyst.[444] When benzylamines with a chloroacetylene moiety[445] were heated with a Rh catalyst, an intramolecular debenzylative cyclization gave butyrolactams.

[423] See Huynh, K.; Livinghouse, T.; Lovick, H.M. *Synlett* ***2014***, *25*, 1721.
[424] Hussein, L.; Purkait, N.; Biyikal, M. Tasch, E.; Roesky, P.W.; Blechert, S. *Chem. Commun.* ***2014***, *50*, 3862.
[425] Yang, Y.; Wong, N.I.; Teo, P. *Eur. J. Org. Chem.* ***2015***, 1207.
[426] Singh, S.; Nicholas, K.M. *Synth. Commun.* ***2001***, *31*, 3087.
[427] Hesp, K.D. *Angew. Chem. Int. Ed.* ***2014***, *53*, 2034.
[428] Peltier, J.L.; Jazzar, R.; Melaii, M.; Bertrand, G. *Chem. Commun.* ***2016***, *52*, 2733.
[429] See Chekulaeva, I.A.; Kondrat'eva, L.V. *Russ. Chem. Rev.* ***1965***, *34*, 669; Patel, M.; Saunthwal, R.K.; Verma, A.K. *Acc. Chem. Res.* ***2017***, *50*, 240.
[430] See Kruse, C.W.; Kleinschmidt, R.F. *J. Am. Chem. Soc.* ***1961***, *83*, 213, 216.
[431] Mahdi, T.; Stephan, D.W. *Angew. Chem. Int. Ed.* ***2013***, *52*, 12418.
[432] Patil, N.T.; Lutete, L.M.; Wu, H.; Pahadi, N.K.; Gridnev, I.D.; Yamamoto, Y. *J. Org. Chem.* ***2006***, *71*, 4270.
[433] Sakai, K.; Kochi, T.; Kakiuchi, F. *Org. Lett.* ***2011***, *13*, 3928.
[434] Khedkar, V.; Tillack, A.; Beller, M. *Org. Lett.* ***2003***, *5*, 4767; Yim, J.C.-H.; Bexrud, J.A.; Ayinla, R.O.; Leitch, D.C.; Schafer, L.L. *J. Org. Chem.* ***2014***, *79*, 2015.
[435] Anderson, L.L.; Arnold, J.; Bergman, R.G. *Org. Lett.* ***2004***, *6*, 2519; Cao, C.; Li, Y.; Shi, Y.; Odom, A.L. *Chem. Commun.,* ***2004***, 2002.
[436] Manan, R.S.; Kilaru, P.; Zhao, P. *J. Am. Chem. Soc.* ***2015***, *137*, 6136.
[437] Shanbhag, G.V.; Kumbar, S.M.; Joseph, T.; Halligudi, S.B. *Tetrahedron Lett.* ***2006***, *47*, 141. Ishikawa, T.; Sonehara, T.; Minakawa, M.; Kawatsura, M. *Org. Lett.* ***2016***, *18*, 1422; Bahri, J.; Blieck, R.; Jamoussi, B.; Taillefer, M.; Monnier, F. *Chem. Commun.* ***2015***, *51*, 11210.
[438] Zhang, X.; Yang, B.; Li, G.; Xin, S.; Mungra, D.C.; Zhu, J. *Synlett* ***2012***, *23*, 622.
[439] Dörfler, J.; Doye, S. *Eur. J. Org. Chem.* ***2014***, 2790.
[440] Li, L.; Huang, G.; Chen, Z.; Liu, W.; Wang, X.; Chen, Y.; Yang, L.; Li, W.; Li, Y. *Eur. J. Org. Chem.* ***2012***, 5564.
[441] Born, K.; Doye, S. *Eur. J. Org. Chem.* ***2012***, 764.
[442] Zhang, Y.C.; Furkert, D.P.; Guéret, S.M.; Lombard, F.; Brimble, M.A. *Tetrahedron Lett.* ***2011***, *52*, 3896; Kovács, G.; Lledós, A.; Ujaque, G. *Angew. Chem. Int. Ed.* ***2011***, *50*, 11147. For a magnetically recoverable catalyst, see Fujita, K.-i.; Fujii, A.; Sato, J.; Yasuda, H. *Synlett* ***2016***, *27*, 1941.
[443] Zhou, L.; Bohle, D.S.; Jiang, H.-F.; Li, C.-J. *Synlett* ***2009***, 937.
[444] Alamsetti, S.K.; Persson, A.K.Å.; Bäckvall, J.-E. *Org. Lett.* ***2014***, *16*, 1434.
[445] Oh, Y.T.; Senda, K.; Hata, T.; Urabe, H. *Tetrahedron Lett.* ***2011***, *52*, 2458.

Many heterocycles have been prepared by this methodology. An intramolecular addition of amines to an alkyne unit in the presence of a Pd catalyst generated heterocyclic[446] or cyclic amine compounds.[447] A variation treats an alkynyl imine with CuI to form pyrroles.[448] *N*,*N*-Diphenylhydrazine reacts with diphenyl acetylene and a Ti catalyst to give indole derivatives.[449] Treatment of an imine of 2-alkynyl benzaldehyde with iodide gave a functionalized isoquinoline.[450] Ammonia and primary amines (aliphatic and aromatic) add to conjugated diynes to give pyrroles.[451]

The enantioselective, Au-catalyzed hydroamination of dienes has been reported.[452] Conjugated dienes reacted with amines in the presence of a Ti catalyst to give homoallylic amines.[453] 1,3-Dienes[454] and also allenes[455] undergo hydroamination in the presence of an Au catalyst. Allenes are reaction partners,[456] and amines add to allenes in the presence of a catalytic amount of Cu,[457] Au,[458] or Pd compounds.[459] The Rh-catalyzed hydroamination of terminal allenes gave branched allylic amines.[460] Asymmetric Brønsted acids have been used to catalyze the hydroamination of dienes and allenes.[461] Hypervalent iodine has been used for the amination of allenes.[462] Intramolecular reaction of allene amines leads to dihydropyrroles, using a Au catalyst.[463]

A NH_2 or NR_2 unit can be added to double bonds (even ordinary double bonds) in an indirect manner by the use of hydroboration (**15-11**) followed by treatment with NH_2Cl or NH_2OSO_2OH (**12-31**). This produces a primary amine with *anti-Markovnikov* orientation. An indirect way of adding a primary or secondary amine to a double bond consists of aminomercuration to give an amino mercuric acetate, followed by reduction with $NaBH_4$ to give the amine.[464] The addition of a secondary amine produces a tertiary amine, while addition of a primary amine gives a secondary amine. The overall orientation follows *Markovnikov's rule*.

Phosphines add to alkenes to give alkylphosphines (C—PR_2) and to alkynes[465] to give vinylphosphines. Alkenes reacted with triphenylphosphonium tetrafluoroborate under

[446] Hiroya, K.; Matsumoto, S.; Sakamoto, T. *Org. Lett.* ***2004***, *6*, 2953.
[447] Lutete, L.M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2004***, *126*, 1622; Chen, Q.-A.; Chen, Z.; Dong, V.M. *J. Am. Chem. Soc.* ***2015***, *137*, 8392. See also, Karur, S.; Kotti, S.R.S.S.; Xu, X.; Cannon, J.F.; Headley, A.; Li, G. *J. Am. Chem. Soc.* ***2003***, *125*, 13340.
[448] Kel'in, A.; Sromek, A.W.; Gevorgyan, V. *J. Am. Chem. Soc.* ***2001***, *123*, 2074.
[449] Ackermann, L.; Born, R. *Tetrahedron Lett.* ***2004***, *45*, 9541. For a different approach using hypervalent iodine, see Barluenga, J.; Trincado, M.; Rubio, E.; González, J.M. *Angew. Chem. Int. Ed.* ***2003***, *42*, 2406.
[450] Huang, Q.; Hunter, J.A.; Larock, R.C *J. Org. Chem.* ***2002***, *67*, 3437.
[451] Schult, K.E.; Reisch, J.; Walker, H. *Chem. Ber.* ***1965***, *98*, 98.
[452] Kanno, O.; Kuriyama, W.; Wang, Z.J.; Toste, F.D. *Angew. Chem. Int. Ed.* ***2011***, *50*, 9919.
[453] Preuß, T.; Saak, W.; Doye, S. *Chem. Eur. J.* ***2013***, *19*, 3833.
[454] Brouwer, C.; He, C. *Angew. Chem. Int. Ed.* ***2006***, *45*, 1744.
[455] Nishina, N.; Yamamoto, Y. *Angew. Chem. Int. Ed.* ***2006***, *45*, 3314.
[456] Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* ***1998***, *39*, 5421.
[457] See Blieck, R.; Bahri, J.; Taillefer, M.; Monnier, F. *Org. Lett.* ***2016***, *18*, 1482.
[458] Zeng, X.; Soleilhavoup, M.; Bertrand, G. *Org. Lett.* ***2009***, *11*, 3166.
[459] Davies, I.W.; Scopes, D.I.C.; Gallagher, T. *Synlett* ***1993***, 85.
[460] Cooke, M.L.; Xu, K.; Breit, B. *Angew. Chem. Int. Ed.* ***2012***, *51*, 10876.
[461] Dion, I.; Beauchemin, A.M. *Angew. Chem. Int. Ed.* ***2011***, *50*, 8233.
[462] Purkait, N.; Okumura, S.; Souto, J.A.; Muñiz, K. *Org. Lett.* ***2014***, *16*, 4750.
[463] Morita, N.; Krause, N. *Org. Lett.* ***2004***, *6*, 4121.
[464] See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 443–504. See also, Barluenga, J.; Perez-Prieto, J.; Asensio, G. *Tetrahedron* ***1990***, *46*, 2453.
[465] Unoh, Y.; Hirano, K.; Miura, M. *J. Am. Chem. Soc.* ***2017***, *139*, 6106.

radical initiation conditions, or under photochemical conditions, to give phosphonium salts.[466] Alkenes reacted with $Ph_2P(O)PPh_2$, with a radical initiator, to give radical addition that led to 1-phosphinyl-2-phosphinoalkanes regioselectively.[467] The microwave-assisted hydrophosphinylation of alkenes at 180 °C, using aqueous H-phosphoric acids, did not require added metal or a radical initiator.[468] The transition metal-catalyzed addition reaction is known, using Ni[469] or Pd[470] catalysts. The hydrophosphinylation of ynamides has been reported using a Cu catalyst.[471] A Pd-catalyzed reaction of alkenes and triarylphosphines gives alkyltriarylphosphonium salts.[472] Alkenes also react with diarylphosphines and a Ni catalyst to give the alkylphosphine.[473] Silylphosphines ($R_3Si{-}PAr_2$) react with alkenes and Bu_4NF to give the anti-Markovnikov allylphosphine.[474]

Chiral α-amino phosphonates were prepared by the enantioselective phosphonylation of allylamine with phosphites in the presence of a chiral Brønsted acid catalyst and silver carbonate.[475]

Phosphonate esters were similarly prepared from alkenes, diethyl phosphite [$(EtO)_2P(=O)H$], and a Mn catalyst in a reaction exposed to oxygen.[476] Similar addition was observed in the reaction of an alkene with NaH_2PO_2 to give the phosphinate:[477]

$$RCH{=}CH_2 \rightarrow RCH_2CH_2PH(=O)ONa$$

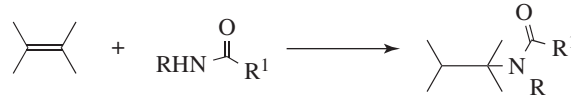
The reaction of terminal alkynes with dimethyl phosphite and a Ni catalyst gave the *Markovnikov* vinyl phosphonate ester.[478] Phosphine oxides can be prepared by the reaction of an aryl-substituted alkene and diphenylphosphine oxide, $Ph_2P(=O)H$.[479]

In the presence of an Yb catalyst, diphenylphosphine added to diphenyl acetylene to give the corresponding vinylphosphine.[480] A Pd catalyst was used for the addition of diphenylphosphine to terminal alkynes, giving the anti-Markovnikov vinylphosphine, but a Ni catalyst led to the *Markovnikov* vinylphosphine.[481] A Co catalyst has also been used.[482] Diphenylphosphine oxide also reacted with terminal alkynes to give the anti-Markovnikov vinylphosphine oxide using a Rh catalyst.[483] Other phosphites were added to dienes to give an allylic phosphonate ester using a Pd catalyst.[484]

[466] Daeffler, C.S.; Grubbs, R.H. *Org. Lett.* ***2011***, *13*, 6429.
[467] Sato, Y.; Kawaguchi, S.-i.; Nomoto, A.; Ogawa, A. *Angew. Chem. Int. Ed.* ***2016***, *55*, 9700.
[468] Troupa, P.; Katsiouleri, G.; Vassiliou, S. *Synlett* ***2015***, *26*, 2714.
[469] Ortial, S.; Fisher, H.C.; Montchamp, J.-L. *J. Org. Chem.* ***2013***, *78*, 6599.
[470] Pullarkat, S.A. *Synthesis* ***2016***, *48*, 493.
[471] Kinbara, A.; Sato, M.; Yumita, K.; Yamagishi, T. *Tetrahedron* ***2017***, *73*, 1705.
[472] Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* ***2006***, *128*, 50. See Kawaguchi, S.-i.; Nagata, S.; Nomoto, A.; Sonoda, M.; Ogawa, A. *J. Org. Chem.* ***2008***, *73*, 7928.
[473] Shulyupin, M.O.; Kazankova, M.A.; Beletskaya, I.P. *Org. Lett.* ***2002***, *4*, 761.
[474] Hayashi, M.; Matsuura, Y.; Watanabe, Y. *Tetrahedron Lett.* ***2004***, *45*, 9167.
[475] Cheng, M.-X.; Ma, R.-S.; Yang, Q.; Yang, S.-D. *Org. Lett.* ***2016***, *18*, 3262.
[476] Tayama, O.; Nakano, A.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2004***, *69*, 5494.
[477] Deprèle, S.; Montchamp, J.-L. *J. Org. Chem.* ***2001***, *66*, 6745.
[478] Han, L.-B.; Zhang, C.; Yazawa, H.; Shimada, S. *J. Am. Chem. Soc.* ***2004***, *126*, 5080.
[479] Bunlaksananusorn, T.; Knochel, P. *J. Org. Chem.* ***2004***, *69*, 4595.
[480] Takaki, K.; Koshoji, G.; Komeyama, K.; Takeda, M.; Shishido, T.; Kitani, A.; Takehira, K. *J. Org. Chem.* ***2003***, *68*, 6554.
[481] Kazankova, M.A.; Efimova, I.V.; Kochetkov, A.N.; Atanas'ev, V.V.; Beletskaya, I.P.; Dixneuf, P.H. *Synlett* ***2001***, 497.
[482] Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* ***2005***, *44*, 2368.
[483] Han, L.-B.; Zhao, C.-Q.; Tanaka, M. *J. Org. Chem.* ***2001***, *66*, 5929.
[484] Mirzaei, F.; Han, L.-B.; Tanaka, M. *Tetrahedron Lett.* ***2001***, *42*, 297.

OS **I**, 196; **III**, 91, 93, 244, 258; **IV**, 146, 205; **V**, 39, 575, 929; **VI**, 75, 943; **VIII**,188, 190, 536; **80**, 75. See also, OS **VI**, 932.

15-9 Addition of Amides



Under certain conditions, primary and secondary amides can add directly to alkenes to form *N*-alkylated amides. Sulfonamides react in a similar manner. Styrene derivatives reacted with a hypervalent iodine(III) reagent as an oxidant and bis-tosylimide as a nitrogen source to give the tosylamide addition product.[485] Treatment of triflamide alkenes with triflic acid gives the corresponding *N*-triflyl cyclic amine.[486]

Alkenes react with amides and related compounds in the presence of certain transition metals.[487] The Pd-catalyzed amidation of alkenes gives the corresponding amides with good enantioselectivity.[488] The Cu-catalyzed amidation and imidation of alkenes has been reported.[489] The reaction of amines and conjugated dienes using a Co/Ir-co-catalyzed, photoredox-generated α-amino radical species gave homoallylic amines.[490] Conjugated dienes reacted with aniline and CO with a Pd catalyst to give an amide.[491] A Rh catalyst was used with alkenes.[492]

The amidation of alkenes can be done intramolecularly.[493] 3-Pentenamide cyclized to 5-methyl-2-pyrrolidinone by treatment with trifluorosulfonic acid.[494] *N*-Benzyl pent-4-ynamide reacted with tetrabutylammonium fluoride to form an alkylidene lactam.[495] Chiral 2-piperidinone compounds were prepared via a Pd-catalyzed asymmetric 6-*endo* cyclization of dienamides.[496] The Ti-catalyzed reaction of alkenyl *N*-tosylamines gave *N*-tosyl cyclic amines. Homopropargylic *N*-tosylamides gave pyrrolidinone derivatives upon treatment with a Au catalyst and mcpba in the presence of mesitoic acid.[497] Lactams were prepared by the intramolecular hydroamidation of benzamide derivatives that bear an *ortho* alkenyl unit, by using a Ru catalyst and a base.[498]

Alkynes and allenes also react with amides. The Ru/In-,[499] Pd-,[500] Bi-, or Hf-catalyzed[501] reaction of sulfonamides with alkynes gave cyclic *N*-sulfonyl derivatives.

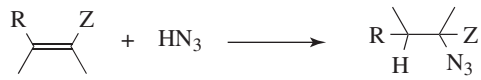
[485] See Souto, J.A.; Becker, P.; Iglesias, Á.; Muñiz, K. *J. Am. Chem. Soc.* ***2012***, *134*, 15505.
[486] Schlummer, B.; Hartwig, J.F. *Org. Lett.* ***2002***, *4*, 1471; Haskins, C.M.; Knight, D.W. *Chem. Commun.* ***2002***, 2724.
[487] See Breder, A. *Synlett* ***2014***, *25*, 899.
[488] McDonald, R.I.; White, P.B.; Weinstein, A.B.; Tam, C.P.; Stahl, S.S. *Org. Lett.* ***2011***, *13*, 2830.
[489] Tran, B.L.; Li, B.; Driess, M.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2014***, *136*, 2555.
[490] Thullen, S.M.; Rovis, T. *J. Am. Chem. Soc.* ***2017***, *139*, 15504.
[491] Fang, X.; Li, H.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* ***2014***, *136*, 16039.
[492] Dong, K.; Fang, X.; Jackstell, R.; Laurenczy, G.; Li, Y.; Beller, M. *J. Am. Chem. Soc.* ***2015***, *137*, 6053.
[493] Miura, K.; Hondo, T.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *Org. Lett.* ***2000***, *2*, 385.
[494] Marson, C.M.; Fallah, A. *Tetrahedron Lett.* ***1994***, *35*, 293.
[495] Jacobi, P.A.; Brielmann, H.L.; Hauck, S.I. *J. Org. Chem.* ***1996***, *61*, 5013.
[496] Tsuchikawa, H.; Maekawa, Y.; Katsumura, S. *Org. Lett.* ***2012***, *14*, 2326.
[497] Shu, C.; Liu, M.-Q.; Wang, S.-S.; Li, L.; Ye, L.-W. *J. Org. Chem.* ***2013***, *78*, 3292.
[498] Miura, H.; Terajima, S.; Tsutsui, K.; Shishido, T. *J. Org. Chem.* ***2017***, *82*, 1231.
[499] Trost, B.M.; Maulide, N.; Livingston, R.C. *J. Am. Chem. Soc.* ***2008***, *130*, 16502.
[500] See Narsireddy, M.; Yamamoto, Y. *J. Org. Chem.* ***2008***, *73*, 9698.
[501] Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Chem. Asian J.* ***2007***, *2*, 150.

Phenylthiomethyl alkynes were converted to *N*-Boc-*N*-phenylthio allenes with Boc azide and an iron catalyst.[502] Enamides were prepared by the Pd-,[503] Re-,[504] or Ru-catalyzed[505] hydroamidation of terminal alkynes with amides. The Pd-catalyzed reaction of an allene amide with iodobenzene leads to *N*-sulfonyl aziridines having an allylic group at C-1.[506] Other allene *N*-tosylamines similarly give *N*-tosyl tetrahydropyridines.[507] The reaction of amines and alkynes in supercritical carbon dioxide gave amides.[508] The reaction of alkynes with $TMSN_3$ using a Au/Ag co-catalyst gave the amide.[509]

When a carbamate was treated with Bu_3SnH and AIBN, addition to an alkene led to a bicyclic lactam.[510] Alkenyl amides and carbamates react with transition metal catalysts to form lactams or cyclic carbamates. Both Pd-[511] and Au-catalyzed[512] cyclization reactions of carbamates are known, and Os compounds have also been used.[513] Ionic liquids have been used to catalyze these reactions.[514] Imides can also add to alkenes or alkynes. Phthalimide reacts with an alkene in the presence of a Pd catalyst.[515]

Ni-catalyzed hydrophosphinylation, such as the reaction of an alkyne with an alkyl phosphinate, gave a vinyl phosphinate ester.[516] Both H-phosphinates and secondary phosphine oxides add to alkenes in an anti-Markovnikov manner, induced by air, in what is likely a radical reaction.[517]

15-10 Addition of Hydrazoic Acid and Alkyl Azides



Hydrazoic acid (HN_3) can be added to certain Michael-type substrates (Z is an electron-withdrawing group) to give β-azido compounds.[518] The reaction apparently fails if R is phenyl. HN_3 also adds to enol ethers $CH_2{=}CHOR$ to give $CH_3{-}CH(OR)N_3$, and to silyl

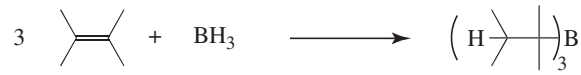
[502] Bacci, J.P.; Greenman, K.L.; van Vranken, D.L. *J. Org. Chem.* ***2003***, *68*, 4955.
[503] Panda, N.; Mothkuri, R. *J. Org. Chem.* ***2012***, *77*, 9407.
[504] Yudha S.S.; Kuninobu, Y.; Takai, K. *Org. Lett.* ***2007***, *9*, 5609.
[505] Gooßen, L.J.; Salih, K.S.M.; Blanchot, M. *Angew. Chem. Int. Ed.* ***2008***, *47*, 8492. For a mechanistic investigation, see Arndt, M.; Salih, K.S.M.; Fromm, A.; Goossen, L.J.; Menges, F.; Niedner-Schatteburg, G. *J. Am. Chem. Soc.* ***2011***, *133*, 7428.
[506] Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* ***1999***, *64*, 2992.
[507] Na, S.; Yu, F.; Gao, W. *J. Org. Chem.* ***2003***, *68*, 5943; Ma, S.; Gao, W. *Org. Lett.* ***2002***, *4*, 2989.
[508] Mak, X.Y.; Ciccolini, R.P.; Robinson, J.M.; Tester, J.W.; Danheiser, R.L. *J. Org. Chem.* ***2009***, *74*, 9381.
[509] Qin, C.; Feng, P.; Ou, Y.; Shen, T.; Wang, T.; Jiao, N. *Angew. Chem. Int. Ed.* ***2013***, *52*, 7850.
[510] Callier, A.-C.; Quiclet-Sire, B.; Zard, S.Z. *Tetrahedron Lett.* ***1994***, *35*, 6109.
[511] Michael, F.E.; Cochran, B.M. *J. Am. Chem. Soc.* ***2006***, *128*, 4246. For a related reaction, see Zabawa, T.P.; Kasi, D.; Chemler, S.R. *J. Am. Chem. Soc.* ***2005***, *127*, 11250.
[512] LaLonde, R.L.; Sherry, B.D.; Kang, E.J.; Toste, F.D. *J. Am. Chem. Soc.* ***2007***, *129*, 2452.
[513] Donohoe, T.J.; Chughtai, M.J.; Klauber, D.J.; Griffin, D.; Campbell, A.D. *J. Am. Chem. Soc.* ***2006***, *128*, 2514.
[514] Yang, L.; Xu, L.-W.; Xia, C.-G. *Synthesis* ***2009***, 1969.
[515] See Liu, G.; Stahl, S.S. *J. Am. Chem. Soc.* ***2006***, *128*, 7179.
[516] Ribière, P.; Bravo-Altamirano, K.; Antczak, M.I.; Hawkins, J.D.; Montchamp, J.-L. *J. Org. Chem.* ***2005***, *70*, 4064.
[517] Hirai, T.; Han, L.-B. *Org. Lett.* ***2007***, *9*, 53.
[518] Harvey, G.R.; Ratts, K.W. *J. Org. Chem.* ***1966***, *31*, 3907. See Biffin, M.E.C.; Miller, J.; Paul, D.B. in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 120–136.

enol ethers.[519] However, HN_3 does not add to ordinary alkenes unless a Lewis acid catalyst, such as $TiCl_4$, is used, in which case good yields of azide can be obtained.[519] Hydrazoic acid can also be added indirectly to ordinary alkenes by azidomercuration, followed by demercuration,[520] analogous to the similar procedures mentioned in **15-3**, **15-5**, **15-6**, and **15-8**. The method can be applied to terminal alkenes or strained cycloalkenes (e.g., norbornene) but fails for unstrained internal alkenes. A variation is the hydroazidation reaction of alkenes using a Co catalyst and *tert*-BuOOH to give the alkyl azide.[521]

The reaction of alkenes with $NaIO_4$ and 3 equivalents of NaN_3 in DMSO/AcOH gave the diazide.[522] Diazides were also prepared using an Fe catalyst.[523] The Au-catalyzed reaction of azides and allenes has been reported.[524] 1,6-Dienes that were reacted first with CatBH and then with $PhSO_2N_3$ and an initiator gave a six-membered ring with a pendant azide moiety.[525] Terminal alkynes reacted with trimethylsilyl azide (in the presence of H_2O and a silver catalyst to give the corresponding vinyl azides.[526]

E. A Metal on the Other Side

15-11 Hydroboration



Alkenes react with borane,[527] in ether solvents, such that B and H add across the double bond to form an organoborane.[528] The boron reacts as a Lewis acid with the alkene. Since BH_3 dimerizes to diborane B_2H_6, it cannot be prepared as a stable pure compound,[529] but it is commercially available in the form of "ate" complexes with THF, Me_2S,[530] phosphines, or tertiary amines. Pyridine/borane can be used for the hydroboration of alkenes at room temperature.[531]

In all cases the boron goes to the side of the double bond that is less substituted, whether the substituents are aryl or alkyl.[532] This regioselectivity is due mostly to steric factors,

[519] Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* ***1984***, *49*, 4237.
[520] Heathcock, C.H. *Angew. Chem. Int. Ed.* ***1969***, *8*, 134. See Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 522–527.
[521] Waser, J.; Nambu, H.; Carreira, E.M. *J. Am. Chem. Soc.* ***2005***, *127*, 8294.
[522] Kamble, D.A.; Karabal, P.U.; Chouthaiwale, P.V.; Sudalai, A. *Tetrahedron Lett.* ***2012***, *53*, 4195.
[523] Yuan, Y.A.; Lu, D.F.; Chen, Y.R.; Xu, H. *Angew. Chem. Int. Ed.* ***2016***, *55*, 534.
[524] Hurtado-Rodrigo, C.; Hoehne, S.; Paz-Muñoz, M. *Chem. Commun.* ***2014***, *50*, 1494.
[525] Kapat, A.; König, A.; Montermini, F.; Renaud, P. *J. Am. Chem. Soc.* ***2011***, *133*, 13890.
[526] Liu, Z.; Liao, P.; Bi, X. *Org. Lett.* ***2014***, *16*, 3668.
[527] See Lane, C.F. in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, ***1977***, pp. 1–191.
[528] See Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***; *Organic Syntheses Via Boranes*, Wiley, NY, ***1975***; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***; Suzuki, A.; Dhillon, R.S. *Top. Curr. Chem.* ***1986***, *130*, 23. Alkene borane complexes have been reported, see Zhao, X.; Stephan, D.W. *J. Am. Chem. Soc.* ***2011***, *133*, 12448.
[529] Fehlner, T.P. *J. Am. Chem. Soc.* ***1971***, *93*, 6366.
[530] See Hutchins, R.O.; Cistone, F. *Org. Prep. Proced. Int.* ***1981***, *13*, 225; Cadot, C.; Dalko, P.I.; Cossy, J. *Tetrahedron Lett.* ***2001***, *42*, 1661.
[531] Clay, J.M.; Vedejs, E. *J. Am. Chem. Soc.* ***2005***, *127*, 5766.
[532] Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 63–84, 137–197; Brown, H.C.; Vara Prasad, J.V.N.; Zee, S. *J. Org. Chem.* ***1986***, *51*, 439.

although electronic factors also play a part. For most substrates, the addition in hydroboration is highly regioselective and *syn*, with delivery of B and H[533] occurring from the less-hindered side.[534] The mechanism[535] probably involves a *four-center transition state rather than a formal intermediate*.[536] When both sides of the double bond are monosubstituted or both disubstituted, about equal amounts of each regioisomer are obtained. However, it is possible in such cases to make the addition regioselective by the use of a large borane molecule.[537] When the substrate is an allylic alcohol or amine, the addition is generally *anti*,[538] although the stereoselectivity can be changed to *syn* by the use of catecholborane and Rh complexes.[539] Organoboranes are useful intermediates for the preparation of a wide variety of compounds. The organoborane product is oxidized to an alcohol with hydrogen peroxide and NaOH (see **18-23**), *with anti-Markovnikov regioselectivity* in what is probably the most-used application. The hydroboration-oxidation of alkenes has been done using flow conditions (Sec. 7.D).[540] Note that organoboranes can be analyzed using ^{11}B NMR.[541]

With relatively unhindered alkenes, the process cannot be stopped with the addition of one molecule of BH_3 because the resulting RBH_2 adds to another molecule of alkene to give R_2BH, which in turn adds to a third alkene molecule, so that the isolated product is a trialkylborane R_3B. When the alkene is moderately hindered, *the product is the dialkylborane R_2BH or even the monalkylborane RBH_2*.[542] For example, 2-methylbut-2-ene and borane gives *disiamylborane* and 2,3-dimethylbut-2-ene and borane gives *thexylborane*.[543] Surprisingly, when methylborane $MeBH_2$,[544] which is not a bulky molecule, adds to alkenes in the solvent THF, the reaction can be stopped with one addition to give the dialkylboranes RMeBH.[545] Monochloroborane[546] BH_2Cl coordinated with dimethyl sulfide shows greater regioselectivity than BH_3 for terminal alkenes or those of the form $R_2C{=}CHR$, and the hydroboration product is a dialkylchloroborane R_2BCl.[547] Treatment of alkenes with dichloroborane/dimethyl sulfide $BHCl_2/SMe_2$ in the presence of BF_3[548] or with BCl_3 and Me_3SiH[549] gives alkyldichloroboranes $RBCl_2$. A useful reagent is

[533] Brown, H.C.; Sharp, R.L. *J. Am. Chem. Soc.* ***1966***, *88*, 5851; Klein, J.; Dunkelblum, E.; Wolff, M.A. *J. Organomet. Chem.* ***1967***, *7*, 377. See also, Mo, Y.; Jiao, H.; Schleyer, P.v.R. *J. Org. Chem.* ***2004***, *69*, 3493.

[534] Kabalka, G.W.; Newton Jr., R.J.; Jacobus, J. *J. Org. Chem.* ***1978***, *43*, 1567.

[535] See Brown, H.C.; Chandrasekharan, J. *J. Org. Chem.* ***1988***, *53*, 4811.

[536] Narayana, C.; Periasamy, M. *J. Chem. Soc., Chem. Commun.* ***1987***, 1857. See, however, Jones, P.R. *J. Org. Chem.* ***1972***, *37*, 1886.

[537] Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1961***, *83*, 1241.

[538] See Still, W.C.; Barrish, J.C. *J. Am. Chem. Soc.* ***1983***, *105*, 2487.

[539] See Burgess, K.; Ohlmeyer, M.J. *J. Org. Chem.* ***1991***, *56*, 1027.

[540] Souto, J.A.; Stockman, R.A.; Ley, S.V. *Org. Biomol. Chem.* ***2015***, *13*, 3871.

[541] Medina, J.R.; Cruz, G.; Cabrera, C.R.; Soderquist, J.A. *J. Org. Chem.* ***2003***, *68*, 4631.

[542] Srebnik, M.; Cole, T.E.; Ramachandran, P.V.; Brown, H.C. *J. Org. Chem.* ***1989***, *54*, 6085. Note that mono- and dialkylboranes actually exist as hydrogen-bridged dimers: Brown, H.C.; Klender, G.J. *Inorg. Chem.* ***1962***, *1*, 204.

[543] See Negishi, E.; Brown, H.C. *Synthesis* ***1974***, 77.

[544] See Brown, H.C.; Cole, T.E.; Srebnik, M.; Kim, K. *J. Org. Chem.* ***1986***, *51*, 4925.

[545] Srebnik, M.; Cole, T.E.; Brown, H.C. *J. Org. Chem.* ***1990***, *55*, 5051. See Kulkarni, S.U.; Basavaiah, D.; Zaidlewicz, M.; Brown, H.C. *Organometallics* ***1982***, *1*, 212.

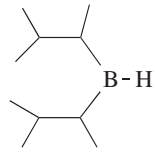
[546] See Brown, H.C.; Kulkarni, S.U. *J. Organomet. Chem.* ***1982***, *239*, 23.

[547] Brown, H.C.; Ravindran, N.; Kulkarni, S.U. *J. Org. Chem.* ***1979***, *44*, 2417.

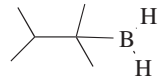
[548] Brown, H.C.; Racherla, U.S. *J. Org. Chem.* ***1986***, *51*, 895.

[549] Soundararajan, R.; Matteson, D.S. *J. Org. Chem.* ***1990***, *55*, 2274.

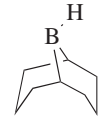
bis(pinacolato)diboron, B_2pin_2, which contains two boron atoms and two pinacolato ligands.[550]



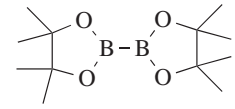
Disiamylborane



Thexylborane



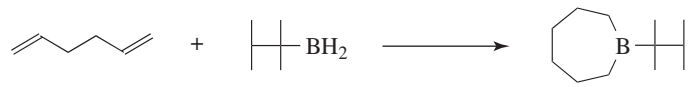
9-BBN



bis(Pinacolato)diboron

Intramolecular hydroboration reactions are possible.[551] When cycloocta-1,5-diene reacts with borane, one C═C reacts and a remaining B—H unit reacts intramolecularly to give 9-borabicyclo[3.3.1]nonane (9-BBN)[552] which has the advantage that it is stable in air. Disiamylborane, 9-BBN, and similar molecules are far more selective than BH_3, and preferentially react at the less-hindered bonds, so it is often possible to hydroborate one double bond in a molecule and leave others unaffected or to hydroborate one alkene in the presence of a less reactive alkene.[553]

Thexylborane[543] is particularly useful for achieving the cyclic hydroboration of dienes, conjugated or nonconjugated, as in the formation of **23**.[554]



23

Rings of five, six, or seven members can be formed in this way. Similar cyclization can also be accomplished with other monoalkylboranes and, in some instances, with BH_3 itself.[555] One example is the formation of 9-BBN, and another is conversion of 1,5,9-cyclododecatriene to perhydro-9*b*-boraphenalene.[556]

Asymmetric hydroboration has been developed as a very useful extension of the basic methodology. The reagent diisopinocampheylborane **24** was prepared by treating optically active α-pinene with BH_3.[557] The reagent is used in a hydroboration-oxidation to give enantioselective formation of alcohols.[558] Since both (+)- and (−)-α-pinene are readily available, both enantiomers can be prepared.

[550] Liu, X. *Synlett* ***2003***, 2442; Ishiyama, T.; Murata, M.; Ahiko, T.; Miyaura, N. *Org. Synth. Coll. Vol.* ***2004***, *10*, 115; Kleeberg, C.; Crawford, A.G.; Batsanov, A.S.; Hodgkinson, P.; Apperley, D.C.; Cheung, M.S.; Lin, Z.; Marder, T.B. *J. Org. Chem.* ***2012***, *77*, 785.

[551] See Shapland, P.; Vedejs, E. *J. Org. Chem.* ***2004***, *69*, 4094.

[552] See Brown, H.C.; Chen, J.C. *J. Org. Chem.* ***1981***, *46*, 3978; Soderquist, J.A.; Brown, H.C. *J. Org. Chem.* ***1981***, *46*, 4599.

[553] Brown, H.C.; Sharp, R.L. *J. Am. Chem. Soc.* ***1966***, *88*, 5851; Klein, J.; Dunkelblum, E.; Wolff, M.A. *J. Organomet. Chem.* ***1967***, *7*, 377.

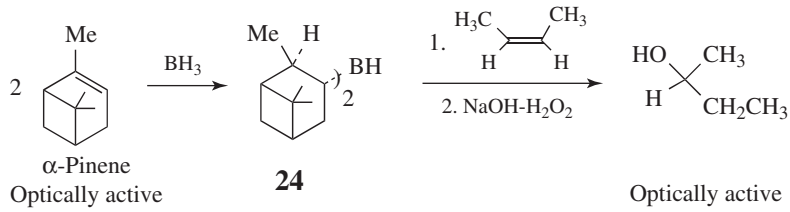
[554] Brown, H.C.; Negishi, E. *J. Am. Chem. Soc.* ***1972***, *94*, 3567.

[555] See Brown, H.C.; Negishi, E. *Tetrahedron* ***1977***, *33*, 2331; Brown, H.C.; Pai, G.G.; Naik, R.G. *J. Org. Chem.* ***1984***, *49*, 1072.

[556] Brown, H.C.; Negishi, E.; Dickason, W.C. *J. Org. Chem.* ***1985***, *50*, 520.

[557] Brown, H.C.; Vara Prasad, J.V.N. *J. Am. Chem. Soc.* ***1986***, *108*, 2049.

[558] Brown, H.C.; Singaram, B. *Acc. Chem. Res.* ***1988***, *21*, 287; Srebnik, M.; Ramachandran, P.V. *Aldrichimica Acta* ***1987***, *20*, 9; Brown, H.C.; Jadhav, P.K. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***, pp. 1–43. For a study of electronic effects, see Garner, C.M.; Chiang, S.; Nething, M.; Monestel, R. *Tetrahedron Lett.* ***2002***, *43*, 8339.



α-Pinene
Optically active

24

Optically active

However, **24** does not give good results with even moderately hindered alkenes; a better reagent for these compounds is isopinocampheylborane,[559] although optical yields are lower. Limonylborane,[560] 2- and 4-dicaranylboranes,[561] a myrtanylborane,[562] and dilongifolylborane[563] have also been used.

Other new asymmetric boranes have also been developed. The chiral cyclic boranes, *trans*-2,15-dimethylborolanes, add enantioselectively to alkenes (except alkenes of the form $RR'C{=}CH_2$) to give organoboranes of high optical purity.[564] When chiral boranes are added to trisubstituted alkenes of the form $RR'C{=}CHR''$, two new stereogenic centers are created, and, with some reagents, only one of the four possible diastereomers is predominantly produced, in yields greater than 90%.[564] This approach has been called *double-asymmetric synthesis*. 1,1-Dialkylalkenes reacted with HBPin in the presence of a chiral Co catalyst to give the corresponding borane, with excellent enantioselectivity.[565] A supramolecular catalyst has been used for catalytic asymmetric hydroboration.[566]

The hydroboration of triple bonds[567] gives vinylic boranes. Subsequent oxidation of vinylboranes derived from terminal alkynes give aldehydes whereas internal alkynes give vinylboranes that are oxidized to ketones. However, terminal alkynes give vinylic boranes[568] (and hence aldehydes) *only* when treated with a hindered borane[569] or with $BHBr_2/SMe_2$.[570] The reaction between terminal alkynes and BH_3 produces 1,1-dibora compounds, which can be oxidized either to primary alcohols or to carboxylic acids (with mcpba).[571] Double bonds can be hydroborated in the presence of triple bonds if the reagent is 9-BBN.[572] On the other hand, dimesitylborane selectively hydroborates triple bonds in

[559] Brown, H.C.; Jadhav, P.K.; Mandal, A.K. *J. Org. Chem.* ***1982***, *47*, 5074. See also, Brown, H.C.; Weissman, S.A.; Perumal, P.T.; Dhokte, U.P. *J. Org. Chem.* ***1990***, *55*, 1217. For the crystal structure of this adduct, see Soderquist, J.A.; Hwang-Lee, S.; Barnes, C.L. *Tetrahedron Lett.* ***1988***, *29*, 3385.

[560] Jadhav, P.K.; Kulkarni, S.U. *Heterocycles* ***1982***, *18*, 169.

[561] Brown, H.C.; Vara Prasad, J.V.N.; Zaidlewicz, M. *J. Org. Chem.* ***1988***, *53*, 2911.

[562] Kiesgen de Richter, R.; Bonato, M.; Follet, M.; Kamenka, J. *J. Org. Chem.* ***1990***, *55*, 2855.

[563] Jadhav, P.K.; Brown, H.C. *J. Org. Chem.* ***1981***, *46*, 2988.

[564] Masamune, S.; Kim, B.M.; Petersen, J.S.; Sato, T.; Veenstra, J.S.; Imai, T. *J. Am. Chem. Soc.* ***1985***, *107*, 4549. See Thomas, S.P.; Aggarwal, V.K. *Angew. Chem. Int. Ed.* ***2009***, *48*, 1896.

[565] Zhang, L.; Zuo, Z.; Wan, X.; Huang, Z. *J. Am. Chem. Soc.* ***2014***, *136*, 15501.

[566] Moteki, S.A.; Toyama, K.; Liu, Z.; Ma, J.; Holmes, A.E.; Takacs, J.M. *Chem. Commun.* ***2012***, *48*, 263.

[567] See Hudrlik, P.F.; Hudrlik, A.M. in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 203–219; Barbeyron, R.; Benedetti, E.; Cossy, J.; Vasseur, J.-J.; Arseniyadis, S.; Smietana, M. *Tetrahedron* ***2014***, *70*, 8431.

[568] Brown, H.C.; Campbell Jr., J.B. *Aldrichimica Acta* ***1981***, *14*, 1.

[569] Brown, H.C.; Gupta, S.K. *J. Am. Chem. Soc.* ***1975***, *97*, 5249. See Garrett, C.E.; Fu, G.C. *J. Org. Chem.* ***1996***, *61*, 3224.

[570] Brown, H.C.; Campbell Jr., J.B. *J. Org. Chem.* ***1980***, *45*, 389.

[571] Zweifel, G.; Arzoumanian, H. *J. Am. Chem. Soc.* ***1967***, *89*, 291.

[572] Brown, H.C.; Coleman, R.A. *J. Org. Chem.* ***1979***, *44*, 2328.

the presence of double bonds.[573] Terminal alkynes reacted with $B_2(Pin)_2$ with 0.5 equivalents of LiO*t*-Bu to give a metal-free hydroboration reaction and formation of the alkyl boronate.[574] Alkynes reacted with pinacolborane using a carboxylic acid catalyst to give the vinyl boronate.[575]

Transition metal-catalyzed reactions are known for the hydroboration of alkenes or alkynes, including Co-,[576] Cu-,[577] and Rh-catalyzed[578] reactions. When the reagent is catecholborane, hydroboration is catalyzed by Rh complexes,[579] such as *Wilkinson's catalyst* [chloridotrisrhodium(I); $RhCl(PPh_3)_3$], and[580] SmI_2,[581] Fe,[582] Ag,[583] or lanthanide[584] reagents. The Fe-catalyzed addition of pinacolborane to alkenes was reported, with selectivity for terminal alkenes.[585] The hydroboration of allyl or vinyl arenes reacted with $B_2(Pin)_2$ gave the corresponding alkylboranes by use of a Cu catalyst.[586] The Cu-catalyzed alkene hydroboration gave the alkylated organoborane.[587] Alkenes reacted with aryl halides and $B_2(pin)$, in the presence of a Pd catalyst, to give the 2-aryl alkyl boronate.[588]

The reaction of alkynes and pinacolborane gave the vinyl boronate with a dialkylaluminum hydride catalyst.[589] Alkynes reacted with $B_2(pin)_2$ in the presence of a Cu catalyst and alkyl halides to give the corresponding alkylated vinyl boronate.[590] *N*-Boc-propargylamines reacted with $B_2(pin)_2$ with a catalytic amount of a *N*-heterocyclic carbene (NHC)/Cu complex to give the vinyl boronate.[591] Either the α- or the β-boryl isomer was prepared by the choice of ligand with an NHC/Cu catalyst, in which propargylic alcohols and ethers were converted to the appropriate vinyl boronate by reaction with $B_2(Pin)_2$.[592] The reaction of terminal alkynes with $B_2(pin)_2$ and a Ag *N*-heterocyclic carbene complex as catalyst gave the vinyl boronate.[593] Terminal alkynes reacted with $B_2(pin)_2$ in aqueous

[573] Pelter, A.; Singaram, S.; Brown, H.C. *Tetrahedron Lett.* ***1983***, *24*, 1433.
[574] Hong, S.; Zhang, W.; Liu, M.; Yao, Z.J.; Deng, W. *Tetrahedron Lett.* ***2016***, *57*, 1.
[575] Ho, H.E.; Asao, N.; Yamamoto, Y.; Jin, T. *Org. Lett.* ***2014***, *16*, 4670.
[576] Zhang, L.; Zuo, Z.; Leng, X.; Huang, Z. *Angew. Chem. Int. Ed.* ***2014***, *53*, 2696.
[577] Jang, W.J.; Song, S.M.; Moon, J.H.; Lee, J.Y.; Yun, J. *J. Am. Chem. Soc.* ***2017***, *139*, 13660; Tanaka, C.; Nakamura, K.; Nishikata, T. *Tetrahedron* ***2017***, *73*, 3999.
[578] Smith, J.R.; Collins, B.S.L.; Hesse, M.J.; Graham, M.A.; Myers, E.L.; Aggarwal, V.K. *J. Am. Chem. Soc.* ***2017***, *139*, 9148.
[579] Burgess, K.; van der Donk, W.A.; Westcott, S.A.; Marder, T.B.; Baker, R.T.; Calabrese, J.C. *J. Am. Chem. Soc.* ***1992***, *114*, 9350; Evans, D.A.; Fu, G.C.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1992***, *114*, 6671.
[580] Burgess, K.; Ohlmeyer, M.J. *Chem. Rev.* ***1991***, *91*, 1179.
[581] Evans, D.A.; Muci, A.R.; Stürmer, R. *J. Org. Chem.* ***1993***, *58*, 5307.
[582] Rawat, V.S.; Sreedhar, B. *Synlett* ***2014***, *25*, 1132.
[583] Hu, J.-R.; Liu, L.-H.; Hu, X.; Ye, H.-D. *Tetrahedron* ***2014***, *70*, 5815.
[584] Harrison, K.N.; Marks, T.J. *J. Am. Chem. Soc.* ***1992***, *114*, 9220.
[585] Zhang, L.; Peng, D.; Leng, X.; Huang, Z. *Angew. Chem. Int. Ed.* ***2013***, *52*, 3676. See Zhang, L.; Huang, Z. *Synlett* ***2013***, *24*, 1745.
[586] Wen, Y.; Xie, J.; Deng, C.; Li, C. *J. Org. Chem.* ***2015***, *80*, 4142.
[587] Smith, K.B.; Logan, K.M.; You, W.; Brown, M.K. *Chem. Eur. J.* ***2014***, *20*, 12032.
[588] Yang, K.; Song, Q. *J. Org. Chem.* ***2016***, *81*, 1000. For a Cu-catalyzed reaction, see Jang, W.J.; Lee, W.L.; Moon, J.H.; Lee, J.Y.; Yun, J. *Org. Lett.* ***2016***, *18*, 1390. For a Ni-catalyzed reaction, see Semba, K.; Ohtagaki, Y.; Nakao, Y. *Org. Lett.* ***2016***, *18*, 3956.
[589] Bismuto, A.; Thomas, S.P.; Cowley, M.J. *Angew. Chem. Int. Ed.* ***2016***, *55*, 1356.
[590] Alfaro, R.; Parra, A.; Alemán, J.; Ruano, J.L.G.; Tortosa, M. *J. Am. Chem. Soc.* ***2012***, *134*, 15165; Itoh, T.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* ***2016***, *138*, 7528.
[591] Jang, H.; Zhugralin, A.R.; Lee, Y.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2011***, *133*, 7859. See Moure, A.L.; Arrayás, R.G.; Cárdenas, D.J.; Alonso, I.; Carretero, J.C. *J. Am. Chem. Soc.* ***2012***, *134*, 7219.
[592] Park, J.K.; Ondrusek, B.A.; McQuade, D.T. *Org. Lett.* ***2012***, *14*, 4790. Also see Ojha, D.P.; Prabhu, K.R. *Org. Lett.* ***2016***, *18*, 432.
[593] Yoshida, H.; Kageyuki, I.; Takaki, K. *Org. Lett.* ***2014***, *16*, 3512.

methanol with NaOH, $CuBr_2$, and cyclodextrin/bis(pyridine) to give the vinyl boronate.[594] The Rh-catalyzed hydroboration of terminal alkynes with pinacolborane was reported.[595] *o*-Bromostyrene derivatives reacted with $B_2(Pin)_2$ and a Pd catalyst to give β,β-disubstituted vinyl boronates via an aryl to vinyl Pd 1,4-migration and trapping of the Pd complex with the diboron compound.[596] Vinylarenes and methyl crotonate reacted with aryl halides and $B_2(Pin)_2$ catalyzed by Pd/Cu to give 2-boryl-1,1-diarylethanes and an α-aryl-β-boryl ester.[597] The Fe-,[598] Rh-,[599] or Cu[600]-catalyzed reactions have been reported.

The double bonds in a conjugated diene are hydroborated separately, that is, there is no 1,4-addition. However, it is difficult to hydroborate just one double bond in a conjugated system, since conjugated double bonds are less reactive than isolated ones. With Cu catalysis, the asymmetric conjugate addition (**15-24**) of organoboron reagents to conjugated enones has been reported.[601] Conjugated ketones reacted with $B_2(Pin)_2$ in the presence of a *N*-heterocyclic carbene/Cu complex to give β-boration of acyclic enones, producing β-boryl ketones with high enantioselectivity.[602]

The presence of certain functional groups has directing effects on hydroboration reactions. Amides direct hydroboration reactions in alkenyl amides, for example.[603] Intramolecular hydroboration is directed by amine groups in alkenyl amines.[604] Alkenyl alcohols or ethers also undergo hydroboration, where delivery of boron is directed by the oxygen.[605] Functional groups such as OR, OH, NH_2, SMe, halogen, and CO_2R may be present in the molecule,[606] but not groups that are reducible by borane, such as COOH.

Boronate esters are prepared from alkenes. The reaction of an alkene with pyridine iodoborane, followed by treatment with pinacol and NaOH, for example, leads to the pinacol boronate ester.[607] Various cyclopropane derivatives were converted to the cyclopropyl boronate, catalyzed by the combination of (η^6-mes)IrBpin$_3$ and a phenanthroline to give selective reaction at the methylene C—H bonds rather than methine or methyl C—H bonds.[608]

OS **VI**, 719, 852, 919, 943; **VII**, 164, 339, 402, 427; **VIII**, 532.

15-12 Other Hydrometalation

Metal hydrides of Groups 13 and 14 of the periodic table (e.g., AlH_3, GaH_3) as well as many of their alkyl and aryl derivatives (e.g., R_2AlH, Ar_3SnH) add to double bonds to give

[594] Yao, Z.-J.; Hong, S.; Zhang, W.; Liu, M.; Deng, W. *Tetrahedron Lett.* ***2016***, *57*, 910.
[595] Morimoto, M.; Miura, T.; Murakami, M. *Angew. Chem. Int. Ed.* ***2015***, *54*, 12659.
[596] Hu, T.-J.; Zhang, G.; Chen, Y.-H.; Feng, C.-G.; Lin, G.-Q. *J. Am. Chem. Soc.* ***2016***, *138*, 2897.
[597] Semba, K.; Nakao, Y. *J. Am. Chem. Soc.* ***2014***, *136*, 7567. Also see Nelson, H.M.; Williams, B.D.; Miró, J.; Toste, F.D. *J. Am. Chem. Soc.* ***2015***, *137*, 3213.
[598] Chen, X.; Cheng, Z.; Lu, Z. *Org. Lett.* ***2017***, *19*, 969.
[599] Wang, K.; Bates, R.W. *Synthesis* ***2017***, *49*, 2749.
[600] Hong, S.; Liu, M.; Zhang, W.; Zeng, Q.; Deng, W. *Tetrahedron Lett.* ***2015***, *56*, 2297.
[601] Wu, C.; Yue, G.; Nielsen, C.D.-T.; Xu, K.; Hirao, H.; Zhou, J. *J. Am. Chem. Soc.* ***2016***, *138*, 742.
[602] Zhao, L.; Ma, Y.; He, F.; Duan, W.; Chen, J.; Song, C. *J. Org. Chem.* ***2013***, *78*, 1677.
[603] Smith, S.M.; Thacker, N.C.; Takacs, J.M. *J. Am. Chem. Soc.* ***2008***, *130*, 3734.
[604] Scheideman, M.; Wang, G.; Vedejs, E. *J. Am. Chem. Soc.* ***2008***, *130*, 8669.
[605] Rarig, R.-A.F.; Scheideman, M.; Vedejs, E. *J. Am. Chem. Soc.* ***2008***, *130*, 9182.
[606] See Brown, H.C.; Sharp, R.L. *J. Am. Chem. Soc.* ***1968***, *90*, 2915.
[607] Karatjas, A.G.; Vedejs, E. *J. Org. Chem.* ***2008***, *73*, 9508.
[608] Liskey, C.W.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2013***, *135*, 3375.

organometallic compounds.[609] The hydroboration reaction (**15-11**) is the most important example but, as mentioned, other important metals in this reaction are Al,[610] Sn,[611] and Zr[612] (which is a Group 4 metal). Some of these reactions are uncatalyzed, but in other cases various types of catalyst have been used.[613] The mechanism with Group 13 hydrides seems to be electrophilic (or four-centered pericyclic with some electrophilic characteristics) while with Group 14 hydrides a mechanism involving free radicals seems more likely.

Other metals add to π bonds. Hydrozirconation of alkenes or alkynes is the addition of Zr—H across a π bond.[614] Hydrozirconation is most commonly carried out with Cp_2ZrHCl (Cp = cyclopentadienyl; zirconocene hydrochloride or zirconocene chloride hydride), known as *Schwartz's reagent*.[615] The Co-catalyzed alkenylzincation of alkynes has been reported.[616] The Fe-catalyzed hydromagnesiation[617] is known, and dialkylmagnesium reagents have been obtained by adding MgH_2 to double bonds.[618] Some reagents can add 1 or 2 equivalents[619] to triple bonds.[620] When 2 molar equivalents are added, electrophilic addition generally gives 1,1-dimetallic products (as with hydroboration), while free-radical addition usually gives the 1,2-dimetallic products. Hydronickelation of allenes[621] and the metal-catalyzed hydrostannation of alkenes[622] and alkynes[623] are known. The *trans*-selective hydrogermylation of alkynes was reported, by reaction with methyliron and a bis(germyl)hydroiron catalyst.[624] The hydroalumination of alkynes has been reported.[625] The hydromagnesiation of alkynes is also known.[626] The magnesiation or zincation of acrylonitriles, acrylates, and nitroalkenes has been reported using

[609] Negishi, E. *Adv. Met.-Org. Chem.* ***1989***, *1*, 177; Eisch, J.J. *The Chemistry of Organometallic Compounds*, Macmillan, NY, ***1967***, pp. 107–111; Eisch, J.J.; Fichter, K.C. *J. Organomet. Chem.* ***1983***, *250*, 63.

[610] See Dzhemilev, U.M.; Vostrikova, O.S.; Tolstikov, G.A. *Russ. Chem. Rev.* ***1990***, *59*, 1157; Maruoka, K.; Yamamoto, H. *Tetrahedron* ***1988***, *44*, 5001.

[611] See Negishi, E. *Organometallics in Organic Synthesis*, Vol. 1, Wiley, NY, ***1980***, pp. 45–48, 357–363, 406–412; Speier, J.L. *Adv. Organomet. Chem.* ***1979***, *17*, 407; Andrianov, K.A.; Soucek, J.; Khananashvili, L.M. *Russ. Chem. Rev.* ***1979***, *48*, 657.

[612] Negishi, E.; Takahashi, T. *Synthesis* ***1988***, 1; Dzhemilev, U.M.; Vostrikova, O.S.; Tolstikov, G.A. *J. Organomet. Chem.* ***1986***, *304*, 17. Also see, Hoveyda, A.H.; Morken, J.P. *J. Org. Chem.* ***1993***, *58*, 4237.

[613] Doyle, M.P.; High, K.G.; Nesloney, C.L.; Clayton Jr., T.W.; Lin, J. *Organometallics* ***1991***, *10*, 1225.

[614] Sun, R.C.; Okabe, M.; Coffen, D.L.; Schwartz, J. *Org. Synth. Coll. Vol.* ***1998***, *9*, 640; Panek, J.S.; Hu, T. *J. Org. Chem.* ***1997***, *62*, 4912.

[615] See Schwartz, J.; Labinger, J.A. *Angew. Chem. Int. Ed.* ***2003***, *15*, 330; Hart, D.W.; Blackburn, T.F.; Schwartz, J. *J. Am. Chm. Soc.* ***1975***, *97*, 679; Lipshutz, B.H.; Keil, R.; Ellsworth, E.L. *Tetrahedron Lett.* ***1990***, *31*, 7257.

[616] Wu, J.; Yoshikai, N. *Angew. Chem. Int. Ed.* ***2016***, *55*, 336.

[617] Ilies, L.; Yoshida, T.; Nakamura, E. *J. Am. Chem. Soc.* ***2012***, *134*, 16951.

[618] See Bogdanovic, B. *Angew. Chem. Int. Ed.* ***1985***, *24*, 262.

[619] See Eisch, J.J.; Rhee, S. *Liebigs Ann. Chem.* ***1975***, 565.

[620] See Hudrlik, P.F.; Hudrlik, A.M. in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 219–232.

[621] Amako, Y.; Hori, H.; Arai, S.; Nishida, A. *J. Org. Chem.* ***2013***, *78*, 10763.

[622] Ghosh, B.; Maleczka Jr., R.E. *Tetrahedron Lett.* ***2011***, *52*, 5285; Darwish, A.; Chong, J.M. *Tetrahedron* ***2012***, *68*, 654; Maleczka Jr., R.E.; Ghosh, B.; Gallagher, W.P.; Baker, A.J.; Muchnij, J.A.; Szymanski, A.L. *Tetrahedron* ***2013***, *69*, 4000; Gupta, S.; Do, Y.; Lee, J.H.; Lee, M.; Han, J.; Rhee, Y.H.; Park, J. *Chem. Eur. J.* ***2014***, *20*, 1267.

[623] Rummelt, S.M.; Fürstner, A. *Angew. Chem. Int. Ed.* ***2014***, *53*, 3626.

[624] Itazaki, M.; Kamitani, M.; Nakazawa, H. *Chem. Commun.* ***2011***, *47*, 7854.

[625] Andrews, P.; Latham, C.M.; Magre, M.; Wilcox, D.; Wodward, S. *Chem. Commun.* ***2013***, *49*, 1488.

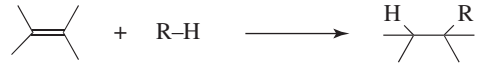
[626] Jones, A.S.; Paliga, J.F.; Greenhalgh, M.D.; Quibell, J.M.; Steven, A.; Thomas, S.P. *Org. Lett.* ***2014***, *16*, 5964.

continuous flow techniques (Sec. 7.D).[627] The hydrostannylation of arynes has been reported.[628]

OS **VII**, 456; **VIII**, 268, 295, 507; **80**, 104. See also, OS **VIII**, 277, 381.

F. Carbon or Silicon on the Other Side

15-13 Addition of Alkanes



There are two important ways of adding alkanes to alkenes: (i) direct heating and (ii) acid catalysis.[629] Both give mixtures, and neither is useful for the preparation of relatively pure compounds in reasonable yields. However, both are useful industrially. In the thermal method, the reactants are heated to high temperatures (∼500 °C) at high pressures (150–300 atm) without a catalyst. As an example, propane and ethylene gave 55.5% isopentane, 7.3% hexanes, 10.1% heptanes, and 7.4% alkenes.[630] There is kinetic evidence that the initiation takes place primarily by steps that are called *symproportionation* steps[631] (the opposite of disproportionation, Sec. 5.C.ii).

In the acid-catalysis method, a protonic or Lewis acid is used as the catalyst and the reaction is carried out at temperatures between −30 and 100 °C. This is a *Friedel-Crafts* process that proceeds via a carbocation mechanism.[632] An alkene reacts with H^+ to give a carbocation, which abstracts hydride (H^-) from R—H to give an alkane and R^+, which reacts with more alkene to give a new carbocation The initially formed carbocation often rearranges before a hydride is transferred, explaining, for example, why the principal product from the reaction between isobutane and ethylene is 2,3-dimethylbutane. Instead of abstracting a hydride, it is also possible for either of the carbocation intermediates to add to another molar equivalent of alkene, so that not only rearrangement products but also dimeric and polymeric products are frequent. If the tri- or tetrasubstituted alkenes are treated with Me_4Si, HCl, and $AlCl_3$, protonation gives a tertiary carbocation, which reacts with the Me_4Si to give a product that is the result of addition of H and Me to the original alkene.[633] An intramolecular cyclization of dodec-1-ene to cyclododecane was reported using aluminum chloride in an ionic liquid.[634]

Alkanes add to alkynes under photolysis conditions to give an alkene.[635] The reaction can also be base catalyzed, in which case there is nucleophilic addition and a carbanion mechanism.[636] The carbanions that are most often used are those stabilized by one or more

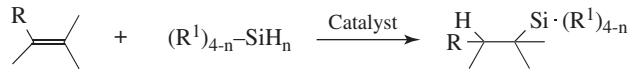
[627] Ganiek, M.A.; Becker, M.R.; Ketels, M.; Knochel, P. *Org. Lett.* ***2016***, *18*, 828. Also see González, M.J.; López, L.A.; Vicente, R. *Tetrahedron Lett.* ***2015***, *56*, 1600.
[628] Spiteri, C.; Burnley, J.; Moses, J.E. *Synlett* ***2011***, *22*, 2533.
[629] See Shuikin, N.I.; Lebedev, B.L. *Russ. Chem. Rev.* ***1966***, *35*, 448; Schmerling, L. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, pp. 1075–1111, 1121–1122.
[630] Frey, E.J.; Hepp, H.J. *Ind. Eng. Chem.* ***1936***, *28*, 1439.
[631] See Hartmanns, J.; Klenke, K.; Metzger, J.O. *Chem. Ber.* ***1986***, *119*, 488.
[632] See Mayr, H. *Angew. Chem. Int. Ed.* ***1990***, *29*, 1371.
[633] Bolestova, G.I.; Parnes, Z.N.; Kursanov, D.N. *J. Org. Chem. USSR* ***1983***, *19*, 2175.
[634] Qiao, K.; Deng, Y. *Tetrahedron Lett.* ***2003***, *44*, 2191.
[635] Geraghty, N.W.A.; Hannan, J.J. *Tetrahedron Lett.* ***2001***, *42*, 3211.
[636] See Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 240–422; Pines, H. *Acc. Chem. Res.* ***1974***, *7*, 155.

α-aryl groups. For example, toluene adds to styrene in the presence of sodium to give 1,3-diphenylpropane.[637] Conjugated dienes give 1,4-addition.[638]

There are transition metal-catalyzed addition reactions of alkyl units to alkenes,[639] often proceeding with metal hydride elimination to form an alkene. An intramolecular cyclization reaction of an *N*-pyrrolidino amide alkene was reported, using an iridium catalyst for addition of the carbon α to nitrogen at the alkene unit.[640]

OS **I**, 229; **IV**, 665; **VII**, 479.

15-14 Addition of Silanes (Hydrosilation)



Silanes bearing at least one Si—H unit do not generally react with alkenes or alkynes, but transition metals catalyze the addition to give the corresponding alkylsilane or vinylsilane.[641] This reaction is known as hydrosilation. Transition metals used to catalyze the reaction of an alkylsilane and an alkene include Ru,[642] Rh,[643] Pd,[644] Re,[645] La,[646] Y,[647] Pt,[648] Co,[649] Fe,[650] Cu,[651] or Sm,[652] giving the alkylsilane with high anti-Markovnikov selectivity. In the presence of BEt_3, silanes add to alkenes to give the alkylsilane with anti-Markovnikov selectivity,[653] or add to alkynes to give the corresponding vinylsilane.[654] Silanes add to alkenes under radical conditions (using AIBN) with high anti-Markovnikov selectivity.[655] Silanes also add to alkenes to form the anti-Markovnikov alkylsilane (R_3Si—C—C—R′) in the presence of a hyponitrite.[656] Transfer hydrosilation is known.[657]

[637] Pines, H.; Wunderlich, D. *J. Am. Chem. Soc.* ***1958***, *80*, 6001.
[638] See Pines, H.; Stalick, W.M. *Tetrahedron Lett.* ***1968***, 3723.
[639] Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* ***2002***, *35*, 826.
[640] DeBoef, B.; Pastine, S.J.; Sames, D. *J. Am. Chem. Soc.* ***2004***, *126*, 6556.
[641] Buch, F.; Brettar, J.; Harder, S. *Angew. Chem. Int. Ed.* ***2006***, *45*, 2741. See Chen, J.; Cao, M.; Cheng, B.; Lu, Z. *Synlett* ***2015***, *26*, 2332.
[642] Mutoh, Y.; Mohara, Y.; Saito, S. *Org. Lett.* ***2017***, *19*, 5204.
[643] See Tsuchiya, Y.; Uchimura, H.; Kobayashi, K.; Nishiyama, H. *Synlett* ***2004***, 2099.
[644] Han, J.W.; Hayashi, T. *Tetrahedron: Asymmetry* ***2014***, *25*, 479.
[645] Zhao, W.-G.; Hua, R. *Eur. J. Org. Chem.* ***2006***, 5495.
[646] Takaki, K.; Sonoda, K.; Kousaka, T.; Koshoji, G.; Shishido, T.; Takehira, K. *Tetrahedron Lett.* ***2001***, *42*, 9211.
[647] Molander, G.A.; Julius, M. *J. Org. Chem.* ***1992***, *57*, 6347.
[648] See; Rivero-Crespo, M.A.; Leyva-Pérez, A.; Corma, A. *Chem. Eur. J.* ***2017***, *23*, 1702; Dierick, S.; Vercruysse, E.; Berthon-Gelloz, G.; Markó, I.E. *Chem. Eur. J.* ***2015***, *21*, 17073; Pagliaro, M.; Ciriminna, R.; Pandarus, V.; Béland, F. *Eur. J. Org. Chem.* ***2013***, 6227.
[649] Cheng, B.; Lu, P.; Zhang, H.; Cheng, X.; Lu, Z. *J. Am. Chem. Soc.* ***2017***, *139*, 9439.
[650] Peng, D.; Zhang, Y.; Du, X.; Zhang, L.; Leng, X.; Walter, M.D.; Huang, Z. *J. Am. Chem. Soc.* ***2013***, *135*, 19154; Chen, J.; Cheng, B.; Cao, M.; Lu, Z. *Angew. Chem. Int. Ed.* ***2015***, *54*, 4661.
[651] Nakamura, S.; Uchiyama, M. *J. Am. Chem. Soc.* ***2007***, *129*, 28; Lipshutz, B.H.; Lower, A.; Kucejko, R.J.; Noson, K. *Org. Lett.* ***2006***, *8*, 2969.
[652] Hou, Z.; Zhang, Y.; Tardif, O.; Wakatsuki, Y. *J. Am. Chem. Soc.* ***2001***, *123*, 9216.
[653] Rubin, M.; Schwier, T.; Gevorgyan, V. *J. Org. Chem.* ***2002***, *67*, 1936.
[654] Miura, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* ***1993***, *66*, 2356.
[655] Kopping, B.; Chatgilialoglu, C.; Zehnder, M.; Giese, B. *J. Org. Chem.* ***1992***, *57*, 3994. See Palframan, M.J.; Parsons, A.F.; Johnson, P. *Synlett* ***2011***, *22*, 2811.
[656] Dang, H.-S.; Roberts, B.P. *Tetrahedron Lett.* ***1995***, *36*, 2875.
[657] Oestreich, M. *Angew. Chem. Int. Ed.* ***2016***, *55*, 494.

Silanes add to dienes with a Pd catalyst, and asymmetric induction is achieved by using a chiral additive.[658] Enantioselective hydrosilation has been reported using frustrated Lewis pairs.[659] Dienes reacted with Zr,[660] Ru,[661] or Pt[662] compounds and silanes to produce cyclic compounds in which the silyl group has also added to one C=C unit. Rhodium compounds allow silanes to add to enamides to give the α-silyl amide.[663] Formation of silanes via reaction with alkenes can be followed by reaction with fluoride ion and then oxidation to give an alcohol[664] (see **10-16**; *Tamao-Fleming oxidation*). A variation of this reaction generated allylic silanes from terminal alkenes and a dianion-type zincate using a Ti catalyst.[665]

The reaction of enynes with Me_2SHCl, using a Pd catalyst, showed selectivity for hydrosilation of the triple bond rather than the alkene moiety.[666] The use of an Ir catalyst allowed selectivity for the alkene unit rather than the alkyne.[667] Hydrosilation of alkynes is accomplished using transition metal catalysts[668] such as Ru,[669] Pt,[670] Ti,[671] Pd,[672] Cu,[673] Co,[674] or Ir.[675] Organocatalysts have been used as well.[676] Siloxanes such as $(RO)_3SiH$ add to alkynes with a Ru catalyst to give the corresponding vinylsilane.[677] The reaction of Cl_2MeSiH and terminal alkynes, in ethanol/triethylamine with a Ru catalyst, give primarily the Markovnikov vinylsilane.[678] However, Et_3SiH adds to terminal alkynes with a Rh[679] or a Pt[680] catalyst to give the anti-Markovnikov vinylsilane. Intramolecular reactions are possible, such as the reaction of but-3-yn-1-yldimethyl(phenyl)silane with $HfClO_4$ to give the cyclized vinylsilane, 1,1-dimethyl-4-phenyl-2,3-dihydro-1*H*-silole. The addition of $PhMe_2SiB(Pin)$ to terminal alkynes using a Cu catalyst gave primarily Markovnikov

[658] Hatanaka, Y.; Goda, K.; Yamashita, F.; Hiyama, T. *Tetrahedron Lett.* ***1994***, *35*, 7981.
[659] Chen, D.; Leich, V.; Pan, F.; Klankermayer, J. *Chem. Eur. J.* ***2012***, *18*, 5184.
[660] Molander, G.A.; Corrette, C.P. *Tetrahedron Lett.* ***1998***, *39*, 5011.
[661] Szudkowska-Frątczak, J.; Marciniec, B.; Hreczycho, G.; Kubicki, M.; Pawluć, P. *Org. Lett.* ***2015***, *17*, 2366.
[662] Parker, S.E.; Börgel, J.; Ritter, T. *J. Am. Chem. Soc.* ***2014***, *136*, 4857.
[663] Murai, T.; Oda, T.; Kimura, F.; Onishi, H.; Kanda, T.; Kato, S. *J. Chem. Soc., Chem. Commun.* ***1994***, 2143.
[664] Jensen, J.F.; Svendsen, B.H.; la Cour, T.V.; Pedersen, H.L.; Johannsen, M. *J. Am. Chem. Soc.* ***2002***, *124*, 4558.
[665] Nakamura, S.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* ***2005***, *127*, 13116.
[666] Zhou, H.; Moberg, C. *Org. Lett.* ***2013***, *15*, 1444.
[667] Muchnij, J.A.; Kwaramba, F.B.; Rahaim, R.J. *Org. Lett.* ***2014***, *16*, 1330.
[668] For a mechanistic discussion, see Shirobokov, O.G.; Kuzmina, L.G.; Nikonov, G.I. *J. Am. Chem. Soc.* ***2011***, *133*, 6487.
[669] Trost, B.M.; Ball, Z.T. *J. Am. Chem. Soc.* ***2005***, *127*, 17644; Maifeld, S.V.; Tran, M.N.; Lee, D. *Tetrahedron Lett.* ***2005***, *46*, 105.
[670] Rooke, D.A.; Menard, Z.A.;. Ferreira, E.M. *Tetrahedron* ***2014***, *70*, 4232; Rivero-Crespo, M.A.; Leyva-Pérez, A.; Corma, A. *Chem. Eur. J.* ***2017***, *23*, 1702.
[671] Takahashi, T.; Bao, F.; Gao, G.; Ogasawara, M. *Org. Lett.* ***2003***, *5*, 3479.
[672] Sumida, Y.; Kato, T.; Yoshida, S.; Hosoya, T. *Org. Lett.* ***2012***, *14*, 1552.
[673] García-Rubia, A.; Romero-Revilla, J.A.; Mauleón, P.; Arrayás, R.G.; Carretero, J.C. *J. Am. Chem. Soc.* ***2015***, *137*, 6857.
[674] Liu, Y.; Deng, L. *J. Am. Chem. Soc.* ***2017***, *139*, 1798. For a solvent-free reaction, see Chen, C.; Hecht, M.B.; Kavara, A.; Brennessel, W.W.; Mercado, B.Q.; Weix, D.J.; Holland, P.L. *J. Am. Chem. Soc.* ***2015***, *137*, 13244; Rivera-Hernández, A.; Fallon, B.J.; Ventre, S.; Simon, C.; Tremblay, M.-H.; Gontard, G.; Derat, E.; Amatore, M.; Aubert, C.; Petit, M. *Org. Lett.* ***2016***, *18*, 4242; Guo, J.; Lu, Z. *Angew. Chem. Int. Ed.* ***2016***, *55*, 10835. For a *Z* selective reaction, see Teo, W.J.; Wang, C.; Tan, Y.W.; Ge, S. *Angew. Chem. Int. Ed.* ***2017***, *56*, 4328.
[675] Miyake, Y.; Isomura, E.; Iyoda, M. *Chem. Lett.* ***2006***, *35*, 836.
[676] Berthon-Gelloz, G.; Schumers, J.-M.; De Bo, G.; Markó, I.E. *J. Org. Chem.* ***2008***, *73*, 4190.
[677] Trost, B.M.; Ball, Z.T. *J. Am. Chem. Soc.* ***2001***, *123*, 12726.
[678] Kawanami, Y.; Sonoda, Y.; Mori, T.; Yamamoto, K. *Org. Lett.* ***2002***, *4*, 2825.
[679] Sato, A.; Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* ***2004***, *6*, 2217.
[680] Wu, W.; Li, C.-J. *Chem. Commun.* ***2003***, 1668.

addition and the vinylsilane.[681] The hydrosilation of alkynes with trialkylsilanes gave the vinylsilane when treated with Lewis acids such as organofluorophosphonium salts.[682]

Allenes reacted with trialkylsilanes with a Ni catalyst to give the vinylsilane, whereas using a Pd catalyst gave the allylic silane.[683] Transition metal catalysts such as Au,[684] Pd,[685] or Cu[686] have been used for the regioselective hydrosilation of allenes.

15-15 Addition of Alkenes and/or Alkynes to Alkenes and/or Alkynes

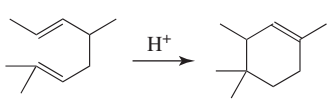
$$CH_2{=}CH_2 + CH_2{=}CH_2 \xrightarrow{H^+} CH_2{=}CHCH_2CH_3$$

Alkenes can be coupled by acid catalysts in the presence of certain substrates, to give an alkene.[687] Transition metal catalysts can also be used.[688] Metal catalysts include alkylaluminum compounds (known as *Ziegler catalysts*)[689] and Rh,[690] Fe,[691] or Ni[692] catalysts. α-Alkenes add to dienes in a 1,4-manner in the presence of an Fe catalyst.[693] The 1,4-addition of alkenes to conjugated dienes to give nonconjugated dienes[694] occurs with various catalysts, as does the dimerization of buta-1,3-dienes to octatrienes.[695] Ethylene adds to alkenes to form a new alkene in the presence of a Ni[696] or a Zr catalyst,[697] and to alkynes in the presence of a Ru catalyst[698] to form a diene. The addition of alkenes to alkenes[699] can also be mediated by bases.[700] Vinyl halides added to conjugated dienes in the presence of a Pd catalyst to give the nonconjugated diene.[701] Alkenes with an electron-withdrawing group added to bicyclic alkenes in the present of a Ru catalyst.[702] The Ti-catalyzed coupling of vinyl sulfones and allenes gave 1,4-dienes.[703] The Pd-catalyzed cyclization reactions of allenes with alkenes or alkynes has been reviewed.[704] The Cu-catalyzed hydroallylation of

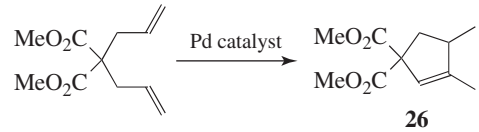
[681] Wang, P.; Yeo, X.-L.; Loh, T.-P. *J. Am. Chem. Soc.* ***2011***, *133*, 1254.
[682] Pérez, M.; Hounjet, L.J.; Caputo, C.B.; Dobrovetsky, R.; Stephan, D.W. *J. Am. Chem. Soc.* ***2013***, *135*, 18308.
[683] See Miller, Z.D.; Dorel, R.; Montgomery, J. *Angew. Chem. Int. Ed.* ***2015***, *54*, 9088.
[684] Kidonakis, M.; Stratakis, M. *Org. Lett.* ***2015***, *17*, 4538.
[685] Tafazolian, H.; Schmidt, J.A.R. *Chem. Commun.* ***2015***, *51*, 5943.
[686] Pashikanti, S.; Calderone, J.A.; Nguyen, M.K.; Sibley, C.D.; Santos, W.L. *Org. Lett.* ***2016***, *18*, 2443.
[687] See Onsager, O.; Johansen, J.E. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 3, Wiley, NY, ***1985***, pp. 205–257.
[688] Pillai, S.M.; Ravindranathan, M.; Sivaram, S. *Chem. Rev.* ***1986***, *86*, 353; Heck, R.F. *Organotransition Metal Chemistry*, Academic Press, NY, ***1974***, pp. 84–94, 150–157. Also see, Kaur, G.; Manju, K.; Trehan, S. *Chem. Commun.* ***1996***, 581.
[689] Fischer, K.; Jonas, K.; Misbach, P.; Stabba, R.; Wilke, G. *Angew. Chem. Int. Ed.* ***1973***, *12*, 943.
[690] Takahashi, N.; Okura, I.; Keii, T. *J. Am. Chem. Soc.* ***1975***, *97*, 7489.
[691] Takacs, J.M.; Myoung, Y.C. *Tetrahedron Lett.* ***1992***, *33*, 317.
[692] Ho, C.-Y.; Schleicher, K.D.; Jamison, T.F. *Pure Appl. Chem.* ***2008***, *80*, 929.
[693] Moreau, B.; Wu, J.Y.; Ritter, T. *Org. Lett.* ***2009***, *11*, 337.
[694] Hilt, G.; du Mesnil, F.-X.; Lüers, S. *Angew. Chem. Int. Ed.* ***2001***, *40*, 387. For a review, see Su, A.C.L. *Adv. Organomet. Chem.* ***1979***, *17*, 269.
[695] See Denis, P.; Jean, A.; Croizy, J.F.; Mortreux, A.; Petit, F. *J. Am. Chem. Soc.* ***1990***, *112*, 1292.
[696] Nomura, N.; Jin, J.; Park, H.; RajanBabu, T.V. *J. Am. Chem. Soc.* ***1998***, *120*, 459.
[697] Takahashi, T.; Xi, Z.; Fischer, R.; Huo, S.; Xi, C.; Nakajima, K. *J. Am. Chem. Soc.* ***1997***, *119*, 4561.
[698] Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* ***1997***, *119*, 12388.
[699] Fel'dblyum, V.Sh.; Obeshchalova, N.V. *Russ. Chem. Rev.* ***1968***, *37*, 789.
[700] For a review, see Pines, H. *Synthesis* ***1974***, 309.
[701] Saini, V.; O'Dair, M.; Sigman, M.S. *J. Am. Chem. Soc.* ***2015***, *137*, 608.
[702] Simon, M.-O.; Darses, S. *J. Org. Chem.* ***2013***, *78*, 9981.
[703] Oishi, S.; Hatano, K.; Tsubouchi, A.; Takeda, T. *Chem. Commun.* ***2011***, *47*, 11639.
[704] Ye, J.; Ma, S. *Acc. Chem. Res.* ***2014***, *47*, 989; Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* ***2011***, *111*, 1954; Krause, N.; Winter, C. *Chem. Rev.* ***2011***, *111*, 1994.

allenes using allylic chlorides and hydrosilanes has been reported.[705] With an Fe catalyst and $PhSiH_3$, unactivated alkenes were coupled to electron-deficient alkenes to give the saturated linkage.[706] When the reaction is applied to enynes, compounds are formed using various catalysts, but with only one double bond.[707]

This reaction can also be done intramolecularly, as in the formation of **25** by treatment with an acid catalyst. Transition metal catalysts can be used for cyclization of diynes to (*E*,*E*)-exocyclic dienes, including a Zr,[708] Rh,[709] Ru,[710] Au,[711] or Pt[712] complexes. Carbocyclization was reported using Pd,[713] Rh,[714] Ru,[715] Ir,[716] Y,[717] Ti,[718] or a Zr[719] catalyst. In some cases, internal coupling of two alkenes can form larger rings.[720] A Pd-catalyzed cyclization is known in which dienes are converted to cyclopentene derivatives such as **26**.[721]



25



26

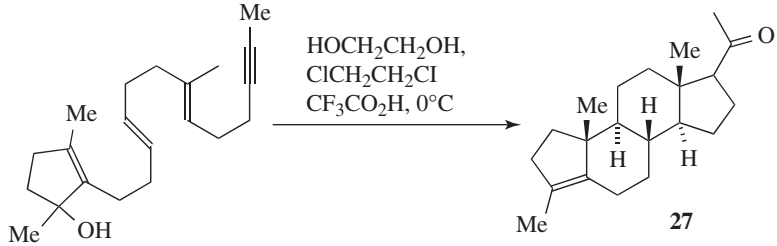
A molecule containing two distal conjugated diene units was cyclized to give a bicyclic molecule with an exocyclic double bond using a Pd catalyst.[722] A Ni catalyst converted a similar system to a saturated five-membered ring containing an allylic group and a vinyl group.[723] Spirocyclic compounds can be prepared from enynes in this manner using formic acid and a Pd catalyst.[724]

The Pd-catalyzed cyclization of enynes in the presence of $ArB(OH)_2$ gave the arylated cyclized product.[725] The intramolecular cyclization reaction of one alkyne to an alkyne

[705] Fujihara, T.; Yokata, K.; Terao, J.; Tsuji, Y. *Chem. Commun.* ***2017***, *54*, 7898.
[706] Lo, J.C.; Yabe, Y.; Baran, P.S. *J. Am. Chem. Soc.* ***2014***, *136*, 1304.
[707] See Lee, P.H.; Kim, S.; Lee, K.; Seomoon, D.; Kim, H.; Lee, S.; Kim, M.; Han, M.; Noh, K.; Livinghouse, T. *Org. Lett.* ***2004***, *6*, 4825.
[708] Nugent, W.A.; Thorn, D.L.; Harlow, R.L. *J. Am. Chem. Soc.* ***1987***, *109*, 2788. See Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* ***1989***, *111*, 6478.
[709] Jang, H.-Y.; Krische, M.J. *J. Am. Chem. Soc.* ***2004***, *126*, 7875.
[710] Varela, J.A.; Rubín, S.G.; González-Rodríguez, C.; Castedo, L.; Saá, C. *J. Am. Chem. Soc.* ***2006***, *128*, 9263.
[711] Zhang, C.; Cui, D.-M.; Yao, L.-Y.; Wang, B.-S.; Hu, Y.-Z.; Hayashi, T. *J. Org. Chem.* ***2008***, *73*, 7811.
[712] Méndez, M.; Muñoz, M.P.; Nevado, C.; Cárdenas, D.J.; Echavarren, A.M. *J. Am. Chem. Soc.* ***2001***, *123*, 10511. See also, Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* ***2001***, *123*, 11863.
[713] Kende, A.S.; Mota Nelson, C.E.; Fuchs, S. *Tetrahedron Lett.* ***2005***, *46*, 8149; See Ohno, H.; Takeoka, Y.; Kadoh, Y.; Miyamura, K.; Tanaka, T. *J. Org. Chem.* ***2004***, *69*, 4541.
[714] See Cao, P.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* ***2000***, *122*, 6490.
[715] Fernández-Rivas, C.; Méndez, M.; Echavarren, A.M. *J. Am. Chem. Soc.* ***2000***, *122*, 1221.
[716] Chatani, N.; Inoue, H.; Morimoto, T.; Muto, T.; Murai, S. *J. Org. Chem.* ***2001***, *66*, 4433.
[717] Molander, G.A.; Dowdy, E.D.; Schumann, H. *J. Org. Chem.* ***1998***, *63*, 3386.
[718] Okamoto, S.; Livinghouse, T. *J. Am. Chem. Soc.* ***2000***, *122*, 1223. See Hart, D.J.; Bennett, C.E. *Org. Lett.* ***2003***, *5*, 1499.
[719] Miura, K.; Funatsu, M.; Saito, H.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* ***1996***, *37*, 9059. Also see, Maye, J.P.; Negishi, E. *Tetrahedron Lett.* ***1993***, *34*, 3359.
[720] Toyota, M.; Majo, V.J.; Ihara, M. *Tetrahedron Lett.* ***2001***, *42*, 1555.
[721] Kisanga, P.; Goj, L.A.; Widenhoefer, R.A. *J. Org. Chem.* ***2001***, *66*, 635.
[722] Takacs, J.M.; Leonov, A.P. *Org. Lett.* ***2003***, *5*, 4317.
[723] Takimoto, M.; Nakamura, Y.; Kimura, K.; Mori, M. *J. Am. Chem. Soc.* ***2004***, *126*, 5956.
[724] Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* ***2003***, *125*, 4704.
[725] Jiang, M.; Jiang, T.; Bäckvall, J.-E. *Org. Lett.* ***2012***, *14*, 3538.

unit within the same molecule, catalyzed by a Pd complex, gave the enyne product with an exocyclic methylene unit.[726] The cycloisomerization of an alkyne with a distal vinyl group, using a gold catalyst, gave the cyclized product.[727] The Au-catalyzed cycloisomerization of 1,5-enynes gave the cyclic alkene.[728]

Processes of this kind are important in the biosynthesis of steroids and tetra- and pentacyclic terpenes, illustrated by the conversion of squalene 2,3-oxide to dammaradienol by enzymatic catalysis. The squalene → lanosterol biosynthesis (which is a key step in the biosynthesis of cholesterol) is similar. The idea that the biosynthesis of such compounds involves this type of multiple ring closing was proposed in 1955 and is known as the *Stork-Eschenmoser hypothesis*.[729] Such reactions can also be carried out in the laboratory, without enzymes.[730] Cation-stabilizing groups were incorporated at positions at which positive charges develop by Johnson and co-workers, and as many as four rings could be closed stereoselectively in high yield, in one operation.[731] An example is formation of **27**,[732] by what is known as the *Johnson polyene cyclization*.[733] Lewis acids can be used to initiate this cyclization.[734]



27

A radical cyclization approach (**15-26**) to polyene cyclization using a seleno ester anchor gave a tetracyclic system.[735] Both InI_3 and $InBr_3$ catalyzed the π activation of C≡C bonds to initiate the conversion of polyene molecules that contain a chiral propargylic alcohol unit to the corresponding polycyclic compound.[736] A Bi-catalyzed cyclization of trienes to bicyclic hydrocarbons was reported.[737] A hypervalent iodine polycyclization process of an aryl derivative with a pendant enyne moiety has been reported.[738] An alkene-terminated cation-alkene cascade reaction was initiated by a dicationic Pt complex and gave a polycyclic compound.[739]

[726] Trost, B.M.; Masters, J.T.; Le Vaillant, F.; Lumb, J.-P. *J. Org. Chem.* ***2016***, *81*, 10023.
[727] Inagaki, F.; Matsumoto, C.; Okada, Y.; Maruyama, N.; Mukai, C. *Angew. Chem. Int. Ed.* ***2015***, *54*, 818.
[728] Chen, G.-Q.; Fang, W.; Wei, Y.; Tang, X.-Y.; Shi, M. *Chem. Commun.* ***2016***, *52*, 10799.
[729] Stork, G.; Burgstahler, A.W. *J. Am. Chem. Soc.* ***1955***, *77*, 5068; Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* ***1955***, *38*, 1890.
[730] Gnonlonfoun, N. *Bull. Soc. Chim. Fr.* ***1988***, 862; Johnson, W.S. *Angew. Chem. Int. Ed.* ***1976***, *15*, 9; van Tamelen, E.E. *Acc. Chem. Res.* ***1975***, *8*, 152.
[731] Guay, D.; Johnson, W.S.; Schubert, U. *J. Org. Chem.* ***1989***, *54*, 4731 and references cited therein.
[732] Johnson, W.S.; Gravestock, M.B.; McCarry, B.E. *J. Am. Chem. Soc.* ***1971***, *93*, 4332.
[733] Johnson, W.S. *Acc. Chem. Res.* ***1968***, *1*, 1; Kametani, T.; Fukumoto, K. *Synthesis* ***1972***, 657.
[734] Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* ***1999***, *121*, 4906.
[735] Chen, L.; Gill, G.B.; Pattenden, G. *Tetrahedron Lett.* ***1994***, *35*, 2593.
[736] Surendra, K.; Qiu, W.; Corey, E.J. *J. Am. Chem. Soc.* ***2011***, *133*, 9724. See Hong, Y.J.; Tantillo, D.J. *J. Am. Chem. Soc.* ***2011***, *133*, 18249.
[737] Godeau, J.; Olivero, S.; Antoniotti, S.; Duñach, E. *Org. Lett.* ***2011***, *13*, 3320.
[738] Desjardins, S.; Andrez, J.-C.; Canesi, S. *Org. Lett.* ***2011***, *13*, 3406. Also see Rivera-Fuentes, P.; von Wantoch Rekowski, M.; Schweizer, W.B.; Gisselbrecht, J.-P.; Boudon, C.; Diederich, F. *Org. Lett.* ***2012***, *14*, 4066.
[739] Sokol, J.G.; Korapala, C.S.; White, P.S.; Becker, J.J.; Gagné, M.R. *Angew. Chem. Int. Ed.* ***2011***, *50*, 5658.

In the presence of cuprous chloride and ammonium chloride, acetylene undergoes self-coupling to give vinylacetylene. Alkynes are coupled to dienes to give enynes in the presence of a Ni catalyst.[740] Nonconjugated enynes were prepared by the Cu-catalyzed coupling of propargyl alcohols and alkenes.[741] Conjugated enynes were prepared by the Co-catalyzed, Zn-mediated, coupling of terminal alkenes and allenes.[742] A Rh-catalyzed coupling reaction of alkenes and electron-deficient internal alkynes leads to 1,3-dienes.[743] Alkynes can also be coupled to allylic silyl ethers with a Ru catalyst to give dienes.[744] Other alkyne-allylic coupling reactions are known to give dienes.[745] The reaction of an alkyne with a *Grignard reagent*, followed by an Fe complex and then an alkene, leads to enynes.[746] Alkynes are coupled to give enynes using Ni,[747] Pd,[748] Lu,[749] and Ru[750] catalysts. Alkynes added to allylic *N*-tosylamines using a Ru catalyst to give the alkenyl enamide.[751] Alkynes with a distal vinyl group were cyclized to a ring compound with an exo-methylene group using a Ru catalyst and a catalytic amount of Ag in ethanol.[752] *trans*-Disubstituted alkenes were prepared by the Co-catalyzed coupling of alkynes and activated alkenes.[753] Alkynes were coupled to conjugated esters using a Ru catalyst to give the conjugated dienyl ester.[754] The Ni-catalyzed, three-component cross-trimerization reaction between triisopropylsilylacetylene, diarylacetylene, and a terminal alkyne gave the diene-yne product via oxidative addition of the terminal silylacetylene.[755] The Cu-catalyzed coupling of potassium alkynyl carboxylates with 1,1-dibromo-1-alkenes gave unsymmetrical 1,3-diyne and 1,3,5-triyne derivatives.[756]

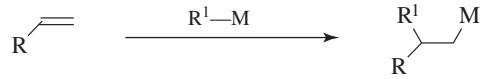
Enynes gave cyclic compounds with an endocyclic double bond conjugated to another alkene unit (a conjugated diene) when treated with $GaCl_3$[757] or a Pt catalyst in an ionic liquid.[758] Enynes can also be converted to cyclic and bicyclic compounds using Au,[759] Rh,[760] Fe,[761] or Pd[762] catalysts. The Rh-catalyzed cyclization of 1,6-enynes, triggered by

[740] Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* ***2008***, *130*, 5410; Buchwald, S.L.; Nielsen, R.B. *J. Am. Chem. Soc.* ***1989***, *111*, 2870.
[741] Huang, G.B.; Wang, X.; Pan, Y.-M.; Wang, H.-S.; Yao, G.-Y.; Zhang, Y. *J. Org. Chem.* ***2013***, *78*, 2742.
[742] Sawano, T.; Ou, K.; Nishimura, T.; Hayashi, T. *J. Org. Chem.* ***2013***, *78*, 8986.
[743] Shibata, Y.; Hirano, M.; Tanaka, K. *Org. Lett.* ***2008***, *10*, 2829; Katagiri, T.; Tsurugi, H.; Satoh, T.; Miura, M. *Chem. Commun.* ***2008***, 3405.
[744] Trost, B.M.; Surivet, J.-P.; Toste, F.D. *J. Am. Chem. Soc.* ***2001***, *123*, 2897.
[745] Giessert, A.J.; Snyder, L.; Markham, J.; Diver, S.T. *Org. Lett.* ***2003***, *5*, 1793.
[746] Hatakeyama, T.; Yoshimoto, Y.; Gabriel, T.; Nakamura, M. *Org. Lett.* ***2008***, *10*, 5341.
[747] Ogoshi, S.; Ueta, M.; Oka, M.-a.; Kurosawa, H. *Chem. Commun.* ***2004***, 2732.
[748] Yang, C.; Nolan, S.P. *J. Org. Chem.* ***2002***, *67*, 591.
[749] Nishiura, M.; Hou, Z.; Wakatsuki, Y.; Yamaki, T.; Miyamoto, T. *J. Am. Chem. Soc.* ***2003***, *125*, 1184.
[750] Bassetti, M.; Pasquini, C.; Raneri, A.; Rosato, D. *J. Org. Chem.* ***2007***, *72*, 4558.
[751] Trost, B.M.; Cregg, J.J. *J. Am. Chem. Soc.* ***2015***, *137*, 620.
[752] Park, J.H.; Kim, S.M.; Chung, Y.K. *Chem. Eur. J.* ***2011***, *17*, 10852.
[753] Mannathan, S.; Cheng, C.-H. *Chem. Eur. J.* ***2012***, *18*, 11771.
[754] Zhang, J.; Ugrinov, A.; Zhang, Y.; Zhao, P. *Angew. Chem. Int. Ed.* ***2014***, *53*, 8437.
[755] Ogata, K.; Atsuumi, Y.; Fukuzawa, S. *Org. Lett.* ***2011***, *13*, 122.
[756] Huang, Z.; Shang, R.; Zhang, Z.-R.; Tan, X.-D.; Xiao, X.; Fu, Y. *J. Org. Chem.* ***2013***, *78*, 4551.
[757] Chatani, N.; Inoue, H.; Kotsuma, T.; Morai, S. *J. Am. Chem. Soc.* ***2002***, *124*, 10294.
[758] Miyanohana, Y.; Inoue, H.; Chatani, N. *J. Org. Chem.* ***2004***, *69*, 8541.
[759] See Zhang, L.; Kozmin, S.A. *J. Am. Chem. Soc.* ***2005***, *127*, 6962.
[760] Kim, H.; Lee, C. *J. Am. Chem. Soc.* ***2006***, *128*, 6336. See Denmark, S.E.; Liu, J.H.-C. *J. Am. Chem. Soc.* ***2007***, *129*, 3737.
[761] Fürstner, A.; Martin, R.; Majima, K. *J. Am. Chem. Soc.* ***2005***, *127*, 12236.
[762] Corkey, B.K.; Toste, F.D. *J. Am. Chem. Soc.* ***2007***, *129*, 2764.

arylboronic acids, leads to rings with an exocyclic alkylidene group.[763] The reaction has been carried out internally to convert diynes to large-ring cycloalkynes with an exocyclic double bond.[764] Enynes having a conjugated alkene unit also undergo this reaction in the presence of $ZnBr_2$.[765] Using mercury(II) triflate in water, cyclization leads to five-membered rings having an exocyclic double bond and a pendant alcohol group.[766]

OS **VIII**, 190, 381, 505; **IX**, 310.

15-16 Metallo-Alkylation of Non-Conjugated Double and Triple Bonds



In the absence of a transition metal catalyst, neither *Grignard reagents* nor lithium dialkylcopper reagents generally add to ordinary C=C double bonds to form a new organometallic.[767] Cyclopropenes are an exception, and an excess of a Grignard reagent will add at low temperatures.[768] However, active Grignard reagents (benzylic, allylic) also add to the double bonds of allylic amines,[769] and of allylic and homoallylic alcohols,[770] as well as to the triple bonds of propargyl alcohols and certain other alkynols.[771] Grignard reagents can add to double bonds that are susceptible to nucleophilic attack (e.g., fluoroalkenes and tetracyanoethylene).[772] Transition metal complexes facilitate the addition of Grignard reagents to alkenes, and typical metals include Ti,[773] Mn,[774] Zr,[775] Ni,[776] Fe,[777] and Cu[778] compounds. Cyclopropene derivatives also react with CuI and then allyl bromide.[779]

The Fe/Cu-catalyzed coupling of alkynes and alkyl Grignard reagents (RMgX) led to addition of the addition of "R" and "MgX" to the π bond (carbomagnesiation) and formation of a vinyl Grignard reagent.[780] The Ag-catalyzed carbomagnesiation of alkynes with alkyl halides and Grignard reagents has been reported.[781] The Pd[782] and also the

[763] Miura, T.; Shimada, M.; Murakami, M. *J. Am. Chem. Soc.* ***2005***, *127*, 1094.
[764] Trost, B.M.; Matusbara, S.; Carninji, J.J. *J. Am. Chem. Soc.* ***1989***, *111*, 8745.
[765] Yamazaki, S.; Yamada, K.; Yamabe, S.; Yamamoto, K. *J. Org. Chem.* ***2002***, *67*, 2889.
[766] Nishizawa, M.; Yadav, V.K.; Skwarczynski, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* ***2003***, *5*, 1609.
[767] Wardell, J.L.; Paterson, E.S. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 219–338 (pp. 268–296).
[768] Liu, X.; Fox, J.M. *J. Am. Chem. Soc.* ***2006***, *128*, 5600.
[769] Richey Jr., H.G.; Moses, L.M.; Domalski, M.S.; Erickson, W.F.; Heyn, A.S. *J. Org. Chem.* ***1981***, *46*, 3773.
[770] Kang, J. *Organometallics* ***1984***, *3*, 525.
[771] Eisch, J.J.; Merkley, J.H. *J. Am. Chem. Soc.* ***1979***, *101*, 1148. See also, Duboudin, J.G.; Jousseaume, B. *J. Organomet. Chem.* ***1979***, *168*, 1; *Synth. Commun.* ***1979***, *9*, 53.
[772] Gardner, H.C.; Kochi, J.K. *J. Am. Chem. Soc.* ***1976***, *98*, 558.
[773] See Sato, F. *J. Organomet. Chem.* ***1985***, *285*, 53–64; Dzhemilev, U.M.; D'yakonov, V.A.; Khafizova, L.O.; Ibragimov, A.G. *Russ. J. Org. Chem.* ***2005***, *41*, 352.
[774] Yorimitsu, H.; Tang, J.; Okada, K.; Shinokubo, H.; Oshima, K. *Chem. Lett.* ***1998***, 11.
[775] de Armas, J.; Hoveyda, A.H. *Org. Lett.* ***2001***, *3*, 2097.
[776] Pellet-Rostaing, S.; Saluzzo, C.; Ter Halle, R.; Breuzard, J.; Vial, L.; LeGuyader, F.; Lemaire, M. *Tetrahedron: Asymmetry* ***2001***, *12*, 1983.
[777] Zhang, D.; Ready, J.M. *J. Am. Chem. Soc.* ***2006***, *128*, *1*5050.
[778] Shirakawa, E.; Yamagami, T.; Kimura, T.; Yamaguchi, S.; Hayashi, T. *J. Am. Chem. Soc.* ***2005***, *127*, 17164.
[779] Yan, N.; Liu, X.; Fox, J.M. *J. Org. Chem.* ***2008***, *73*, 563.
[780] Shirakawa, E.; Ikeda, D.; Masui, S.; Yoshida, M.; Hayashi, T. *J. Am. Chem. Soc.* ***2012***, *134*, 272.
[781] Kambe, N.; Moriwaki, Y.; Fujii, Y.; Iwasaki, T.; Terao, J. *Org. Lett.* ***2011***, *13*, 4656.
[782] Krämer, K.; Leong, P.; Lautens, M. *Org. Lett.* ***2011***, *13*, 819.

Cu[783]-catalyzed carbozincation of cyclopropanes has been reported as has the Co-catalyzed carbozincation of ynamides.[784] The hydroalumination and carbocupration of alkynes has been reported.[785] The Ta-catalyzed carboalumination of alkenes has been reported.[786] An arylmagnesiation of alkynes has been reported.[787] The Cu-catalyzed carbomagnesiation of cyclopropanes has been reported.[788]

The intramolecular addition of RMgX to completely unactivated double and triple bonds has been demonstrated.[789] The reaction of tosylates bearing a remote alkene unit and a Grignard reagent leads to cyclization when a Zr catalyst is used.[790] The intramolecular addition of a CH_2Br unit to the C=C unit of an allylic ether was accomplished using PhMgBr and a Co catalyst, giving a functionalized tetrahydrofuran and incorporation of the phenyl group on the C=C unit as well.[791]

Conjugated dienes react with arylmagnesium halides, Ph_3SiCl, and a Pd catalyst to give a coupling product involving the reaction of 2 equivalents of the diene and incorporation of two $SiPh_3$ units.[792] The Cr-catalyzed formation of arylmagnesium compounds[793] and the Rh-catalyzed hydroarylation[794] of alkynes are also known. The Pd-catalyzed hydroarylation[795] of alkynes is possible using arenediazonium salts as substrates[796] or hydroarylation of 1,3-dienes with boronic acids.[797]

15-17 Addition of Alkyls or Aryls to Alkenes (Hydroalkylation; Hydroarylation)

The addition of alkyl groups to alkenes or alkynes[798] leads to saturated hydrocarbon fragments, or alkylated alkenes.[799] Such a reaction is known as hydroalkylation, in which an alkyl group, R, and a hydrogen atom add across the π bond.[800] Such a reaction usually involves an organometallic reagent, and often the formation of a new organometallic that reacts with a proton source.

Organolithium reagents add to the double and triple bonds of allylic and propargylic alcohols[801] (tetramethylethylenediamine is a catalyst) and also to certain other alkenes containing hetero groups, such as OR, NR_2, or SR. Mixing an organolithium reagent with

[783] Müller, D.S.; Marek, I. *J. Am. Chem. Soc.* ***2015***, *137*, 15415.
[784] Sallio, R.; Corpet, M.; Habert, L.; Durandetti, M.; Gosmini, C.; Gillaizeau, I. *J. Org. Chem.* ***2017***, *82*, 1254.
[785] Ortial, S.; Montchamp, J.-L. *Org. Lett.* ***2011***, *13*, 3134.
[786] Sultanov, R.M.; Samoilova, E.V.; Popod'ko, N.R.; Tulyabaev, A.R.; Sabirov, D.Sh.; Dzhemilev, U.M. *Tetrahedron Lett.* ***2013***, *54*, 6619.
[787] Xue, F.; Zhao, J.; Hor, T.S.A. *Chem. Commun.* ***2013***, *49*, 10121.
[788] Dian, L.; Müller, D.S.; Marek, I. *Angew. Chem. Int. Ed.* ***2017***, *56*, 6783.
[789] Hill, E.A.; Myers, M.M. *J. Organomet. Chem.* ***1979***, *173*, 1. See also, Yang, D.; Gu, S.; Yan, Y.-L.; Zhu, N.-Y.; Cheung, K.-K. *J. Am. Chem. Soc.* ***2001***, *123*, 8612.
[790] Cesati III, R.R.; de Armas, J.; Hoveyda, A.H. *Org. Lett.* ***2002***, *4*, 395.
[791] Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* ***2001***, *123*, 5374.
[792] Terao, J.; Oda, A.; Kambe, N. *Org. Lett.* ***2004***, *6*, 3341.
[793] Murakami, K.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2007***, *9*, 1569.
[794] Schipper, D.J.; Hutchinson, M.; Fagnou, K. *J. Am. Chem. Soc.* ***2010***, *132*, 6910.
[795] The mechanism of the phosphine free Pd-catalyzed reaction has been studied. See Ahlquist M.; Fabrizi, G.; Cacchi, S.; Norrby, P.-O. *J. Am. Chem. Soc.* ***2006***, *128*, 12785.
[796] Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Persiani, D. *Org. Lett.* ***2008***, *10*, 1597.
[797] Liao, L.; Sigman, M.S. *J. Am. Chem. Soc.* ***2010***, *132*, 10209.
[798] See Trost, B.M.; Ball, Z.T. *Synthesis* ***2005***, 853.
[799] Shang, X.; Liu, Z.-Q. *Synthesis* ***2015***, *47*, 1706.
[800] See Zhou, Y.; Zhang, Y.; Wang, J. *Org. Biomol. Chem.* ***2016***, *14*, 6638.
[801] See García, G.V.; Budelman, N.S. *Org. Prep. Proceed. Int.* ***2003***, *35*, 445.

transition metal compounds, such as $CeCl_3$[802] or $Fe(acac)_3$,[803] leads to addition of the alkyl group. Organolithium reagents add to the less substituted C=C unit of conjugated dienes.[804] Addition of butyllithium to alkenes has been observed with good enantioselectivity when sparteine was added.[805]

The intramolecular addition of RLi and R_2CuLi has been reported.[806] Cyclization[807] can occur at low temperatures when an organolithium reagents contains an alkene[808] or alkyne[809] unit. Tandem cyclization is possible with dienes and enynes to form more than one ring,[810] including bicyclic compounds.[811] Alkyl iodides add intramolecularly to alkenes with a Ti catalyst[812] or add to alkynes using In metal and additives.[813] The intramolecular hydroalkylation gave the cyclic alkene using an organocatalyst, a chiral organophosphine.[814] Alkenes reacted with 5-(trifluoromethyl)dibenzothiophenium trifluoromethanesulfonate (*Utemoto's reagent*) in the presence of a Rh catalyst, exposure to visible light, and methanol as a proton source to give the anti-Markovnikov trifluoromethyl hydroalkylation product.[815] The Fe-catalyzed hydromethylation reaction of alkenes used formaldehyde, $PhSiH_3$, and octanesulfonyl hydrazine.[816] The Cu-catalyzed hydromethylation of alkenes used $Cp_2ZrMeCl$.[817] Silyl enol ethers with a distal vinyl group reacted via a Pd catalyst to give the cyclic ketone with a ß-exo methylene compound.[818] Trimethylaluminum reacts with alkynes.[819] Ruthenium catalysts have been used to mediate the addition of allylic alcohols to alkynes.[820] Allyl manganese compounds add to allenes to give nonconjugated dienes.[821]

The stereochemistry of the metal-catalyzed, intramolecular carboalkylation of 1,6-dienes to give cyclic compounds has been discussed.[822] The metal-catalyzed cyclization of alkynes and their adherence to Baldwin's rules has been reviewed.[823] Cyclobutanes

[802] Bartoli, G.; Dalpozzo, R.; DeNino, A.; Procopio, A.; Sanbri, L.; Tagarelli, A. *Tetrahedron Lett.* ***2001***, *42*, 8823.
[803] Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem. Int. Ed.* ***2001***, *40*, 621.
[804] Norsikian, S.; Baudry, M.; Normant, J.F. *Tetrahedron Lett.* ***2000***, *41*, 6575.
[805] Norsikian, S.; Marek, I.; Poisson, J.-F.; Normant, J.F. *J. Org. Chem.* ***1997***, *62*, 4898.
[806] Wender, P.A.; White, A.W. *J. Am. Chem. Soc.* ***1988***, *110*, 2218; Bailey, W.F.; Nurmi, T.T.; Patricia, J.J.; Wang, W. *J. Am. Chem. Soc.* ***1987***, *109*, 2442.
[807] A conformational radical clock has been developed to evaluate organolithium-mediated cyclization reactions. See Rychnovsky, S.D.; Hata, T.; Kim, A.I.; Buckmelter, A.J. *Org. Lett.* ***2001***, *3*, 807.
[808] See Bailey, W.F.; Daskapan, T.; Rampalli, S. *J. Org. Chem.* ***2003***, *68*, 1334. See Kanno, K.-i.; Igarashi, E.; Mizukami, Y.; Nakajima, K.; Song, Z.; Takahashi, T. *Org. Lett.* ***2016***, *18*, 6217.
[809] Bailey, W.F.; Ovaska, T.V. *J. Am. Chem. Soc.* ***1993***, *115*, 3080, and references cited therein. See Funk, R.L.; Bolton, G.L.; Brummond, K.M.; Ellestad, K.E.; Stallman, J.B. *J. Am. Chem. Soc.* ***1993***, *115*, 7023.
[810] Bailey, W.F.; Ovaska, T.V. *Chem. Lett.* ***1993***, 819.
[811] Bailey, W.F.; Khanolkar, A.D.; Gavaskar, K.V. *J. Am. Chem. Soc.* ***1992***, *114*, 8053. See Harada, T.; Fujiwara, T.; Iwazaki, K.; Oku, A. *Org. Lett.* ***2000***, *2*, 1855.
[812] Zhou, L.; Hirao, T. *J. Org. Chem.* ***2003***, *68*, 1633.
[813] Yanada, R.; Obika, S.; Oyama, M.; Takemoto, Y. *Org. Lett.* ***2004***, *6*, 2825.
[814] Gong, J.-J.; Li, T.-Z.; Pan, K.-P.; Wu, X.-Y. *Chem. Commun.* ***2011***, *47*, 1491.
[815] Mizuta, S.; Verhoog, S.; Engle, K.M.; Khotavivattana, T.; O'Duill, M.; Wheelhouse, K.; Rassias, G.; Médebielle, M.; Gouverneur, V. *J. Am. Chem. Soc.* ***2013***, *135*, 2505.
[816] Dao, H.T.; Li, C.; Michaudel, Q.; Maxwell, B.D.; Baran, P.S. *J. Am. Chem. Soc.* ***2015***, *137*, 8046.
[817] Garrec, K.; Fletcher, S.P. *Org. Lett.* ***2016***, *18*, 3814.
[818] Le Bras, J.; Muzart, J. *Tetrahedron* ***2015***, *71*, 9035.
[819] Wipf, P.; Lim, S. *Angew. Chem. Int. Ed.* ***1993***, *32*, 1068.
[820] Trost, B.M.; Indolese, A.F.; Müller, T.J.J.; Treptow, B. *J. Am. Chem. Soc.* ***1995***, *117*, 615.
[821] Nishikawa, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* ***2003***, *5*, 4623.
[822] Aïssa, C. *Synlett* ***2014***, *25*, 2379. See Comprido, L.N.d.S.; Hashmi, A.S.K. *Isr. J. Chem.* ***2013***, *53*, 883.
[823] Gilmore, K.; Alabugin, I.V. *Chem. Rev.* ***2011***, *111*, 6513.

have been prepared by the Cu-catalyzed cyclization of alkenes that have a distal halide.[824] The Pd-catalyzed addition of alkynes to cyclopropenes gave stereodefined alkylcyclopropanes.[825] The Zr-catalyzed dimerization of alkynes gave the (*Z*)-enyne.[826] The Fe-catalyzed cyclization of 1,6- and 1,7-enynes has been reported.[827] The Cu-catalyzed, anti-Markovnikov hydroallylation of allylic phosphates and internal alkynes gave the skipped 1,4-diene.[828] The hydroalkylation of alkynes gave the corresponding alkene using PHMS, alcohols, and a Cu catalyst.[829] The mechanism of the Cu-catalyzed hydroalkylation of alkynes has been discussed.[830] The reaction of terminal alkynes and alkyl triflates (ROTf), in the presence of a Cu catalyst, 2 equivalents of CsF, and $(Me_2HSi)_2O$ as a hydride donor, gave the (*E*)-alkene.[831]

Manganese triacetate [$Mn(OAc)_3$], in the presence of cupric acetate, facilitates intramolecular cyclization of a halide unit to an alkene.[832] Alkynes react with In reagents to form dienes.[833] Allyltin reagents add to alkynes in a similar manner in the presence of $ZrCl_4$.[834] Alkylzinc reagents add to alkynes to give substituted alkenes in the presence of a Pd catalyst,[835] and allylzinc reagents add to alkynes in the presence of a Co catalyst.[836]

Chiral *N*-heterocyclic carbenes catalyzed the addition of styrenes to simple alkenes to give the α-benzylic-α-alkyl alkene.[837] Terminal alkynes were converted to the (*E*)-vinyl boronate, which reacted with alkyl halides to give the corresponding (*E*)-alkene using a Ni catalyst and NaOMe.[838] The Ir-catalyzed hydroalkylation of enamides has been reported.[839]

Aromatic hydrocarbons, such as benzene, add to alkenes using a Ru catalyst,[840] a catalytic mixture of Au/Ag,[841] a Pd catalyst,[842] or a Rh catalyst.[843] Ruthenium complexes catalyze the addition of heteroaromatic compounds, such as pyridine, to alkynes.[844] Aromatic compounds with electron-donating substituents gave the hydroarylation product in open air using a catalytic amount of TMSCl and $ZnBr_2$.[845] Aryl halides were coupled to cyclic alkenes to give the aryl alkene using a Pd catalyst.[846]

[824] Wang, Y.-M.; Bruno, N.C.; Placeres, Á.L.; Zhu, S.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2015***, *137*, 10524.
[825] Tenaglia, A.; Le Jeune, K.; Giordano, L.; Buono, G. *Org. Lett.* ***2011***, *13*, 636.
[826] Platel, R.H.; Schafer, L.L. *Chem. Commun.* ***2012***, *48*, 10609.
[827] Xi, T.; Chen, X.; Zhang, H.; Lu, Z. *Synthesis* ***2016***, *48*, 2837.
[828] Mailig, M.; Hazra, A.; Armstrong, M.K.; Lalic, G. *J. Am. Chem. Soc.* ***2017***, *139*, 6969.
[829] Suess, A.M.; Lalic, G. *Synlett* ***2016***, *27*, 1165.
[830] Suess, A.M.; Uehling, M.R.; Kaminsky, W.; Lalic, G. *J. Am. Chem. Soc.* ***2015***, *137*, 7747.
[831] Uehling, M.R.; Suess, A.M.; Lalic, G. *J. Am. Chem. Soc.* ***2015***, *137*, 1424.
[832] Snider, B.B.; Merritt, J.E. *Tetrahedron* ***1991***, *47*, 8663. See Nakao, J.; Inoue, R.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* ***1997***, *62*, 1910.
[833] See Klaps, E.; Schmid, W. *J. Org. Chem.* ***1999***, *64*, 7537.
[834] Asao, N.; Matsukawa, Y.; Yamamoto, Y. *Chem. Commun.* ***1996***, 1513.
[835] Luo, F.-T.; Fwu, S.-L.; Huang, W.-S. *Tetrahedron Lett.* ***1992***, *33*, 6839.
[836] Nishikawa, T.; Yorimitsu, H.; Oshima, K. *Synlett* ***2004***, 1573.
[837] Ho, C.-Y.; Chan, C.-W.; He, L. *Angew. Chem. Int. Ed.* ***2015***, *54*, 4512.
[838] Di Franco, T.; Epenoy, A.; Hu, X. *Org. Lett.* ***2015***, *17*, 4910.
[839] Bai, X.-Y.; Wang, Z.-X.; Li, B.-J. *Angew. Chem. Int. Ed.* ***2016***, *55*, 9007.
[840] Lail, M.; Arrowood, B.N.; Gunnoe, T.B. *J. Am. Chem. Soc.* ***2003***, *125*, 7506. With microwave irradiation, see Vo-Thanh, G.; Lahrache, H.; Loupy, A.; Kim, I.-J.; Chang, D.-H.; Jun, C.-H. *Tetrahedron* ***2004***, *60*, 5539.
[841] Reetz, M.T.; Sommer, K. *Eur. J. Org. Chem.* ***2003***, 3485.
[842] Tsukada, N.; Mitsuboshi, T.; Setoguchi, H.; Inoue, Y. *J. Am. Chem. Soc.* ***2003***, *125*, 12102.
[843] Thalji, R.K.; Ellman, J.A.; Bergman, R.G. *J. Am. Chem. Soc.* ***2004***, *126*, 7192.
[844] See Alonso, F.; Beletskaya, I.P.; Yus, M. *Chem. Rev.* ***2004***, *104*, 3079.
[845] Lee, S.Y.; Villani-Gale, A.; Eichman, C.C. *Org. Lett.* ***2016***, *18*, 5034.
[846] Wu, X.; Zhou, J. *Chem. Commun.* ***2013***, *49*, 4794.

Aryl iodides add to alkynes using a Pt complex in conjunction with a Pd catalyst.[847] A Pd catalyst has been used alone for the same purpose,[848] and the intramolecular addition of a arene to an alkene was accomplished with a Pd,[849] Ga,[850] or a Ru[851] catalyst. The Mn-catalyzed hydroarylation of alkynes has been done using continuous flow techniques (Sec. 7.D).[852] The Ir-catalyzed, asymmetric hydroheteroarylation of bicyclic alkenes has been reported,[853] and a Rh-catalyzed hetereoarylation has been reported.[854] The hydroarylation of conjugated alkynyl ketones with aryl iodides used a Ni catalyst and a Mn reductant.[855]

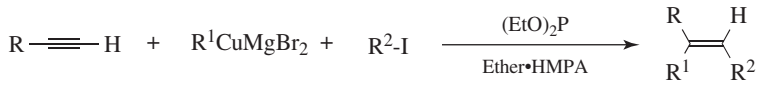
Phenylboronic acids add to alkynes in the presence of a Co[856] or a Pd[857] catalyst. Arylboronic acids (see **13-13**) add to alkynes to give the substituted alkene using a Rh catalyst.[858] Allenes react with phenylboronic acid and an aryl iodide, in the presence of a Pd catalyst, to give a substituted alkene.[859]

Ketones with an α-hydrogen can add to alkenes intramolecularly when heated in a sealed tube with $CuCl_2$ and a Pd catalyst.[860] A similar reaction was reported using $Yb(OTf)_3$ and a Pd,[861] In,[862] or an Au[863] catalyst. 1,3-Diketones add to dienes (1,4-addition) using a Pd,[864] Rh,[865] Au/Ag,[866] or Au/Ga[867] catalyst. This addition has been done intramolecularly using 2.4 molar equivalents of $CuCl_2$ and a Pd catalyst.[868] The intermolecular addition of diesters, such as malonates, to alkynes was accomplished in acetic acid and using a Pd catalyst under microwave irradiation.[869] Silyl enol ethers add to alkynes using a W catalyst.[870]

OS **81**, 121.

[847] Denmark, S.E.; Wang, Z. *Org. Lett.* ***2001***, *3*, 1073.
[848] Havránek, M.; Dvorák, D. *J. Org. Chem.* ***2002***, *67*, 2125. See also, Lee, K.; Seomoon, D.; Lee, P.H. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3901.
[849] See Podhajsky, S.M.; Iwai, Y.; Sneathen, A.C.; Sigman, M.S. *Tetrahedron* ***2011***, *67*, 4435.
[850] Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* ***2002***, *67*, 1414.
[851] Schinkel, M.; Marek, I.; Ackermann, L. *Angew. Chem. Int. Ed.* ***2013***, *52*, 3977.
[852] Wang, H.; Pesciaioli, F.; Oliveira, J.C.A.; Warratz, S.; Ackermann, L. *Angew. Chem. Int. Ed.* ***2017***, *56*, 15063.
[853] Sevov, C.S.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2013***, *135*, 2116.
[854] Ryu, J.; Cho, S.H.; Chang, S. *Angew. Chem. Int. Ed.* ***2012***, *51*, 3677.
[855] Dorn, S.C.M.; Olsen, A.K.; Kelemen, R.E.; Shrestha, R.; Weix, D.J. *Tetrahedron Lett.* ***2015***, *56*, 3365.
[856] Lin, P.-S.; Jeganmohan, M.; Cheng, C.-H. *Chem. Eur. J.* ***2008***, *14*, 11296.
[857] Gupta, A.K.; Kim, K.S.; Oh, C.H. *Synlett* ***2005***, 457.
[858] See Genin, E.; Michelet, V.; Genêt, J.-P. *Tetrahedron Lett.* ***2004***, *45*, 4157.
[859] Yoshida, M.; Gotou, T.; Ihara, M. *Chem. Commun.* ***2004***, 1124.
[860] Wang, X.; Pei, T.; Han, X.; Widenhoefer, R.A. *Org. Lett.* ***2003***, *5*, 2699.
[861] Yang, D.; Li, J.-H.; Gao, Q.; Yan, Y.-L. *Org. Lett.* ***2003***, *5*, 2869.
[862] Itoh, Y.; Tsuji, H.; Yamagata, K.-i.; Endo, K.; Tanaka, I.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* ***2008***, *130*, 17161.
[863] Xiao, Y.-P.; Liu, X.-Y.; Che, C.-M. *Angew. Chem. Int. Ed.* ***2011***, *50*, 4937.
[864] Leitner, A.; Larsen, J.; Steffens, C.; Hartwig, J.F. *J. Org. Chem.* ***2004***, *69*, 7552; Trost, B.M.; Simas, A.B.C.; Plietker, B.; Jäkel, C.; Xie, J. *Chem. Eur. J.* ***2005***, *11*, 7075.
[865] Beck, T.M.; Breit, B. *Org. Lett.* ***2016***, *18*, 124.
[866] Yao, X.; Li, C.-J. *J. Am. Chem. Soc.* ***2004***, *126*, 6884.
[867] Xi, Y.; Wang, D.; Ye, X.; Akhmedov, N.G.; Petersen, J.L.; Shi, X. *Org. Lett.* ***2014***, *16*, 306.
[868] Pei, T.; Wang, X.; Widenhoefer, R.A. *J. Am. Chem. Soc.* ***2003***, *125*, 648.
[869] Patil, N.T.; Khan, F.N.; Yamamoto, Y. *Tetrahedron Lett.* ***2004***, *45*, 8497.
[870] Iwasawa, N.; Miura, T.; Kiyota, K.; Kusama, H.; Lee, K.; Lee, P.H. *Org. Lett.* ***2002***, *4*, 4463.

15-18 The Addition of Two Alkyl Groups to an Alkyne



Two different alkyl groups can be added to a terminal alkyne[871] in one laboratory step by treatment with an alkylcopper/magnesium bromide reagent (called *Normant reagents*)[872] and an alkyl iodide in ether/HMPA containing triethyl phosphite.[873] The groups add stereoselectively *syn*. The reaction, which has been applied to primary[874] R^1 and to primary, allylic, benzylic, vinylic, and α-alkoxyalkyl R^1, involves initial addition of an intermediate alkylcopper reagent,[875] followed by a coupling reaction (**10-57**). Acetylene itself (R = H) undergoes the reaction with R_2CuLi instead of the Normant reagent.[876] If the alkyl iodide is omitted, the vinylic copper intermediate can be converted to a carboxylic acid by the addition of CO_2 and $P(OEt)_2$ in HMPA (see **16-30**) or to an amide by the addition of an isocyanate, and $P(OEt)_2$ and HMPA and a catalytic amount of triethyl phosphite.[877] The use of I_2 results in a vinylic iodide.[878]

Similar reactions, in which two alkyl groups are added to a triple bond, have been carried out with trialkylalanes (R_3Al), with zirconium complexes as catalysts.[879] Internal alkynes undergo bis(allylation) using a Ni catalysts and triallylindium.[880] Allyl ethers and iodobenzene have also been added using a Zr complex.[881]

The Re-catalyzed reaction of β-keto sulfones with terminal alkynes gave unsaturated δ-keto sulfones in good to excellent yields.[882] The Mn-catalyzed carboacylation of alkenes with alkyl iodides has been reported.[883] The β-selective hydrocarboxylation of styrenes has been done under flow conditions (Sec. 7.D).[884] Arylboronic acids (see **13-14**) react with alkynes and 1 equivalent of an aryl iodide, with a Pd catalyst, to add two aryl groups across the triple bond.[885]

OS **VII**, 236, 245, 290.

[871] Raston, C.L.; Salem, G. in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 159–306, 233–248; Normant, J.F.; Alexakis, A. *Synthesis* ***1981***, 841; Hudrlik, P.F.; Hudrlik, A.M. in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 233–238. See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 452–460.

[872] See Ashby, E.C.; Goel, A.B. *J. Org. Chem.* ***1983***, *48*, 2125.

[873] Gardette, M.; Alexakis, A.; Normant, J.F. *Tetrahedron* ***1985***, *41*, 5887 and references cited therein. For an extensive list of references, see Marfat, A.; McGuirk, P.R.; Helquist, P. *J. Org. Chem.* ***1979***, *44*, 3888.

[874] See Rao, S.A.; Periasamy, M. *Tetrahedron Lett.* ***1988***, *29*, 4313.

[875] See Westmijze, H.; Kleijn, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* ***1981***, *100*, 98, and references cited therein.

[876] Furber, M.; Taylor, R.J.K.; Burford, S.C. *J. Chem. Soc., Perkin Trans. 1* ***1986***, 1809.

[877] Normant, J.F.; Cahiez, G.; Chuit, C.; Villieras, J. *J. Organomet. Chem.* ***1973***, *54*, C53.

[878] Alexakis, A.; Cahiez, G.; Normant, J.F. *Org. Synth.* ***VII***, 290.

[879] See Negishi, E. *Acc. Chem. Res.* ***1987***, *20*, 65; *Pure Appl. Chem.* ***1981***, *53*, 2333.

[880] Hirashita, T.; Akutagawa, K.; Kamei, T.; Araki, S. *Chem. Commun.* ***2006***, 2598.

[881] Hara, R.; Nishihara, Y.; Landré, P.D.; Takahashi, T. *Tetrahedron Lett.* ***1997***, *38*, 447.

[882] Kuninobu, Y.; Matsuzaki, H.; Nishi, M.; Takai, K. *Org. Lett.* ***2011***, *13*, 2959.

[883] McMahon, C.M.; Renn, M.S.; Alexanian, E.J. *Org. Lett.* ***2016***, *18*, 4148.

[884] Seo, H.; Liu, A.; Jamison, T.F. *J. Am. Chem. Soc.* ***2017***, *139*, 13969.

[885] See Zhou, C.; Larock, R.C. *J. Org. Chem.* ***2005***, *70*, 3765.

15-19 The Ene Reaction[886]

An interesting addition of R—H to a double bond involves the reaction of alkenes with an alkene having an allylic hydrogen (C=C—CH), and is called the *ene reaction, the Alder ene reaction,* or the *ene synthesis.*[887] The reaction can proceed thermally without a catalyst, but one of the components must be a reactive dienophile (reacts with a diene; see **15-56**), such as maleic anhydride, but the other (which supplies the hydrogen) may be a simple alkene such as propene *as long as there is an allylic hydrogen atom.* Rather high reaction temperatures (250–450 °C) are common unless the substrates are very activated, but steric acceleration of the uncatalyzed ene reaction is known.[888] The reaction is compatible with a variety of functional groups that can be appended to the ene and the dienophile. A retro-ene reaction is known with allylic dithiocarbonate.[889] The reaction can be extended to less-reactive enophiles by the use of Lewis acid catalysts, especially alkylaluminum halides.[890] Titanium,[891] Sc,[892] $LiClO_4$,[893] Y,[894] In,[895] Pd,[896] Co,[897] Ni,[898] as well as a combination of Ag and Au have been used as catalysts.[899] An Ir-catalyzed ene reaction has been done in an ionic liquid.[900]

There has been much discussion of the mechanism of this reaction,[901] and both concerted pericyclic (as shown in the generic reaction) and stepwise mechanisms have been suggested. Mechanistic studies have been reported for the intramolecular aryne ene reaction.[902] The mechanism of the ene reaction of singlet ($^1\Delta_g$) oxygen with simple alkenes was found to involve two steps, with no intermediate.[903] The Lewis acid-catalyzed

[886] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 852–858.

[887] Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Elmsford, NY, ***1990***; Boyd, G.V. in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups,* Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 477–525; Hoffmann, H.M.R. *Angew. Chem. Int. Ed.* ***1969***, *8*, 556. For reviews of intramolecular ene reactions see Taber, D.F. *Intramolecular Diels-Alder and Alder Ene Reactions*, Springer, NY, ***1984***, pp. 61–94; Oppolzer, W.; Snieckus, V. *Angew. Chem. Int. Ed.* ***1978***, *17*, 476–486; Conia, J.M.; Le Perchec, P. *Synthesis* ***1975***, 1. See Desimoni, G.; Faita, G.; Righetti, P.P.; Sfulcini, A.; Tsyganov, D. *Tetrahedron* ***1994***, *50*, 1821 for solvent effects in the ene reaction.

[888] Choony, N.; Kuhnert, N.; Sammes, P.G.; Smith, G.; Ward, R.W. *J. Chem. Soc., Perkin Trans. 1* ***2002***, 1999.

[889] Eto, M.; Nishimoto, M.; Kubota, S.; Matsuoka, T.; Harano, K. *Tetrahedron Lett.* ***1996***, *37*, 2445.

[890] See Chaloner, P.A. in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 456–460; Snider, B.B. *Acc. Chem. Res.* ***1980***, *13*, 426.

[891] Sturla, S.J.; Kablaoui, N.M.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1999***, *121*, 1976.

[892] Aggarwal, V.K.; Vennall, G.P.; Davey, P.N.; Newman, C. *Tetrahedron Lett.* ***1998***, *39*, 1997.

[893] Davies, A.G.; Kinart, W.J. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 2281.

[894] Molander, G.A.; Corrette, C.P. *J. Org. Chem.* ***1999***, *64*, 9697.

[895] Hatakeyama, S. *Pure Appl. Chem.* ***2009***, *81*, 217.

[896] Corkey, B.K.; Toste, F.D. *J. Am. Chem. Soc.* ***2005***, *127*, 17168.

[897] Hilt, G.; Treutwein, J. *Angew. Chem. Int. Ed.* ***2007***, *46*, 8500.

[898] Michelet, V.; Galland, J.-C.; Charruault, L.; Savignac, M.; Genêt, J.-P. *Org. Lett.* ***2001***, *3*, 2065.

[899] Kennedy-Smith, J.J.; Staben, S.T.; Toste, F.D. *J. Am. Chem. Soc.* ***2004***, *126*, 4526.

[900] Shibata, T.; Yamasaki, M.; Kadowaki, S.; Takagi, K. *Synlett* ***2004***, 2812.

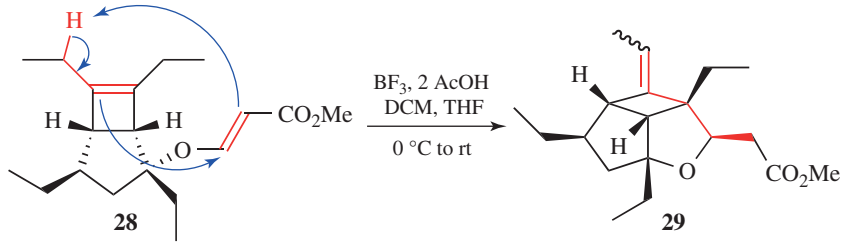
[901] For a DFT study of the polar mechanism, see Domingo, L.R.; Aurell, M.J.; Pérez, P. *Org. Biomol. Chem.* ***2014***, *12*, 7581.

[902] Candito, D.A.; Panteleev, J.; Lautens, M. *J. Am. Chem. Soc.* ***2011***, *133*, 14200.

[903] Singleton, D.A.; Hang, C.; Szymanski, M.J.; Meyer, M.P.; Leach, A.G.; Kuwata, K.T.; Chen, J.S.; Greer, A.; Foote, C.S.; Houk, K.N. *J. Am. Chem. Soc.* ***2003***, *125*, 1319.

reaction probably has a stepwise mechanism.[904] The reaction between maleic anhydride and optically active PhCHMeCH=CH_2 gave an optically active product,[905] which is strong evidence for a concerted rather than a stepwise mechanism.[906] Arynes reacted with alkenes via the ene reaction.[907] An ene reaction of arynes with alkynes gave aryl allenes.[908]

Intramolecular ene reactions are known,[909] including those catalyzed by transition metals such as Cu.[910] An example is the intramolecular ene reaction of **28**, catalyzed by BF_3, which gave **29** in a synthesis of hippolachnin A.[911] The reaction can be highly stereoselective.[912]



28 **29**

Ene reactions with imines[913] and nitrile oxides,[914] as well as nitroso ene reactions,[915] are known. Vinyl boronates have been prepared via a Ru-catalyzed ene reaction.[916] Tetrahydrothiopyrans were formed via a (3,5)-thionium ene cyclization,[917] and a transition metal photoredox thiol-ene reaction is known.[918]

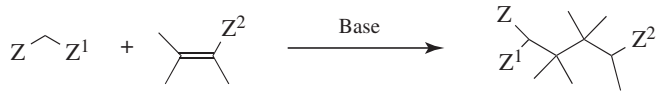
Ene reactions of imines are sometimes called *imino-ene reactions*.[919] An *aza-ene reaction*[920] has been used in a synthesis of enantioenriched piperidines, using two different imines as starting materials.[921] An enantioselective aza-ene reaction in the presence of an organocatalyst led to 1,4-dihydropyridines.[922] A Au carbene-catalyzed reaction is known.[923]

[904] See Snider, B.B.; Ron, E. *J. Am. Chem. Soc.* ***1985***, *107*, 8160.
[905] Nahm, S.H.; Cheng, H.N. *J. Org. Chem.* ***1986***, *51*, 5093.
[906] See Thomas IV, B.E.; Loncharich, R.J.; Houk, K.N. *J. Org. Chem.* ***1992***, *57*, 1354.
[907] Chen, Z.; Liang, J.; Yin, J.; Yu, G.-A.; Liu, S.-H. *Tetrahedron Lett.* ***2013***, *54*, 5785.
[908] Jayanth, T.T.; Jeganmohan, M.; Cheng, M.-J.; Chu, S.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* ***2006***, *128*, 2232.
[909] See Liu, X.; Zheng, K.; Feng, X. *Synthesis* ***2014***, *46*, 2241.
[910] Arai, N.; Ohkuma, T. *Tetrahedron* ***2011***, *67*, 1617.
[911] Ruider, S.A.; Sandmeier, T.; Carreira, E.M. *Angew. Chem. Int. Ed.* ***2015***, *54*, 2378.
[912] Ooi, T.; Maruoka, K.; Yamamoto, H. *Tetrahedron* ***1994***, *50*, 6505; Thomas IV, B.E.; Houk, K.N. *J. Am. Chem. Soc.* ***1993***, *115*, 790; Also see, Masaya, K.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* ***1994***, *35*, 7965.
[913] Yamanaka, M.; Nishida, A.; Nakagawa, M.; *Org. Lett.* ***2000***, *2*, 159; For a theoretical study, see Yang, Q.; Liu, Y.; Zhang, W. *Org. Biomol. Chem.* ***2011***, *9*, 6343.
[914] See Yu, Z.-X.; Houk, K.N. *J. Am. Chem. Soc.* ***2003***, *125*, 13825.
[915] Lu, X. *Org. Lett.* ***2004***, *6*, 2813. See also, Adam, W.; Krebs, O. *Chem. Rev.* ***2003***, *103*, 4131; Baidya, M.; Yamamoto, H. *Synthesis* ***2013***, *45*, 1931.
[916] Hansen, E.C.; Lee, D. *J. Am. Chem. Soc.* ***2005***, *127*, 3252.
[917] Bondalapati, S.; Gogoi, P.; Indukuri, K.; Saikia, A.K. *J. Org. Chem.* ***2012***, *77*, 2508.
[918] Fadeyi, O.O.; Mousseau, J.J.; Feng, Y.; Allais, C.; Nuhant, P.; Chen, M.Z.; Pierce, B.; Robinson, R. *Org. Lett.* ***2015***, *17*, 5756; Keylor, M.H.; Park, J.E.; Wallentin, C.J.; Stephenson, C.R.J. *Tetrahedron* ***2014***, *70*, 4264; Bhat, V.T.; Duspara, P.A.; Seo, S.; Bakar, N.S.B.A.; Greaney, M.F. *Chem. Commun.* ***2015***, *51*, 4383.
[919] See Pandey, M.K.; Bisai, A.; Pandey, A.; Singh, V.K. *Tetrahedron Lett.* ***2005***, *46*, 5039.
[920] See Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem. Int. Ed.* ***2006***, *45*, 2254.
[921] Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* ***2007***, *129*, 10336.
[922] Noole, A.; Borissova, M.; Lopp, M.; Kanger, T. *J. Org. Chem.* ***2011***, *76*, 1538.
[923] Zhao, F.; Li, N.; Zhang, T.; Han, Z.-Y.; Luo, S.-W.; Gong, L.-Z. *Angew. Chem. Int. Ed.* ***2017***, *56*, 3247.

The *carbonyl-ene reaction*,[924] also called the *Conia ene reaction*,[925] is synthetically useful, especially when catalyzed by Lewis acids.[926] Asymmetric catalysts[927] for enantioselective carbonyl ene reactions have been reported using chiral Sc,[928] In,[929] Rh,[930] La/Ag,[931] Fe,[932] amine/Ag,[933] or Ni.[934] catalysts The Zn-catalyzed carbonyl ene reaction of 2-methylenetetrahydropyrans gave 2-hydroxyalkyldihydropyrans.[935] A confined imidodiphosphate catalyst has been used for the enantioselective carbonyl-ene reaction.[936] A transannular ketone ene reaction has been reported, catalyzed by a chromium tridentate-Schiff base complex.[937] Carbonyl ene cyclization has been reported on silica gel at high pressure (15 kbar).[938]

OS **IV**, 766; **V**, 459. See also, OS **VIII**, 427.

15-20 The Michael Reaction



The reaction of carbanion nucleophiles, including enolate anions, with α,β-unsaturated compounds that contain an electron-withdrawing group gives the conjugate (1,4) addition product. This reaction is called the *Michael reaction*.[939] The product formed, RCH_2Z or RCHZZ′, where Z, an electron-withdrawing group, can include aldehydes,[940] ketones,[941] esters,[942] diesters,[943] diketones,[944] keto esters,[945] carboxylic acids, dicarboxylic

[924] For a review, see Clarke, M.L.; France, M.B. *Tetrahedron* ***2008***, *64*, 9003.
[925] Conia, J.M.; Le Perchec, P. *Synthesis* ***1975***, 1; Hack, D.; Blümel, M.; Chauhan P.; Philipps, A.R.; Enders, D. *Chem. Soc. Rev.* ***2015***, *44*, 6059.
[926] See Achmatowicz, O.; Bialeck-Florjanczyk, E. *Tetrahedron* ***1996***, *52*, 8827; Marshall, J.A.; Andersen, M.W. *J. Org. Chem.* ***1992***, *57*, 5851 for mechanistic discussions of this reaction.
[927] Grachan, M.L.; Tudge, M.T.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* ***2008***, *47*, 1469.
[928] Evans, D.A.; Wu, J. *J. Am. Chem. Soc.* ***2005***, *127*, 8006.
[929] Zhao, J.-F.; Tsui, H.-Y.; Wu, P.-J.; Lu, J.; Loh, T.-P. *J. Am. Chem. Soc.* ***2008***, *130*, 16492.
[930] Xu, X.; Wang, X.; Liu, Y.; Doyle, M.P. *J. Org. Chem.* ***2014***, *79*, 12185.
[931] Matsuzawa, A.; Mashiko, T.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* ***2011***, *50*, 7616.
[932] Shaw, S.; White, J.D. *J. Am. Chem. Soc.* ***2014***, *136*, 13578; Chan, L.Y.; Kim, S.; Park, Y.; Lee, P.H. *J. Org. Chem.* ***2012***, *77*, 5239.
[933] Blümel, M.; Hack, D.; Ronkaartz, L.; Vermeeren, C.; Enders, D. *Chem. Commun.* ***2017***, *53*, 3956.
[934] Zheng, K.; Shi, J.; Liu, X.; Feng, X. *J. Am. Chem. Soc.* ***2008***, *130*, 15770.
[935] Liang, G.; Sharum, D.T.; Lam, T.; Totah, N.I. *Org. Lett.* ***2013***, *15*, 5974.
[936] Liu, L.; Leutzsch, M.; Zheng, Y.; Alachraf, M.W.; Thiel, W.; List, B. *J. Am. Chem. Soc.* ***2015***, *137*, 13268.
[937] Rajapaksa, N.S.; Jacobsen, E.N. *Org. Lett.* ***2013***, *15*, 4238.
[938] Dauben, W.G.; Hendricks, R.T. *Tetrahedron Lett.* ***1992***, *33*, 603.
[939] See Yanovskaya, L.A.; Kryshtal, G.V.; Kulganek, V.V. *Russ. Chem. Rev.* ***1984***, *53*, 744; Bergmann, E.D.; Ginsburg, D.; Pappo, R. *Org. React.* ***1959***, *10*, 179. For a review of α-substitution versus conjugate addition, see Lewandowska, E. *Tetrahedron* ***2007***, *63*, 2107.
[940] See Chi, Y.; Gellman, S.H. *Org. Lett.* ***2005***, *7*, 4253.
[941] Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* ***2003***, *5*, 2559; Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2003***, *125*, 2582.
[942] Kim, S.-G.; Ahn, K.H. *Tetrahedron Lett.* ***2001***, *42*, 4175.
[943] Halland, N.; Aburel, P.S.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* ***2003***, *42*, 661.
[944] da Silva, F.M.; Gomes, A.K.; Jones Jr., J. *Can. J. Chem.* ***1999***, *77*, 624.
[945] Suzuki, T.; Torii, T. *Tetrahedron: Asymmetry* ***2001***, *12*, 1077; García-Gómez, G.; Moretó, J.M. *Eur. J. Org. Chem.* ***2001***, 1359; Kobayashi, S.; Kakumoto, K.; Mori, Y.; Manabe, K. *Isr. J. Chem.* ***2001***, *41*, 247.

acids,[946] nitriles,[947] vinyl sulfones,[948] nitro compounds,[949] and others of the form ZCH_3, ZCH_2R, $ZCHR_2$, and $ZCHRZ'$.[950] Malonate derivatives also add to conjugated ketones,[951] and keto esters add to conjugated esters.[952] Ultrasound has been used to promote asymmetric Michael reactions.[953] In reactions of enolate anions, both the enolate anion and substrate can exist as *Z* or *E* isomers. With enolates derived from ketones or carboxylic esters, the (*E*)-enolates gave the *syn* pair of enantiomers (Sec. 4.G), while (*Z*)-enolates gave the *anti* pair.[954] When the substrate contains *gem*-Z groups, e.g., $C{=}C(CN)CO_2Et$, bulky groups can be added if the reaction is carried out under aprotic conditions.[955]

Transition metal compounds,[956] such as Ce,[957] Yb,[958] Bi,[959] Fe,[960] Ni,[961] Cu,[962] La,[963] Ru,[964] Rh,[965] Pd,[966] or Sc,[967] also induce the reaction. Conjugate addition has also been promoted by Y zeolite,[968] and water-promoted Michael additions have also been reported.[969] Malonate derivatives give conjugate addition using a Ni catalyst,[970] organocatalysts,[971] or genomic salmon testes DNA for reactions in water.[972] Michael addition is known to be

[946] Méou, A.; Lamarque, L.; Brun, P. *Tetrahedron Lett.* ***2002***, *43*, 5301.
[947] Wolckenhauer, S.A.; Rychnovsky, S.D. *Org. Lett.* ***2004***, *6*, 2745; Fleming, F.F.; Wang, Q. *Chem. Rev.* ***2003***, *103*, 2035.
[948] Zhu, Q.; Lu, Y. *Org. Lett.* ***2008***, *10*, 4803.
[949] Ooi, T.; Fujioka, S.; Maruoka, K. *J. Am. Chem. Soc.* ***2004***, *126*, 11790. See Moberg, C. *Angew. Chem. Int. Ed.* ***2013***, *52*, 2160.
[950] Taylor, M.S.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2003***, *125*, 11204.
[951] See Yoshida, M.; Narita, M.; Hara, S. *J. Org. Chem.* ***2011***, *76*, 8513.
[952] Yadav, J.S.; Geetha, V.; Reddy, B.V.S. *Synth. Commun.* ***2002***, *32*, 3519.
[953] Mirza-Aghayan, M.; Etemad-Moghadam, G.; Zaparucha, A.; Berlan, J.; Loupy, A.; Koenig, M. *Tetrahedron: Asymmetry* ***1995***, *6*, 2643.
[954] See Oare, D.A.; Heathcock, C.H. *J. Org. Chem.* ***1990***, *55*, 157.
[955] Holton, R.A.; Williams, A.D.; Kennedy, R.M. *J. Org. Chem.* ***1986***, *51*, 5480.
[956] See Hayashi, M.; Matsubara, R. *Tetrahedron Lett.* ***2017***, *58*, 1793.
[957] Bartoli, G.; Bosco, M.; Bellucci, M.C.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Eur. J. Org. Chem.* ***1999***, 617.
[958] Ding, R.; Katebzadeh, K.; Roman, L.; Bergquist, K.-E.; Lindström, U.M. *J. Org. Chem.* ***2006***, *71*, 352.
[959] Varala, R.; Alam, M.M.; Adapa, S.R. *Synlett* ***2003***, 720.
[960] For a review, see Christoffers, J. *Synlett* ***2001***, 723.
[961] For a discussion of Heck coupling versus Michael addition, see Lin, P.-S.; Jeganmohan, M.; Cheng, C.-H. *Chem. Asian J.* ***2007***, *2*, 1409.
[962] Iguchi, Y.; Itooka, R.; Miyaura, N. *Synlett* ***2003***, 1040; Meyer, O.; Becht, J.-M.; Helmchen, G. *Synlett* ***2003***, 1539. For a discussion of the mechanism, see Comelles, J.; Moreno-Mañas, M.; Pérez, E.; Roglans, A.; Sebastián, R.M.; Vallribera, A. *J. Org. Chem.* ***2004***, *69*, 6834.
[963] Silva, E.M. P.; Silva, A.M.S. *Synthesis* ***2012***, *44*, 3109.
[964] Wadsworth, K.J.; Wood, F.K.; Chapman, C.J.; Frost, C.G. *Synlett* ***2004***, 2022; Hayashi, T.; Yamasaki, K. *Chem. Rev.* ***2003***, *103*, 2829.
[965] Jean, M.; Casanova, B.; Gnoatto, S.; van de Weghe, P. *Org. Biomol. Chem.* ***2015***, *13*, 9168.
[966] Wang, H.; Hearne, Z.; Knauber, T.; Dalko, M.; Hitce, J.; Marat, X.; Moreau, M.; Li, C.-J. *Tetrahedron* ***2015***, *71*, 5866.
[967] Mori, Y.; Kakumoto, K.; Manabe, K.; Kobayashi, S. *Tetahedron Lett.* ***2000***, *41*, 3107.
[968] Sreekumar, R.; Rugmini, P.; Padmakumar, R. *Tetrahedron Lett.* ***1997***, *38*, 6557.
[969] Lubineau, A.; Augé, J. *Tetrahedron Lett.* ***1992***, *33*, 8073.
[970] Evans, D.A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* ***2007***, *129*, 11583.
[971] Wu, L.-Y.; Yan, Z.-Y.; Xie, Y.-X.; Niu, Y.-N.; Liang, Y.-M. *Tetrahedron: Asymmetry* ***2007***, *18*, 2086; Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem. Int. Ed.* ***2006***, *45*, 3093.
[972] De Rosa, M.; Di Marino, S.; Maria D'Ursi, A.; Strianese, M.; Soriente, A. *Tetrahedron* ***2012***, *68*, 3086.

catalyzed by phosphines[973] and other organocatalysts,[974] and catalysts are known that are compatible with an aqueous medium.[975] An organocatalyst has been used for the conjugate addition of malonates to enones,[976] and solvent-free conditions with an organocatalyst have been reported.[977] A chiral phase-transfer catalyst was used for the conjugate addition of malonate derivatives to enones, with an unusual inversion of enantioselectivity that is solvent and substitution dependent.[978]

The 1,2-addition to a C═O or C≡N group often competes and sometimes predominates (**16-38**).[979] Note that α,β-unsaturated *aldehydes* seldom give 1,4-addition.[980] Better yields with fewer side reactions are realized by conversion of the nucleophile to a *preformed enolate*.[981] Phase-transfer catalysts have been used,[982] and ionic liquids have been used in conjunction with phase-transfer catalysis.[983] The kinetics of conjugate addition of β-keto esters to acrylates in ionic liquids has been discussed.[984] The mechanism of the iodine-catalyzed conjugate addition has been discussed.[985] In certain cases, Michael reactions can take place under acidic conditions.[986] Michael-type addition of radicals to conjugated carbonyl compounds is also known.[987] Radical addition can be catalyzed by $Yb(OTf)_3$,[988] but radicals add under standard conditions as well, even intramolecularly.[989] Electrochemical-initiated Michael additions are known.

Silyl enol ethers such as **30** add to α,β-unsaturated ketones and esters when catalyzed[990] by $TiCl_4$[991] or $InCl_3$.[992] A solid-state version of the reaction used alumina•$ZnCl_2$.[993] This reaction has been performed with good diastereoselectivity,[994] and silyl enol ethers have been used in conjunction with chiral additives.[995]

[973] Gimbert, C.; Lumbierres, M.; Marchi, C.; Moreno-Mañas, M.; Sebastián, R.M.; Vallribera, A. *Tetrahedron* ***2005***, *61*, 8598.

[974] Almaşi, D.; Alonso, D.A.; Nájera, C. *Tetrahedron: Asymmetry* ***2007***, *18*, 299; Vicario, J.L.; Badía, D.; Carrillo, L. *Synthesis* ***2007***, 2065.

[975] Chen, X.; She, J.; Shang, Z.; Wu, J.; Zhang, P. *Synthesis* ***2008***, 3931.

[976] Dudziński, K.; Pakulska, A.M.; Kwiatkowski, P. *Org. Lett.* ***2012***, *14*, 4222. For a mechanistic study of organocatalyzed malonate addition reactions, see Yoshida, M.; Nagasawa, Y.; Kubara, A.; Hara, S.; Yamanaka, M. *Tetrahedron* ***2013***, *69*, 10003.

[977] Hirashima, S.-i.; Sakai, T.; Nakashima, K.; Watanabe, N.; Koseki, Y.; Mukai, K.; Kanada, Y.; Tada, N.; Itoh, A.; Miura, T. *Tetrahedron Lett.* ***2014***, *55*, 4334.

[978] Vijaya, P.K.; Murugesan, S.; Siva, A. *Tetrahedron Lett.* ***2015***, *56*, 5209.

[979] See Oare, D.A.; Heathcock, C.H. *Top. Stereochem.* ***1989***, *19*, 227 (pp. 232–236).

[980] See Yamaguchi, M.; Yokota, N.; Minami, T. *J. Chem. Soc., Chem. Commun.* ***1991***, 1088.

[981] See Oare, D.A.; Heathcock, C.H. *Top. Stereochem.* ***1991***, *20*, 87; ***1989***, *19*, 227.

[982] Kim, D.Y.; Huh, S.C. *Tetrahedron* ***2001***, *57*, 8933.

[983] Kotrusz, P.; Toma, S.; Schamlz, H.-G.; Adler, A. *Eur. J. Org. Chem.* ***2004***, 1577.

[984] Bradford, B.N.; Miller, K.M. *Tetrahedron Lett.* ***2012***, *53*, 1855.

[985] von der Heiden, D.; Bozkus, S.; Klussmann, M.; Breugst, M. *J. Org. Chem.* ***2017***, *82*, 4037.

[986] See Hajos, Z.G.; Parrish, D.R. *J. Org. Chem.* ***1974***, *39*, 1612; *Org. Synth.* ***VII***, 363.

[987] Bertrand, S.; Glapski, C.; Hoffmann, N.; Pete, J.-P. *Tetrahedron Lett.* ***1999***, *40*, 3169.

[988] Sibi, M.P.; Jasperse, C.P.; Ji, J. *J. Am. Chem. Soc.* ***1995***, *117*, 10779. See Wu, J.H.; Radinov, R.; Porter, N.A. *J. Am. Chem. Soc.* ***1995***, *117*, 11029 for a related reaction.

[989] Enholm, E.J.; Kinter, K.S. *J. Org. Chem.* ***1995***, *60*, 4850.

[990] See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1576–1582; Mukaiyama, T.; Kobayashi, S. *J. Organomet. Chem.* ***1990***, *382*, 39.

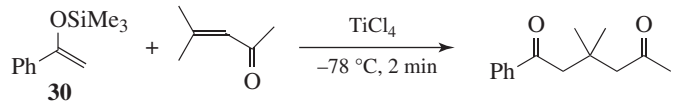
[991] Matsuda, I. *J. Organomet. Chem.* ***1987***, *321*, 307; Narasaka, K. *Org. Synth. 65*, 12. See also, Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* ***1985***, *18*, 284.

[992] Loh, T.-P.; Wei, L.-L. *Tetrahedron* ***1998***, *54*, 7615.

[993] Ranu, B.C.; Saha, M.; Bhar, S. *Tetrahedron Lett.* ***1993***, *34*, 1989.

[994] See Heathcock, C.H.; Uehling, D.E. *J. Org. Chem.* ***1986***, *51*, 279; Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett.* ***1987***, 743.

[995] Harada, T.; Adachi, S.; Wang, X. *Org. Lett.* ***2004***, *6*, 4877.



Vinylogous Michael reactions are well known, using a variety of nucleophilic species[996] (Sec. 6.B for vinylogy). 1,6-Additions are also known.[997] The *N*-heterocyclic carbene-catalyzed umpolung of Michael acceptors has been reported.[998] The Co-catalyzed 1,6-addition of trialkylsilylacetylene derivatives has been reported.[999] The conjugated addition of triallyl(aryl)silanes to conjugated carbonyl compounds used a Rh catalyst.[1000]

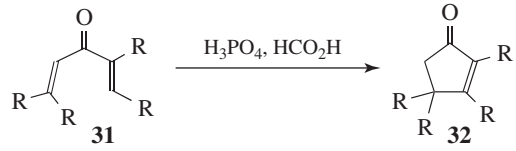
Intramolecular versions of Michael addition are known.[1001] The stereochemical course of the intramolecular reaction has been discussed.[1002] The intramolecular Michael addition of an α-chloro ketone enolate anion, formed *in situ* using DABCO, leads to formation of a bicyclo[4.1.0] diketone.[1003] A double Michael process is possible, where conjugate addition to an alkynyl ketone is followed by an intramolecular Michael reaction to form a functionalized ring.[1004] The Co-catalyzed, intramolecular conjugate addition of alkene moieties gave cyclic compounds with a γ,δ-alkene unit.[1005] Alkenyl aldehydes cyclized via an intramolecular conjugate addition when treated with KO*t*-Bu and imidazolium carbenes to give cyclic compounds with a pendant aldehyde[1006] or ketone moiety.[1007] The intramolecular reaction of alkenes to conjugated carbonyl compounds used a Cu catalyst to give the cyclic alkene.[1008] Alkynes with an electron-withdrawing group such as CO_2R or CN reacted intramolecular with a distal alkene unit in the presence of TMSCN and a trialkylphosphine to give the cyclic alkene nitrile.[1009]

Alkynes are reactive, and Michael reactions are sometimes applied to substrates of the type C≡C–Z, where Z is an electron-withdrawing group; the co-products are conjugated systems of the type C=C–Z.[1010] Terminal alkynes add to conjugated systems.[1011] Due to the greater susceptibility of triple bonds to nucleophilic attack, it is even possible for non-activated alkynes, e.g., acetylene, to be substrates in this reaction.[1012] The Pd-catalyzed conjugate addition of terminal alkynes to enones has been reported.[1013]

An important cyclization procedure involves the acid-catalyzed addition of diene ketones such as **31**, where one conjugated alkene adds to the other conjugated

[996] Ballini, R.; Bosica, G.; Fiorini, D. *Tetrahedron Lett.* ***2001***, *42*, 8471. See Guo, Q.; Fraboni, A.J.; Brenner-Moyer, S.E. *Org. Lett.* ***2016***, *18*, 2628.
[997] Bernardi, L.; López-Cantarero, J.; Niess, B.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2007***, *129*, 5772.
[998] Biju, A.T.; Padmanaban, M.; Wurz, N.E.; Glorius, F. *Angew. Chem. Int. Ed.* ***2011***, *50*, 8412.
[999] Sawano, T.; Ashouri, A.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* ***2012***, *134*, 18936.
[1000] Kamei, T.; Uryu, M.; Shimada, T. *Tetrahedron Lett.* ***2016***, *57*, 1622.
[1001] Fonseca, M.T.H.; List, B. *Angew. Chem. Int. Ed.* ***2004***, *43*, 3958.
[1002] Kwan, E.E.; Scheerer, J.R.; Evans, D.A. *J. Org. Chem.* ***2013***, *78*, 175.
[1003] Bremeyer, N.; Smith, S.C.; Ley, S.V.; Gaunt, M.J. *Angew. Chem. Int. Ed.* ***2004***, *43*, 2681.
[1004] Holeman, D.S.; Rasne, R.M.; Grossman, R.B. *J. Org. Chem.* ***2002***, *67*, 3149.
[1005] Zhao, C.; Toste, F.D.; Bergman, R.G. *J. Am. Chem. Soc.* ***2011***, *133*, 10787.
[1006] Kim, H.; Byeon, S.R.; Leed, M.G.D.; Hong, J. *Tetrahedron Lett.* ***2011***, *52*, 2468.
[1007] Zhao, X.; Gong, J.-J.; Yuan, K.; Sha, F.; Wu, X.-Y. *Tetrahedron Lett.* ***2015***, *56*, 2526.
[1008] Qin, Y.; Lv, J.; Luo, S.; Cheng, J.-P. *Org. Lett.* ***2014***, *16*, 5032.
[1009] MacKay, J.A.; Landis, Z.C.; Motika, S.E.; Kench, M.H. *J. Org. Chem.* ***2012***, *77*, 7768.
[1010] Rudorf, W.-D.; Schwarz, R. *Synlett* ***1993***, 369.
[1011] Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* ***2010***, *132*, 10275.
[1012] See Makosza, M. *Tetrahedron Lett.* ***1966***, 5489.
[1013] Villarino, L.; García-Fandiño, R.; López, F.; Mascareñas, J.L. *Org. Lett.* ***2012***, *14*, 2996.

alkene to form cyclopentenones (**32**). This transformation is called the *Nazarov cyclization*.[1014]



The addition is formally a *Michael addition*, and structural variations are possible that prepare a variety of cyclopentenones. Substituents on the C=C units lead to cyclopentenones that bear those substituents. The steric influence of substituents[1015] and also the effects of torquoselectivity[1016] have been discussed. The rate-accelerating influence observed in *N*- and *S*-heterocycles has been noted.[1017] Fully substituted dienones have been used.[1018] It is noted that the iso-Nazarov reaction has been reviewed.[1019] The Nazarov reaction of aryl vinyl β-keto esters gave indanone derivatives.[1020] Note that a *retro*-Nazarov is possible with α-bromocyclopentanones.[1021] There is a so-called interrupted Nazarov, in which an amine is trapped after cyclization to give an α-amino conjugated cyclopentenone.[1022] Treatment of a Nazarov diene with BF_3•OEt_2 and then treatment with Br_2 gave the Nazarov product dibromide in an interrupted Nazarov cyclization process.[1023] A decarboxylative Nazarov cyclization, mediated by carbon dioxide, has been reported.[1024] Spirocycles have been prepared via a tandem *Nazarov-Wagner-Meerwein* sequence.[1025] An aza-Nazarov-type reaction is known.[1026] A vinylogous Nazarov reaction is involved in the cyclization of cross-conjugated trienes[1027] (Sec. 6.B for vinylogy). The use of a chiral ligand gave the cyclopentenone with modest enantioselectivity,[1028] although asymmetric Nazarov

[1014] Nazarov, I.N.; Torgov, I.B.; Terekhova, L.N. *Izv. Akad. Nauk. SSSR otd. Khim. Nauk,* ***1942***, 200; Frontier, A.J.; Collison, C. *Tetrahedron* ***2005***, *61*, 7577; Tius, M.A. *Eur. J. Org. Chem.* ***2005***, 2193; Audran, G.; Brémond, P.; Feuerstein, M.; Marque, S.R.A.; Santelli, M. *Tetrahedron* ***2013***, *69*, 8325. See Lebœuf, D.; Gandon, V.; Ciesielski, J.; Frontier, A.J. *J. Am. Chem. Soc.* ***2012***, *134*, 6296. For applications to natural product synthesis, see Vinogradov, M.G.; Turova, O.V.; Zlotin, S.G. *Org. Biomol. Chem.* ***2017***, *15*, 8245.

[1015] Marcus, A.P.; Amy, S.; Lee, A.S.; Davis, R.L.; Tantillo, D.J.; Sarpong, R. *Angew. Chem. Int. Ed.* ***2008***, *47*, 6379.

[1016] Morgan, T.D.R.; LeBlanc, L.M.; Ardagh, G.H.; Boyd, R.J.; Burnell, D.J. *J. Org. Chem.* ***2015***, *80*, 1042; Kerr, D.J.; Miletic, M.; Chaplin, J.H.; White, J.M.; Flynn, B.L. *Org. Lett.* ***2012***, *14*, 1732. The torquoselectivity of retro-Nazarov reactions has been discussed: see Naruse, Y.; Ichihashi, Y.; Shimizu, T.; Inagaki, S. *Org. Lett.* ***2012***, *14*, 3728.

[1017] Cavalli, A.; Pacetti, A.; Recanatini, M.; Prandi, C.; Scarpi, D.; Occhiato, E.G. *Chem. Eur. J.* ***2008***, *14*, 9292.

[1018] Jolit, A.; Rodriguez, S.V.; Yap, G.P.A.; Tius, M.A. *Angew. Chem. Int. Ed.* ***2013***, *52*, 11102.

[1019] Riveira, M.J.; Marsili, L.A.; Mischne, M.P. *Org. Biomol. Chem.* ***2017***, *15*, 9255.

[1020] Xi, Z.-G.; Zhu, L.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* ***2013***, *78*, 606.

[1021] Harmata, M.; Lee, D.R. *J. Am. Chem. Soc.* ***2002***, *124*, 14328. For a discussion of the scope and mechanism of the retro-Nazarov reaction, see Harmata, M.; Schreiner, P.R.; Lee, D.R.; Kirchhoefer, P.L. *J. Am. Chem. Soc.* ***2004***, *126*, 10954. For a torquoselective retro-Nazarov reaction, see Harmata, M.; Lee, D.R.; Barnes, C.L. *Org. Lett.* ***2005***, *7*, 1881.

[1022] Dhoro, F.; Kristensen, T.E.; Stockmann, V.; Yap, G.P.A.; Tius, M.A. *J. Am. Chem. Soc.* ***2007***, *129*, 7256. See also, Grant, T.N.; Rieder, C.J.; West, F.G. *Chem. Commun.* ***2009***, 5676.

[1023] Schatz, D.J.; Kwon, Y.; Scully, T.W.; West, F.G. *J. Org. Chem.* ***2016***, *81*, 12494.

[1024] Komatsuki, K.; Sadamitsu, Y.; Sekine, K.; Saito, K.; Yamada, T. *Angew. Chem. Int. Ed.* ***2017***, *56*, 11594.

[1025] Huang, J.; Frontier, A.J. *J. Am. Chem. Soc.* ***2007***, *129*, 8060.

[1026] Ji, W.; Liu, Y.A.; Liao, X. *Angew. Chem. Int. Ed.* ***2016***, *55*, 13286.

[1027] Rieder, C.J.; Winberg, K.J.; West, F.G. *J. Am. Chem. Soc.* ***2009***, *131*, 7504.

[1028] Aggarwal, V.K.; Belfield, A.J. *Org. Lett.* ***2003***, *5*, 5075.

cyclizations are well known.[1029] The origins of stereoselectivity in the thiourea/primary amine-catalyzed reaction has been discussed.[1030] Nazarov-like cyclization reactions are also known.[1031] Gold,[1032] Cr-salen,[1033] and V-catalyzed[1034] cyclizations have been reported, as well as a Sc-catalyzed cyclization in water.[1035] Heating dienones in DME or an ionic liquid has been shown to give the Nazarov product without addition of a Lewis acid.[1036] Allenes participate in Nazarov cyclization reactions.[1037]

Vinyl sulfones undergo Michael addition.[1038] Nitro compounds add to conjugated ketones via Michael addition.[1039] Nitroalkenes are Michael acceptors[1040] for the enolate anions of ß-keto esters.[1041] Other substrates have been added to nitroalkenes via Michael addition.[1042] The Y-catalyzed conjugate addition of allylic substrates to alkylidene malonates has been reported.[1043] The peptide-catalyzed, enantioselective conjugate addition of nitromethane to conjugated aldehydes gave an all-carbon quaternary stereocenter.[1044]

The synthesis of 4-hydroxycyclopentenone derivatives from 2-furylcarbinols via an acid-catalyzed rearrangement is known as the *Piancatelli rearrangement*.[1045] A dysprosium triflate-catalyzed reaction has been reported.[1046] An intramolecular *aza-Piancatelli rearrangement* has been reported,[1047] and catalytic enantioselective aza-Piancatelli rearrangements are known.[1048]

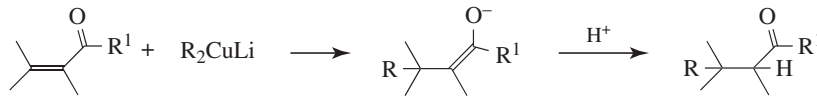
In a diastereoselective process, one of the two pairs is formed exclusively, or predominantly, as a racemic mixture.[1049] When either or both of the reaction components have a chiral substituent, the reaction can be enantioselective, with only one of the four diastereomers formed predominantly.[1050] There are many examples of catalytic enantioselective

[1029] See Shimada, N.; Stewart, C.; Tius, M.A. *Tetrahedron* ***2011***, *67*, 5851.
[1030] Asari, A.H.; Lam, Y.-h.; Tius, M.A.; Houk, K.N. *J. Am. Chem. Soc.* ***2015***, *137*, 13191.
[1031] Di Grandi, M.J. *Org. Biomol. Chem.* ***2014***, *12*, 5331.
[1032] Zhang, L.; Wang, S. *J. Am. Chem. Soc.* ***2006***, *128*, 1442.
[1033] Hutson, G.E.; Türkmen, Y.E.; Rawal, V.H. *J. Am. Chem. Soc.* ***2013***, *135*, 4988.
[1034] Walz, I.; Bertogg, A.; Togni, A. *Eur. J. Org. Chem.* ***2007***, 2650.
[1035] Kokubo, M.; Kobayashi, S. *Chem. Asian J.* ***2009***, *4*, 526.
[1036] Douelle, F.; Tal, L.; Greaney, M.F. *Chem. Commun.* ***2005***, 660.
[1037] Banaag, A.R.; Tius, M.A. *J. Org. Chem.* ***2008***, *73*,8133.
[1038] Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* ***2005***, *127*, 8948.
[1039] See Vakulya, B.; Varga, S.; Soós, T. *J. Org. Chem.* ***2008***, *73*, 3475.
[1040] See Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* ***1985***, *18*, 284; Baer, H.H.; Urbas L. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 2, Wiley, NY, ***1970***, pp. 130–148. See Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* ***2004***, *126*, 11148.
[1041] Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* ***2005***, *127*, 119.
[1042] See Mattson, A.E.; Zuhl, A.M.; Reynolds, T.E.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2006***, *128*, 4932; Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas III, C.F. *J. Am. Chem. Soc.* ***2006***, *128*, 4966; Huang, H.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2006***, *128*, 7170; Malerich, J.P.; Hagihara, K.; Rawal, V.H. *J. Am. Chem. Soc.* ***2008***, *130*, 14416.
[1043] Fallan, C.; Quigley, P.F.; Lam, H.W. *J. Org. Chem.* ***2011***, *76*, 4112.
[1044] Akagawa, K.; Kudo, K. *Angew. Chem. Int. Ed.* ***2012***, *51*, 12786.
[1045] Piancatelli, G.; Scettri, A.; Barbadoro, S. *Tetrahedron Lett.* ***1976***, *17*, 3555; Piutti, C.; Quartieri, F. *Molecules* ***2013***, 12290.
[1046] Fisher, D.; Palmer, L.I.; Cook, J.E.; Davis, J.E.; de Alaniz, J.R. *Tetrahedron* ***2014***, *70*, 4105.
[1047] Xu, Z.-L.; Xing, P.; Jiang, B. *Org. Lett.* ***2017***, *19*, 1028.
[1048] Li, H.; Tong, R.; Sun, J. *Angew. Chem. Int. Ed.* ***2016***, *55*, 15125; Gade, A.B.; Patil, N.T. *Synlett* ***2017***, *28*, 1096.
[1049] See Oare, D.A.; Heathcock, C.H. *Top. Stereochem.* ***1989***, *19*, 237.
[1050] See Töke, L.; Fenichel, L.; Albert, M. *Tetrahedron Lett.* ***1995***, *36*, 5951; Enders, D.; Demir, A.S.; Rendenbach, B.E.M. *Chem. Ber.* ***1987***, *120*, 1731.

Michael additions,[1051] often by the use of a chiral catalyst.[1052] Enantioselective Michael reactions are quite important.[1053] Common chiral catalysts used with carbonyl substrates include Ru,[1054] Ni,[1055] Sr,[1056] and Al(salen) complexes.[1057] Chiral organocatalysts[1058] such as oxazolidinones[1059] have been developed and chiral imines have also been used.[1060] Certain antibodies have been used to facilitate chiral, intramolecular Michael addition reactions.[1061] Enzymes have been used for asymmetric Michael reactions.[1062] Addition of chiral additives to the reaction, such as metal-salen complexes,[1063] proline derivatives,[1064] or (−)-sparteine,[1065] leads to product formation with good to excellent asymmetric induction. 2-Amino-DMAP/squaramide has been used as an organocatalyst.[1066] *Cinchona* alkaloids were used for the enantioselective conjugate addition of nitroalkanes to enones,[1067] and organocatalytic enantioselective conjugate addition reactions are important in synthesis.[1068] Organocatalysts have been used for the asymmetric conjugate addition of acetone[1069] or other ketones[1070] to nitroalkenes.

OS **I**, 272; **II**, 200; **III**, 286; **IV**, 630, 652, 662, 776; **V**, 486, 1135; **VI**, 31, 648, 666, 940; **VII**, 50, 363, 368, 414, 443; **VIII**, 87, 210, 219, 444, 467; **IX**, 526. See also, OS **VIII**, 148.

15-21 Conjugate Addition of Organocuprates and Other Organometallic Compounds



[1051] See Krause, N.; Hoffmann-Röder, A. *Synthesis* ***2001***, 171.
[1052] Desimoni, G.; Quadrelli, P.; Righetti, P.P. *Tetrahedron* ***1990***, *46*, 2927.
[1053] Thirumalaikumar, M. *Org. Prep. Proceed. Int.* ***2011***, *43*, 67.
[1054] Guo, R.; Morris, R.H.; Song, D. *J. Am. Chem. Soc.* ***2005***, *127*, 516.
[1055] Evans, D.A.; Thomson, R.J.; Franco, F. *J. Am. Chem. Soc.* ***2005***, *127*, 10816.
[1056] Agostinho, M.; Kobayashi, S. *J. Am. Chem. Soc.* ***2008***, *130*, 2430.
[1057] Taylor, M.S.; Zalatan, D.N.; Lerchner, A.M.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2005***, *127*, 1313.
[1058] See Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, Á.; Vera, S. *Angew. Chem. Int. Ed.* ***2007***, *46*, 8431.
[1059] Peelen, T.J.; Chi, Y.; Gellman, S.H. *J. Am. Chem. Soc.* ***2005***, *127*, 11598.
[1060] d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* ***1992***, *3*, 459.
[1061] Weinstain, R.; Lerner, R.A.; Barbas III, C.F.; Shabat, D. *J. Am. Chem. Soc.* ***2005***, *127*, 13104.
[1062] Svedendahl, M.; Hult, K.; Berglund, P. *J. Am. Chem. Soc.* ***2005***, *127*, 17988.
[1063] Jha, S.C.; Joshi, N.N. *Tetrahedron: Asymmetry* ***2001***, *12*, 2463.
[1064] Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* ***1996***, *61*, 3520.
[1065] Xu, F.; Tillyer, R.D.; Tschaen, D.M.; Grabowski, E.J.J.; Reider, P.J. *Tetrahedron: Asymmetry* ***1998***, *9*, 1651.
[1066] Işık, M.; Unver, M.Y.; Tanyeli, C. *J. Org. Chem.* ***2015***, *80*, 828.
[1067] Liu, W.; Mei, D.; Wang, W.; Duan, W. *Tetrahedron Lett.* ***2013***, *54*, 3791; Hirashima, S.; Nakashima, K.; Fujino, Y.; Arai, R.; Sakai, T.; Kawada, M.; Koseki, Y.; Murahashi, M.; Tada, N.; Itoh, A.; Miura, T. *Tetrahedron Lett.* ***2014***, *55*, 4619.
[1068] Vicario, J.L.; Badía, D.; Carillo, L.; Reyes, E. *Organocatalytic Enantioselective Conjugate Addition Reactions. A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*, RSC Publishing, Cambridge ***2010***.
[1069] Lu, A.; Liu, T.; Wu, R.; Wang, Y.; Wu, G.; Zhou, Z.; Fang, J.; Tang, C. *J. Org. Chem.* ***2011***, *76*, 3872. Also see Ruiz-Olalla, A.; de Gracia Retamosa, M.; Cossío, F.P. *J. Org. Chem.* ***2015***, *80*, 5588.
[1070] Yu, C.; Qiu, J.; Zheng, F.; Zhong, W. *Tetrahedron Lett.* ***2011***, *52*, 3298; Yu, L.; Li, P. *Tetrahedron Lett.* ***2014***, *55*, 3697. Also see Nakashima, K.; Hirashima, S.; Kawada, M.; Koseki, Y.; Tada, N.; Itoh, A.; Miura, T. *Tetrahedron Lett.* ***2014***, *55*, 2703.

The conjugate addition reaction of organometallic reagents to conjugated compounds generates an enolate anion as the product, which can be hydrolyzed to the carbonyl derivatives.[1071] One of the better known variations reacts lithium dialkylcopper reagents (R_2CuLi reagents,[1072] also known as *Gilman reagents*, see **10-57**) with α,β-unsaturated aldehydes[1073] and ketones (R′ = H, R, Ar) and other systems of the form C≡C–C=O[1074] to give conjugate addition products.[1075] α,β-Unsaturated esters are less reactive,[1076] and the corresponding acids do not react at all. If Me_3SiCl is present, the enolate anion product is trapped as the silyl enol ether and the reaction takes place much faster, and in higher yield.[1077] Solvent effects are important for the reactivity of organocuprates,[1078] which influence aggregation and aggregation state of the dialkyl cuprate.[1079]

Conjugate addition of the cuprate to the α,β-unsaturated ketone leads to substitution at the β position and formation an enolate ion, as noted above. It is possible for this enolate anion to react with an electrophilic species such as an alkyl halide (*tandem vicinal difunctionalization*), in some cases at the O and in most cases at the C.[1080] For example, if an alkyl halide R^2X is present (R^2 = primary alkyl or allylic), the enolate anion can be alkylated directly to give an α-substituted carbonyl compound.[1081]

An excess of the cuprate reagent relative to the conjugated substrate is often required. In general, only one of the R groups of R_2CuLi adds to the substrate; the other is wasted with respect to the conjugated substrate. The difficulty of group transfer can be overcome by using one of the mixed reagents R(R′C≡C)CuLi,[1082] R(O-*t*-Bu)CuLi,[1083] or R(PhS)CuLi,[1084] each of which transfers only the R group. Mixed reagents are easily prepared by the reaction of RLi with R′C≡CCu (R′ = *n*-Pr or *t*-Bu), *t*-BuOCu, or PhSCu, respectively. The mixed reagents R(CN)CuLi[1085] (prepared from RLi and CuCN) and

[1071] Goncalves-Contal, S.; Gremaud, L.; Palais, L.; Babel, L.; Alexakis, A. *Synthesis* ***2016***, *48*, 3301; Huang, Z.; Dong, G. *Tetrahedron Lett.* ***2014***, *55*, 5869. For Rh-catalyzed reactions, see Heravi, M.M.; Dehghani, M.; Zadsirjan, V. *Tetrahedron: Asymmetry* ***2016***, *27*, 513.

[1072] Anderson, R.J.; Corbin, V.L.; Cotterrell, G.; Cox, G.R.; Henrick, C.A.; Schaub, F.; Siddall, J.B. *J. Am. Chem. Soc.* ***1975***, *97*, 1197. See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 616–627.

[1073] Alexakis, A.; Chuit, C.; Commerçon-Bourgain, M.; Foulon, J.P.; Jabri, N.; Mangeney, P.; Normant, J.F. *Pure Appl. Chem.* ***1984***, *56*, 91.

[1074] For reactions with conjugated enynes see Miginiac, L. *J. Organomet. Chem.* ***1982***, *238*, 235.

[1075] See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1599–1613, 1814–1824; Posner, G.H. *Org. React.* ***1972***, *19*, 1; House, H.O. *Acc. Chem. Res.* ***1976***, *9*, 59; Yamanaka, M.; Kato, S.; Nakamura, E. *J. Am. Chem. Soc.* ***2004***, *126*, 6287; Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, ***1980***, pp. 10–67.

[1076] See Nagashima, H.; Ozaki, N.; Washiyama, M.; Itoh, K. *Tetrahedron Lett.* ***1985***, *26*, 657.

[1077] Horiguchi, Y.; Komatsu, M.; Kuwajima, I. *Tetrahedron Lett.* ***1989***, *30*, 7087; Bertz, S.H.; Smith, R.A.J. *Tetrahedron* ***1990***, *46*, 4091. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1491–1492. See Lipshutz, B.H.; James, B. *Tetrahedron Lett.* ***1993***, *34*, 6689.

[1078] See also Yang, J.; Dudley, G.B. *Tetrahedron Lett.* ***2007***, *48*, 7887.

[1079] Henze, W.; Vyater, A.; Krause, N.; Gschwind, R.M. *J. Am. Chem. Soc.* ***2005***, *127*, 17335. See Murphy, M.D.; Ogle, C.A.; Bertz, S.H. *Chem. Commun.* ***2005***, 854.

[1080] Chapdelaine, M.J.; Hulce, M. *Org. React.* ***1990***, *38*, 225; Taylor, R.J.K. *Synthesis* ***1985***, 364; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1609–1612, 1826.

[1081] See Posner, G.H.; Lentz, C.M. *Tetrahedron Lett.* ***1977***, 3215.

[1082] Corey, E.J.; Floyd, D.; Lipshutz, B.H. *J. Org. Chem.* ***1978***, *43*, 3419.

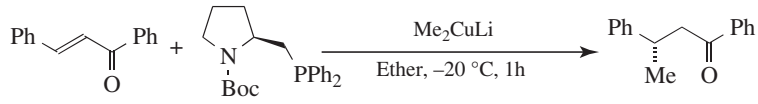
[1083] Posner, G.H.; Whitten, C.E. *Tetrahedron Lett.* ***1973***, 1815.

[1084] Posner, G.H.; Whitten, C.E.; Sterling, J.J. *J. Am. Chem. Soc.* ***1973***, *95*, 7788.

[1085] See Ledlie, D.B.; Miller, G. *J. Org. Chem.* ***1979***, *44*, 1006.

$R_2Cu(CN)Li_2$[1086] also selectively transfer the R group.[1087] With mixed cuprates, one of the ligands may be less prone to transfer than the other, as $R(R'Se)Cu(CN)Li_2$, leading to selective transfer of the R group.[1088] This less transferable ligand is sometimes referred to as a "dummy ligand." The selectivity of ligand transfer depends on two factors, (i) thermodynamics of groups such as alkyl or thioalkyl and (ii) kinetic reactivity of groups such as silylalkyl or vinyl.[1089] A Cu(III) complex has been detected using rapid injection NMR.[1090]

The 1,4-addition of organometallic compounds has been performed diastereoselectively[1091] and enantioselectively.[1092] The influence of solvent and additives on yield and selectivity has been examined.[1093] Addition of chiral ligands to the organocuprate conjugate addition reaction leads to alkylation with good to excellent enantioselectivity.[1094] The conjugate addition of dimethyl cuprate in the presence of a chiral ligand, such as **33**, is an example.[1095]



33 79% (84% ee, S)

Chiral bis(oxazoline) copper catalysts have been used for the conjugate addition of indoles to α,β-unsaturated esters.[1096] Enantioselectivity is effectively controlled by the choice of ligand and its interaction with a Cu compound, where different ligands on the metal may lead to differences in selectivity.[1097]

Conjugated alkynyl ketones also react via 1,4-addition to give substituted alkenyl ketones.[1098] Organocopper reagents RCu as well as certain R_2CuLi reagents add to α,β-unsaturated and acetylenic sulfoxides.[1099] The reaction has been carried out[1100] with α,β-acetylenic ketones,[1101] esters, and nitriles. Conjugate addition to α,β-unsaturated and acetylenic acids and esters, as well as ketones, can be achieved by the use of the coordinated reagents $RCu{\bullet}BF_3$ (R = primary).[1102] The silylcupration of conjugated alkynes in water has been reported.[1103]

[1086] See Lipshutz, B.H. *Tetrahedron Lett.* ***1983***, *24*, 127.
[1087] See Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A. *J. Org. Chem.* ***1984***, *49*, 3938.
[1088] Zinn, F.K.; Ramos, E.C.; Comasseto, J.V. *Tetrahedron Lett.* ***2001***, *42*, 2415.
[1089] Yamanaka, M.; Nakamura, E. *J. Am. Chem. Soc.* ***2005***, *127*, 4697.
[1090] Bertz, S.H.; Cope, S.; Murphy, M.; Ogle, C.A.; Taylor, B.J. *J. Am. Chem. Soc.* ***2007***, *129*, 7208. See Hu, H.; Snyder, J.P. *J. Am. Chem. Soc.* ***2007***, *129*, 7210.
[1091] Page, P.C.B.; Prodger, J.C.; Hursthouse, M.B.; Mazid, M. *J. Chem. Soc., Perkin Trans. 1* ***1990***, 167; Corey, E.J.; Hannon, F.J. *Tetrahedron Lett.* ***1990***, *31*, 1393.
[1092] See Posner, G.H. *Acc. Chem. Res.* ***1987***, *20*, 72. See the articles by Tomioka, K.; Koga, K. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***, pp. 201–224; Posner, G. pp. 225–241.
[1093] Christenson, B.; Ullenius, C.; Håkansson, M.; Jagner, S. *Tetrahedron* ***1992***, *48*, 3623.
[1094] See Naeemi, Q.; Robert, T.; Kranz, D.P.; Velder, J.; Schmalz, H.-G. *Tetrahedron: Asymmetry* ***2011***, *22*, 887.
[1095] Kanai, M.; Koga, K.; Tomioka, K. *Tetrahedron Lett.* ***1992***, *33*, 7193.
[1096] Jensen, K.B.; Thorhauge, J.; Hazell, R.G.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* ***2001***, *40*, 160.
[1097] See Okamoto, M.; Yamamoto, Y.; Sakaguchi, S. *Chem. Commun.* ***2009***, 7363.
[1098] Degl'Innocenti, A.; Stucchi, E.; Capperucci, A.; Mordini, A.; Reginato, G.; Ricci, A. *Synlett* ***1992***, 329, 332.
[1099] Truce, W.E.; Lusch, M.J. *J. Org. Chem.* ***1974***, *39*, 3174; ***1978***, *43*, 2252.
[1100] Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 456–457.
[1101] Lee, P.H.; Park, J.; Lee, K.; Kim, H.-C. *Tetrahedron Lett.* ***1999***, *40*, 7109.
[1102] See Lipshutz, B.H.; Ellsworth, E.L.; Siahaan, T.J. *J. Am. Chem. Soc.* ***1989***, *111*, 1351.
[1103] Linstadt, R.T.H.; Peterson, C.A.; Lippincott, D.J.; Jette, C.I.; Lipshutz, B.H. *Angew. Chem. Int. Ed.* ***2014***, *53*, 4159. See Vercruysse, S.; Jouvin, K.; Riant, O.; Evano, G. *Synthesis* ***2016***, *48*, 3373.

Various functional groups may be present in the substrate when organocuprates are employed.[1104] There is generally little or no competition from 1,2-addition (to the C=O). However, when R is allylic, 1,4-addition is observed with some substrates and 1,2-addition with others.[1105] The diastereoselectivity for the conjugate addition of cuprate to unsaturated lactams was shown to be reversed.[1106] Amine units have been transferred using α-lithio amides, CuCN, and various additives, which gave conjugate addition of an amidomethyl unit, $-CH_2N(Me)Boc$.[1107]

Other organometallic compounds add to conjugated systems. Grignard reagents add to conjugated substrates such as α,β-unsaturated ketones, cyano ketones,[1108] and alkenenitriles,[1109] but 1,2-addition may seriously compete:[1110] In general, substitution at the carbonyl group increases 1,4-addition, while substitution at the double bond increases 1,2-addition. In most cases both products are obtained, but α,β-unsaturated *aldehydes* nearly always give exclusive 1,2-addition when treated with Grignard reagents. Grignard reagents mixed with $CeCl_3$ generate a reactive species that gives primarily 1,4-addition.[1111] The extent of 1,4-addition of Grignard reagents can be increased by the use of a Cu catalyst such as CuCl or $Cu(OAc)_2$,[1112] forming a magnesium cuprate *in situ*. The Cu-catalyzed conjugate addition of Grignard reagents to enones has been done using flow techniques (Sec. 7.D).[1113] Catalytic enantioselective conjugate addition has been reported with Grignard reagents.[1114] Formation of the conjugate addition product is often controlled by steric factors. It is likely that alkylcopper reagents, formed from RMgX and Cu^+ (cupric acetate is reduced to cuprous ion by excess RMgX), are the actual reactive species in these cases.[1073] Grignard reagents add to cyclic enones in the presence of a Cu catalyst.[1115] Chiral templates have also been used with Grignard reagents, both directly[1116] and in the presence of $AlMe_2Cl$.[1117] The enantioselective Grignard addition to nitroalkenes has been discussed.[1118]

The mechanisms of most of these reactions have been studied. The 1,4-uncatalyzed Grignard reaction has been postulated to proceed by a cyclic mechanism, but there is evidence

[1104] Charonnat, J.A.; Mitchell, A.L.; Keogh, B.P. *Tetrahedron Lett.* ***1990***, *31*, 315.
[1105] House, H.O.; Fischer Jr., W.F. *J. Org. Chem.* ***1969***, *34*, 3615. See also, Daviaud, G.; Miginiac, P. *Tetrahedron Lett.* ***1973***, 3345.
[1106] Wright, S.W.; Choi, C.; Chung, S.; Boscoe, B.P.; Drozda, S.E.; Mousseau, J.J.; Trzupek, J.D. *Org. Lett.* ***2015***, *17*, 5204.
[1107] See Dieter, R.K.; Lu, K.; Velu, S.E. *J. Org. Chem.* ***2000***, *65*, 8715. See Dieter, R.K.; Topping, C.M.; Nice, L.E. *J. Org. Chem.* ***2001***, *66*, 2302.
[1108] Kung, L.-R.; Tu, C.-H.; Shia, K.-S.; Liu, H.-J. *Chem. Commun.* ***2003***, 2490.
[1109] Fleming, F.F.; Wang, Q.; Zhang, Z.; Steward, O.W. *J. Org. Chem.* ***2002***, *67*, 5953.
[1110] See Negishi, E. *Organometallics in Organic Synthesis*, Vol. 1, Wiley, NY, ***1980***, pp. 127–133.
[1111] Bartoli, G.; Bosco, M.; Sambri, L.; Marcantoni, E. *Tetrahedron Lett.* ***1994***, *35*, 8651.
[1112] Posner, G.H. *Org. React.* ***1972***, *19*, 1; Martin D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* ***2006***, *128*, 8416.
[1113] Katayama, H.; Matsubara, S. *Chem. Lett.* ***2013***, *42*, 471.
[1114] López, F.; Minnaard, A.J.; Feringa, B.L. *Acc. Chem. Res.* ***2007***, *40*, 179; Harutyunyan, S.R.; den Hartog, T.; Geurts, K.; Minnaard, A.J.; Feringa, B.L. *Chem. Rev.* ***2008***, *108*, 2824; See Germain, N.; Magrez, M.; Kehrli, S.; Mauduit, M.; Alexakis, A. *Eur. J. Org. Chem.* ***2012***, 5301.
[1115] Tissot, M.; Hernández, A.P.; Müller, D.; Mauduit, M.; Alexakis, A. *Org. Lett.* ***2011***, *13*, 1524; Li, J.; Xu, L. *Tetrahedron* ***2015***, *71*, 2858.
[1116] Han, Y.; Hruby, V.J. *Tetrahedron Lett.* ***1997***, *38*, 7317.
[1117] Bongini, A.; Cardillo, G.; Mingardi, A.; Tomasini, C. *Tetrahedron: Asymmetry* ***1996***, *7*, 1457.
[1118] Reddy, P.; Bandichhor, R. *Tetrahedron Lett.* ***2013***, *54*, 3911.

against it.[1119] The R_2CuLi-[1120] and Cu-catalyzed Grignard additions may involve a number of mechanisms, since the actual attacking species and substrates are so diverse.[1121] A free-radical mechanism of some type (perhaps SET) has been suggested[1122] although the fact that retention of configuration at R has been demonstrated in several cases rules out a completely free R• radical.[1123] For simple α,β-unsaturated ketones, such as 2-cyclohexenone, and Me_2CuLi, there is evidence[1124] for a *d*,π* complex, with bonding between copper, as a base supplying a pair of *d* electrons, and the enone, as a Lewis acid using the π* orbital of the allylic system.[122] The ^{13}C NMR spectrum of an intermediate similar to an enolate/Cu complex has been reported.[1125]

Organolithium reagents[1126] generally react with conjugated aldehydes, ketones, and esters by 1,2-addition,[1127] but can be made to give 1,4-addition with α,β-unsaturated ketones[1128] and aldehydes[1129] if the reactions are conducted in the presence of HMPA.[1130] Among organolithium reagents that have been found to add 1,4 in this manner are 2-lithio-1,3-dithianes (see **10-71**)[1131] and vinyllithium reagents.[1132] A reagent based on RMgX/3 MeLi gave conjugate addition with α,β-unsaturated amides and carboxylic acid derivatives.[1133] If the organolithium reagent is complexed, 1,4-addition is more successful. The reaction of an aryllithium reagent with $B(OMe)_3$, for example, led to a Rh-catalyzed conjugate addition with excellent enantioselectivity when a chiral ligand was employed.[1134]

Organozinc compounds add to conjugated systems, especially dialkyl zinc compounds, R_2Zn. Many dialkylzinc compounds can be used, including vinylzinc compounds.[1135] The use of chiral ligands is effective for conjugate addition of dialkylzinc compounds to α,β-unsaturated ketones, esters, and so on,[1136] including conjugated lactones.[1137] The addition of a chiral complex to dialkylzinc compounds leads to enantioselective conjugate addition in conjunction with $Cu(OTf)_2$,[1138] CuCN,[1139] or other Cu

[1119] House, H.O.; Thompson, H.W. *J. Org. Chem.* ***1963***, *28*, 360; Klein, J. *Tetrahedron* ***1964***, *20*, 465. See, however, Marets, J.; Rivière, H. *Bull. Soc. Chim. Fr.* ***1970***, 4320.
[1120] Kingsbury, C.L.; Smith, R.A.J. *J. Org. Chem.* ***1997***, *62*, 4629. See Snyder, J.P. *J. Am. Chem. Soc.* ***1995***, *117*, 11025.
[1121] See Ullenius, C.; Christenson, B. *Pure Appl. Chem.* ***1988***, *60*, 57; Krause, N. *Tetrahedron Lett.* ***1989***, *30*, 5219.
[1122] See Wigal, C.T.; Grunwell, J.R.; Hershberger, J. *J. Org. Chem.* ***1991***, *56*, 3759.
[1123] Whitesides, G.M.; Kendall, P.E. *J. Org. Chem.* ***1972***, *37*, 3718.
[1124] Corey, E.J.; Hannon, F.J.; Boaz, N.W. *Tetrahedron* ***1989***, *45*, 545.
[1125] Bertz, S.H.; Smith, R.A.J. *J. Am. Chem. Soc.* ***1989***, *111*, 8276.
[1126] See Hunt, D.A. *Org. Prep. Proced. Int.* ***1989***, *21*, 705–749.
[1127] Cohen, T.; Abraham, W.D.; Myers, M. *J. Am. Chem. Soc.* ***1987***, *109*, 7923.
[1128] See Roux, M.C.; Wartski, L.; Seyden-Penne, J. *Tetrahedron* ***1981***, *37*, 1927.
[1129] El-Bouz, M.; Wartski, L. *Tetrahedron Lett.* ***1980***, *21*, 2897.
[1130] Sikorski, W.H.; Reich, H.J. *J. Am. Chem. Soc.* ***2001***, *123*, 6527.
[1131] See El-Bouz, M.; Wartski, L. *Tetrahedron Lett.* ***1980***, *21*, 2897. See also, Bürstinghaus, R.; Seebach, D. *Chem. Ber.* ***1977***, *110*, 841.
[1132] See Maezaki, N.; Sawamoto, H.; Yuyama, S.; Yoshigami, R.; Suzuki, T.; Izumi, M.; Ohishi, H.; Tanaka, T. *J. Org. Chem.* ***2004***, *69*, 6335.
[1133] Kikuchi, M.; Niikura, S.; Chiba, N.; Terauchi, N.; Asaoka, M. *Chem. Lett.* ***2007***, *36*, 736.
[1134] Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* ***1999***, *40*, 6957.
[1135] See Ikeda, S.-i.; Cui, D.-M.; Sato, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 4712.
[1136] See Ebisu, Y.; Kawamura, K.; Hayashi, M. *Tetrahedron: Asymmetry* ***2012***, *23*, 959.
[1137] Reetz, M.T.; Gosberg, A.; Moulin, D. *Tetrahedron Lett.* ***2002***, *43*, 1189.
[1138] Alexakis, A.; Polet, D.; Rosset, S.; March, S. *J. Org. Chem.* ***2004***, *69*, 5660, and references cited therein. See Hajra, A.; Yoshikai, N.; Nakamura, E. *Org. Lett.* ***2006***, *8*, 4153.
[1139] Hird, A.W.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2005***, *127*, 14988.

compounds.[1140] The Cu-catalyzed conjugate addition of dialkylzinc reagents to enones proceeds with good enantioselectivity.[1141] Chiral ionic liquids have also been employed.[1142] 1,6-Addition of dialkylzinc compounds has been reported, in the presence of a Rh catalyst.[1143] Other transition metal compounds,[1144] such as Pd,[1145] can be used in conjunction with dialkylzinc compounds or with arylzinc halides[1146] (ArZnCl). Mixed alkylzinc compounds also add to conjugated systems.[1147] Internal alkynes undergo 1,4-addition to conjugated esters using a combination of zinc metal and a Co complex as catalysts.[1148] Alkylzinc reagents undergo 1,6-conjugate addition to para-quinone methides using continuous flow techniques (Sec. 4.D).[1149]

Trialkylalanes (R_3Al) add 1,4 to α,β-unsaturated carbonyl compounds in the presence of nickel acetylacetonate[1150] or $Cu(OTf)_2$.[1151] Alkyl halides react via conjugate addition using BEt_3 or $AlEt_3$.[1152] Other metals are known to catalyze conjugate addition of alkyl or aryl groups, including Co.[1153] An In/Cu-mediated conjugate addition reaction is known using unactivated alkyl iodides.[1154] The Cu-catalyzed conjugate addition of alkenyl alanates to β-substituted cyclic enones has been reported.[1155] Multinuclear Cu/Al complexes were used for the asymmetric conjugate addition of trimethylaluminum.[1156] Conjugated ketoamides are methylated by the Cu-catalyzed reaction of trimethylaluminum.[1157]

The asymmetric conjugate addition of alkylzirconium reagents to α,β-unsaturated lactones has been reported.[1158] Alkylzirconium reagents also undergo conjugate addition to enones.[1159] Arylindium compounds add to conjugated carbonyl compounds in the presence of a rhodium catalyst.[1160]

[1140] Takahashi, Y.; Yamamoto, Y.; Katagiri, K.; Danjo, H.; Yamaguchi, K.; Imamoto, T. *J. Org. Chem.* ***2005***, *70*, 9009. For the use of Pd or Cu catalysts, see Marshall, J.A.; Herold, M.; Eidam, H.S.; Eidam, P. *Org. Lett.* ***2006***, *8*, 5505. Also see Yoshimura, M.; Shibata, N.; Kawakami, M.; Sakaguchi, S. *Tetrahedron* ***2012***, *68*, 3512.

[1141] Endo, K.; Hamada, D.; Yakeishi, S.; Ogawa, M.; Shibata, T. *Org. Lett.* ***2012***, *14*, 2342. Also see Zeng, X.; Gao, J.J.; Song, J.J.; Ma, S.; Desrosiers, J.-N.; Mulder, J.A.; Rodriguez, S.; Herbage, M.A.; Haddad, N.; Qu, B.; Fandrick, K.R.; Grinberg, N.; Lee, H.; Wei, X.; Yee, N.K.; Senanayake, C.H. *Angew. Chem. Int. Ed.* ***2014***, *53*, 12153; Zhao, W.; Wang, T.; Zhao, R.; Xie, H.; Liu, L. *Tetrahedron: Asymmetry* ***2016***, *27*, 157.

[1142] Malhotra, S.V.; Wang, Y. *Tetrahedron: Asymmetry* ***2006***, *17*, 1032.

[1143] Hayashi, T.; Yamamoto, S.; Tokunaga, N. *Angew. Chem. Int. Ed.* ***2005***, *44*, 4224.

[1144] Hirao, T.; Takada, T.; Sakurai, H. *Org. Lett.* ***2000***, *2*, 3659; Yin, Y.; Li, X.; Lee, D.-S.; Yang, T.-K. *Tetrahedron: Asymmetry* ***2000***, *11*, 3329; Shadakshari, U.; Nayak, S.K. *Tetrahedron* ***2001***, *57*, 8185.

[1145] Lorenzo, P.; Aurrecoechea, J.M.; de Lera, A.R.; Álvarez, R. *Eur. J. Org. Chem.* ***2013***, 2621.

[1146] Shitani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* ***2004***, *126*, 6240.

[1147] Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, T.A.; Reddy, C.K. *Angew. Chem. Int. Ed.* ***1997***, *36*, 1496.

[1148] Wang, C.-C.; Lin, P.-S.; Cheng, C.-H. *J. Am. Chem. Soc.* ***2002***, *124*, 9696.

[1149] Jadhav, A.S.; Anand, R.V. *Org. Biomol. Chem.* ***2017***, *15*, 56.

[1150] Bagnell, L.; Meisters, A.; Mole, T. *Aust. J. Chem.* ***1975***, *28*, 817; Ashby, E.C.; Heinsohn, G. *J. Org. Chem.* ***1974***, *39*, 3297. See also, Kunz, H.; Pees, K.J. *J. Chem. Soc., Perkin Trans. 1* ***1989***, 1168.

[1151] Su, L.; Li, X.; Chan, W.L.; Jia, X.; Chan, A.S.C. *Tetrahedron: Asymmetry* ***2003***, *24*, 1865.

[1152] Liu, J.-Y.; Jang, Y.-J.; Lin, W.-W.; Liu, J.-T.; Yao, C.-F. *J. Org. Chem.* ***2003***, *68*, 4030.

[1153] In the presence of Mn, see Amatore, M.; Gosmini, C.; Périchon, J. *J. Org. Chem.* ***2006***, *71*, 6130.

[1154] Shen, Z.-L.; Cheong, H.-L.; Loh, T.-P. *Tetrahedron Lett.* ***2009***, *50*, 1051.

[1155] Müller, D.; Alexakis, A. *Org. Lett.* ***2013***, *15*, 1594. See Gremaud, L.; Alexakis, A. *Angew. Chem. Int. Ed.* ***2012***, *51*, 794.

[1156] Endo, K.; Hamada, D.; Yakeishi, S.; Shibata, T. *Angew. Chem. Int. Ed.* ***2013***, *52*, 606.

[1157] Goncalves-Contal, S.; Gremaud, L.; Alexakis, A. *Angew. Chem. Int. Ed.* ***2013***, *52*, 12701.

[1158] Maciver, E.E.; Maksymowicz, R.M.; Wilkinson, N.; Roth, P.M.C.; Fletcher, S.P. *Org. Lett.* ***2014***, *16*, 3288; Sidera, M.; Roth, P.M.C.; Maksymowicz, R.M.; Fletcher, S.P. *Angew. Chem. Int. Ed.* ***2013***, *52*, 7995.

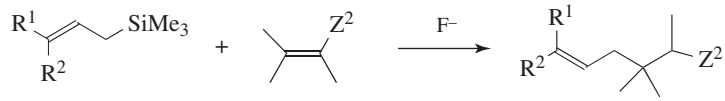
[1159] Maksymowicz, R.M.; Sidera, M.; Roth, P.M.C.; Fletcher, S.P. *Synthesis* ***2013***, *45*, 2662.

[1160] Tato, R.; Riveiros, R.; Sestelo, J.P.; Sarandeses, L.A. *Tetrahedron* ***2012***, *68*, 1606.

Terminal alkynes add to conjugated systems when using a Ru,[1161] Pd,[1162] Ni,[1163] or Rh catalyst.[1164] Intramolecular addition of terminal alkynes, in the presence of phenylboronic acid and a Rh catalyst, leads to cyclic compounds.[1165] Lithium tetraalkylgallium reagents give 1,4-addition.[1166] Trimethyl(phenyl)tin and a Rh catalyst gives conjugate addition of a methyl group[1167] and tetraphenyltin and a Pd catalyst adds a phenyl group.[1168] Triphenylbismuth (Ph_3Bi) and a Rh catalyst give conjugate addition of the phenyl group upon exposure to air.[1169] Similar reactivity is observed with a Pd catalyst in aqueous media.[1170] Allyltin compounds add an allyl group in the presence of a Sc catalyst.[1171] Aryl halides add in the presence of $NiBr_2$.[1172] Vinyl Zr complexes undergo conjugate addition when using a Rh catalyst.[1173]

OS **IV**, 93; **V**, 762; **VI**, 442, 666, 762, 786; **VIII**, 112, 257, 277, 479; **IX**, 328, 350, 640.

15-22 The Sakurai Reaction

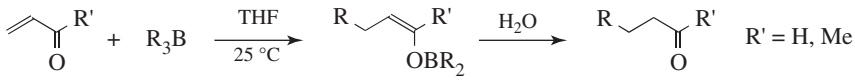


Allylic silanes ($R_2C{=}CHCH_2SiMe_3$) rather than silyl enol ethers can be added to conjugated systems in what is known as the *Sakurai reaction*.[1174] For example, an allyl group can be added to α,β-unsaturated carboxylic esters, amides, and nitriles, with $CH_2{=}CHCH_2SiMe_3$ and F^- ion (see **15-43**).[1175] This reagent gave better results than lithium diallylcuprate (**15-21**). Catalytic Sakurai reactions are known.[1176] The Pd-catalyzed reaction of conjugated ketones with $PhSi(OEt)_3$ with $SbCl_3$ and Bu_4NF in acetic acid gave the 1,4-addition product.[1177] Silicomolybic acid supported on silica gel has been used to catalyze the reaction.[1178] A similar reaction was reported using $PhSi(OMe)_3$ with a Rh catalyst.[1179] Silver fluoride was used to catalyze the reaction with allyl(trimethoxy)silane.[1180] The Sakurai reaction has been used in multi-component reactions.[1181]

[1161] Nishimura, T.; Guo, X.-X.; Uchiyama, N.; Katoh, T.; Hayashi, T. *J. Am. Chem. Soc.* ***2008***, *130*, 1576.
[1162] Chen, L.; Li, C.-J. *Chem. Commun.* ***2004***, 2362.
[1163] Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* ***2008***, *130*, 8132.
[1164] See Lerum, R.V.; Chisholm, J.D. *Tetrahedron Lett.* ***2004***, *45*, 6591.
[1165] Chen, Y.; Lee, C. *J. Am. Chem. Soc.* ***2006***, *128*, 15598.
[1166] Han, Y.; Huang, Y.-Z.; Fang, L.; Tao, W.-T. *Synth. Commun.* ***1999***, *29*, 867.
[1167] Oi, S.; Moro, M.; Ito, H.; Honma, Y.; Miyano, S.; Inoue, Y. *Tetrahedron* ***2002***, *58*, 91.
[1168] Ohe, T.; Uemura, S. *Tetrahedron Lett.* ***2002***, *43*, 1269.
[1169] Venkatraman, S.; Li, C.-J. *Tetrahedron Lett.* ***2001***, *42*, 781.
[1170] Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Commun.* ***2004***, 1822.
[1171] Williams, D.R.; Mullins, R.J.; Miller, N.A. *Chem. Commun.* ***2003***, 2220.
[1172] Condon, S.; Dupré, D.; Falgayrac, G.; Nédélec, J.-Y. *Eur. J. Org. Chem.* ***2002***, 105.
[1173] Kakuuchi, A.; Taguchi, T.; Hanzawa, Y. *Tetrahedron* ***2004***, *60*, 1293.
[1174] Sakurai, H.; Hosomi, A.; Hayashi, J. *Org. Synth.* ***VII***, 443; Kuhnert, N.; Peverley, J.; Robertson, J. *Tetrahedron Lett.* ***1998***, *39*, 3215; Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* ***1989***, *37*, 57 (see pp. 127, 335–370); Schinzer, D. *Synthesis* ***1988***, 263.
[1175] Majetich, G.; Casares, A.; Chapman, D.; Behnke, M. *J. Org. Chem.* ***1986***, *51*, 1745.
[1176] See Lee, P.H.; Lee, K.; Sung, S.-y.; Chang, S. *J. Org. Chem.* ***2001***, *66*, 8646.
[1177] Denmark, S.E.; Amishiro, N. *J. Org. Chem.* ***2003***, *68*, 6997.
[1178] Murugan, K.; Srimurugan, S.; Chen, C. *Tetrahedron* ***2011***, *67*, 5621.
[1179] Oi, S.; Taira, A.; Honma, Y.; Inoue, Y. *Org. Lett.* ***2003***, *5*, 97.
[1180] Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* ***2005***, *127*, 14556.
[1181] Pospíšil, J.; Kumamoto, T.; Markó, I.E. *Angew. Chem. Int. Ed.* ***2006***, *45*, 3357.

An enantioselective aza-Sakurai cyclization has been reported.[1182] The Ce-catalyzed enantioselective Sakurai reaction of aldehydes and allyltrimethylsilane has been reported.[1183] A counteranion-controlled disulfonimide organocatalyst allowed an enantioselective *Hosomi-Sakurai reaction* of (hetero)aromatic aldehydes and allylsilanes.[1184]

15-23 Conjugate Addition of Boranes to Activated Double Bonds



Just as trialkylboranes add to simple alkenes (**15-11**), they rapidly add to the double bonds of conjugated alkenes such as acrolein or methyl vinyl ketone in THF to give enol borinates (also see **10-68**), which can be hydrolyzed to aldehydes or ketones.[1185] If water is present in the reaction medium from the beginning, the reaction can be run in one laboratory step. Since the boranes can be prepared from alkenes (**15-11**), this reaction provides a means of lengthening a carbon chain by three or four carbons, respectively. Compounds containing a terminal alkyl group, such as crotonaldehyde ($CH_3CH{=}CHCHO$) and 3-penten-2-one, fail to react under these conditions, as does acrylonitrile, but slow and controlled addition of O_2 or by initiation with peroxides or UV light allows these compounds to react.[1186] A disadvantage is that only one of the three R groups of R_3B adds to the substrate, so that the other two are wasted. This difficulty is overcome by the use of a β-alkyl borinate,[1187] which permits *tert*-butyl groups to be added. Transition metals catalyze the addition of trialkylboranes to conjugated systems, and enantioselective reactions are known.[1188] The addition of allylboranes in the presence of a Ni catalyst is known,[1189] and this reaction was enhanced by the addition of methanol.[1190]

The conjugate addition of $B_2(Pin)_2$ to conjugated carbonyl compounds was catalyzed by Cu in a reaction that was done in water and open to the air.[1191] The mechanism of the *N*-heterocyclic carbene-catalyzed conjugated addition of $B_2(Pin)_2$ and borosilanes to conjugated carbonyl compounds has been probed.[1192] The asymmetric conjugate arylboration of enones was catalyzed by a binaphthol derivative.[1193] The corresponding β-1-alkynyl-9-BBN compounds also give the reaction.[1194] Vinyl boranes add to conjugated ketones in the

[1182] Park, Y.; Schindler, C.S.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2016***, *138*, 14848.
[1183] Zhao, S.; Zhang, X.; Zhang, Y.; Yang, H.; Huang, Y.; Zhang, K.; Du, T. *New J. Chem.* ***2015***, 7734.
[1184] Mahlau, M.; García-García, P.; List, B. *Chem. Eur. J.* ***2012***, *18*, 16283.
[1185] Köster, R.; Zimmermann, H.; Fenzl, W. *Liebigs Ann. Chem.* ***1976***, 1116. See Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 301–305, 318–323; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithica, NY, ***1972***, pp. 413–433.
[1186] Brown, H.C.; Kabalka, G.W. *J. Am. Chem. Soc.* ***1970***, *92*, 712, 714. See also, Miyaura, N.; Kashiwagi, M.; Itoh, M.; Suzuki, A. *Chem. Lett.* ***1974***, 395.
[1187] Brown, H.C.; Negishi, E. *J. Am. Chem. Soc.* ***1971***, *93*, 3777.
[1188] Nguyen, T.N.; May, J.A. *Tetrahedron Lett.* ***2017***, *58*, 1535.
[1189] Sieber, J.D.; Liu, S.; Morken, J.P. *J. Am. Chem. Soc.* ***2007***, *129*, 2214.
[1190] Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2007***, *9*, 1541.
[1191] Thorpe, S.B.; Calderone, J.A.; Santos, W.L. *Org. Lett.* ***2012***, *14*, 1918. See Kobayashi, S.; Xu, P.; Endo, T.; Ueno, M.; Kitanosono, T. *Angew. Chem. Int. Ed.* ***2012***, *51*, 12763.
[1192] Wu, H.; Garcia, J.M.; Haeffner, F.; Radomkit, S.; Zhugralin, A.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2015***, *137*, 10585.
[1193] Turner, H.M.; Patel, J.; Niljianskul, N.; Chong, J.M. *Org. Lett.* ***2011***, *13*, 5796.
[1194] Sinclair, J.A.; Molander, G.A.; Brown, H.C. *J. Am. Chem. Soc.* ***1977***, *99*, 954. See also, Molander, G.A.; Brown, H.C. *J. Org. Chem.* ***1977***, *42*, 3106.

presence of a Rh catalyst (with high asymmetric induction in the presence of BINAP).[1195] Alkynyl boranes also add to conjugated ketones, in the presence of BF_3.[1196]

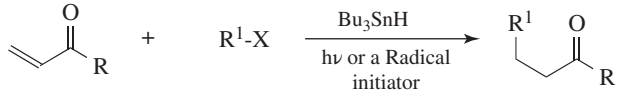
Other boron reagents add to conjugated carbonyl compounds.[1197] Tetraphenyl borates add to conjugated alkynes in the presence of a Pd catalyst in a reaction known as hydrophenylation.[1198] Alkynyl boronate esters (**12-27**) give conjugate addition[1199] in the presence of BF_3•OEt_2,[1200] as do arylboronic acids (**12-27**) with a Rh,[1201] Pd,[1202] or Bi catalyst.[1203] The Rh-catalyzed addition of vinyl tetrafluoroborates has been reported.[1204] The DABCO/boronate-promoted allylation of conjugated aldehydes used a Cu catalyst.[1205] The Pd/chiral amine-catalyzed conjugate addition of aryl boronic esters to conjugated aldehydes is known.[1206] Heteroaryl boronates have been used in the Rh-catalyzed conjugate addition to enones.[1207] The Rh-catalyzed conjugate addition of sodium tetraarylborates to β,β-disubstituted-α,β-unsaturated esters proceeded with good enantioselectivity.[1208] The conjugate addition of lithium aryltriisopropylborates to enones proceeded with good enantioselectivity using flow conditions (Sec. 7.D).[1209]

Boronic acids added to conjugated amides using a Pd catalyst.[1210] The Pd-catalyzed[1211] and the Rh-catalyzed[1212] addition of arylboronic acids to enones has been reported. The Pd-catalyzed asymmetric conjugate addition of arylboronic acids to cyclic enones generated all-carbon quaternary centers.[1213] Other transition metal catalysts have also been used with arylboronic acids, including Rh[1214] and Ni.[1215] Arylboronic acids add to the double bond of vinyl sulfones in the presence of a Rh catalyst.[1216] Vinylboronic acids add directly to conjugated ketones.[1217] An Ir-catalyzed 1,6-addition of arylboronic acids is known.[1218] Conjugated alkynes undergo conjugate addition with arylboronic acids in the presence of a Cu catalyst.[1219] Organocatalysts have also been used for the conjugate addition of arylboronic

[1195] Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* ***1998***, *39*, 8479.
[1196] Fujishima, H.; Takada, E.; Hara, S.; Suzuki, A. *Chem. Lett.* ***1992***, 695.
[1197] Kabalka, G.W.; Das, B.C.; Das, S. *Tetrahedron Lett.* ***2002***, *43*, 2323.
[1198] Zeng, H.; Hua, R. *J. Org. Chem.* ***2008***, *73*, 558.
[1199] Pellegrinet, S.C.; Goodman, J.M. *J. Am. Chem. Soc.* ***2006***, *128*, 3116.
[1200] Chong, J.M.; Shen, L.; Taylor, N.J. *J. Am. Chem. Soc.* ***2000***, *122*, 1822.
[1201] Mariz, R.; Luan, X.; Gatti, M.; Linden, A.; Dorta, R. *J. Am. Chem. Soc.* ***2008***, *130*, 2172.
[1202] Lu, X.; Lin, S. *J. Org. Chem.* ***2005***, *70*, 9651.
[1203] Sakuma, S.; Miyaura, N. *J. Org. Chem.* ***2001***, *66*, 8944.
[1204] Gendrineau, T.; Genet, J.-P.; Darses, S. *Org. Lett.* ***2009***, *11*, 3486.
[1205] Roest, P.C.; Michel, N.W.M.; Batey, R.A. *J. Org. Chem.* ***2016***, *81*, 6774.
[1206] Ibrahem, I.; Ma, G.; Afewerki, S.; Córdova, A. *Angew. Chem. Int. Ed.* ***2013***, *52*, 878.
[1207] Albrecht, F.; Sowada, O.; Fistikci, M.; Boysen, M.M.K. *Org. Lett.* ***2014***, *16*, 5212.
[1208] Shintani, R.; Hayashi, T. *Org. Lett.* ***2011***, *13*, 350.
[1209] Shu, W.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***2012***, *51*, 5355.
[1210] Ji, J.; Yang, Z.; Liu, R.; Ni, Y.; Lin, S.; Pan, Q. *Tetrahedron Lett.* ***2016***, *57*, 2723.
[1211] Lan, Y.; Houk, K.N. *J. Org. Chem.* ***2011***, *76*, 4905.
[1212] Xue, F.; Li, X.; Wan, B. *J. Org. Chem.* ***2011***, *76*, 7256.
[1213] Kikushima, K.; Holder, J.C.; Gatti, M.; Stoltz, B.M. *J. Am. Chem. Soc.* ***2011***, *133*, 6902.
[1214] Nishimura, T.; Takiguchi, Y.; Hayashi, T. *J. Am. Chem. Soc.* ***2012***, *134*, 9086; Zhang, L.; Xie, X.; Fu, L.; Zhang, Z. *J. Org. Chem.* ***2013***, *78*, 3434; Korenaga, T.; Ko, A.; Shimada, K. *J. Org. Chem.* ***2013***, *78*, 9975.
[1215] Hong, Y.-C.; Gandeepan, P.; Mannathan, S.; Lee, W.-T.; Cheng, C.-H. *Org. Lett.* ***2014***, *16*, 2806; Meng, J.-J.; Gao, M.; Dong, M.; Wei, Y.-P.; Zhang, W.-Q. *Tetrahedron Lett.* ***2014***, *55*, 2107.
[1216] With a chiral ligand, see Mauleón, P.; Carretero, J.C. *Org. Lett.* ***2004***, *6*, 3195.
[1217] Wu, T.R.; Chong, J.M. *J. Am. Chem. Soc.* ***2007***, *129*, 4908.
[1218] Nishimura, T.; Yasuhara, Y.; Hayashi, T. *Angew. Chem. Int. Ed.* ***2006***, *45*, 5164.
[1219] Yamamoto, Y.; Kirai, N.; Harada, Y. *Chem. Commun.* ***2008***, 2010.

acids to conjugated systems.[1220] Potassium vinyltrifluoroborates (see **10-59**, **13-13**, **13-14**) give 1,4-addition with a Rh catalyst,[1221] as do aryltrifluoroborates.[1222] The Cu-catalyzed reaction of conjugated compounds with $B_2(OH)_4$ gave β-borylation.[1223] The Pd-catalyzed addition of boronic acids to ynamides gave (*Z*)-α,β-disubstituted enamides.[1224]

15-24 Radical Addition to Activated Double Bonds



In a reaction similar to **15-21**, alkyl groups can be added to alkenes activated by such groups as COR′, CO_2R', CN, and even Ph.[1225] This is a radical addition reaction.[1226] In the method illustrated above, the R^1 group comes from an alkyl halide (R^1 = primary, secondary, or tertiary alkyl; X = Br or I) and the hydrogen from the tin hydride (H atom transfer agents). The reaction of *tert*-butyl bromide, Bu_3SnH, and AIBN (Sec. 14.A.i), for example, adds a *tert*-butyl group to a conjugated ester via 1,4-addition.[1227] The Bu_3SnH can also be generated *in situ*, from R_3SnX and $NaBH_4$. Like **15-23**, these additions have free-radical mechanisms.

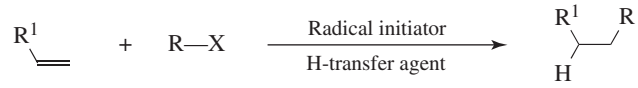
A BEt_3-initiated reaction of conjugated amides with an alkyl iodide, in the presence of Bu_3SnH and O_2, leads to conjugate addition of the alkyl group.[1228] Enantioselective radical addition has been reported.[1229] Conjugate addition is possible using photolysis. The photoinduced 1,4-addition of indoles to enones proceeds when irradiated at 350 nm.[1230]

In the presence of a Rh catalyst, $LiBPh(OMe)_3$ gave conjugate addition of the phenyl group to α,β-unsaturated esters.[1231] The fact that these reactions are catalyzed by free-radical initiators and inhibited by galvinoxyl[1232] (a free-radical inhibitor) indicates that free-radical mechanisms are involved (**15-24**). The Ru-catalyzed reaction of enones with photogenerated α-amino radicals in the presence of TFA gave the γ-amino ketone.[1233]

OS **VII**, 105.

[1220] Sugiura, M.; Tokudomi, M.; Nakajima, M. *Chem. Commun.* ***2010***, 7799.
[1221] Duursma, A.; Boiteau, J.-G.; Lefort, L.; Boogers, J.A.F.; de Vries, A.H.M.; de Vires, J.G.; Minnaard, A.J.; Feringa, B.L. *J. Org. Chem.* ***2004***, *69*, 8045.
[1222] Navarre, L.; Martinez, R.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* ***2008***, *130*, 6159.
[1223] Pan, S.; Endo, K.;Shibata, T. *Org. Lett.* ***2011***, *13*, 4692.
[1224] Yang, Y.; Wang, L.; Zhang, F.; Zhu, G. *J. Org. Chem.* ***2014***, *79*, 9319.
[1225] Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***, pp. 36–68; Giese, B. *Angew. Chem. Int. Ed.* ***1985***, *24*, 553. See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1809–1813.
[1226] Srikanth, G.S.C.; Castle, S.L. *Tetrahedron* ***2005***, *61*, 10377.
[1227] Hayen, A.; Koch, R.; Metzger, J.O. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2758.
[1228] See Sibi, M.P.; Petrovic, G.; Zimmerman, J. *J. Am. Chem. Soc.* ***2005***, *127*, 2390; He, L.; Srikanth, G.S.C.; Castle, S.L. *J. Org. Chem.* ***2005***, *70*, 8140. Also see Sibi, M.P.; Zimmerman, J. *J. Am. Chem. Soc.* ***2006***, *128*, 13346.
[1229] Lee, S.; Lim, C.J.; Kim, S.; Subramaniam, R.; Zimmerman, J.; Sibi, M.P. *Org. Lett.* ***2006***, *8*, 4311.
[1230] Moran, J.; Suen, T.; Beauchemin, A.M. *J. Org. Chem.* ***2006***, *71*, 676.
[1231] Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* ***1999***, *10*, 4047.
[1232] Kabalka, G.W.; Brown, H.C.; Suzuki, A.; Honma, S.; Arase, A.; Itoh, M. *J. Am. Chem. Soc.* ***1970***, *92*, 710. See also, Arase, A.; Masuda, Y.; Suzuki, A. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 2275.
[1233] Espelt, L.R.; Wiensch, E.M.; Yoon, T.P. *J. Org. Chem.* ***2013***, *78*, 4107.

15-25 Radical Addition to Unactivated Double Bonds[1234]



Radical addition to alkenes is usually difficult, except when addition occurs to conjugated carbonyl compounds (**15-20**). An important exception involves radicals bearing a heteroatom α to the carbon bearing the radical center. Such radicals are much more stable and can add to alkenes, usually with *anti-Markovnikov* orientation, as in the radical-induced addition of HBr to alkenes (**15-2**).[1235] The Fe-catalyzed conversion of alkenes to radicals allows their use in the construction of C—C bonds.[1236]

Other radicals can add to alkenes, and the rate constant for the addition of methyl radicals to alkenes has been studied,[1237] and the rate of radical additions to alkenes in general has also been studied.[1238] The kinetic and thermodynamic control of radical addition regiochemistry has also been studied.[1239] Alkynes are generally less reactive than alkenes in radical coupling reactions.[1240] Nonradical nucleophiles usually react faster with alkynes than with alkenes, however.[1241] Radicals generated from a photoorganocatalyst added to alkenes in the presence of *p*-anisaldehyde.[1242]

The Rh-catalyzed addition of alkyl radicals, oxidatively generated from organotrifluoroborates, to alkenes was reported under photoredox conditions.[1243] In the presence of a Co catalyst, THF reacted with alkenes via radical addition.[1244] The photoredox-catalyzed radical addition of α-halo amides to alkenes has been reported.[1245] Alkenes reacted with the alkyl radical generated from hydrazines via treatment with potassium ferrocyanide trihydrate ($K_4[Fe(CN)_6]\cdot 3H_2O$), which promoted aryl radical addition in the presence of oxygen.[1246]

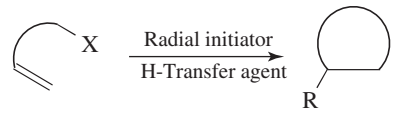
Examples of this type of reaction include the use of alcohol, ester,[1247] amino, and aldehyde-stabilized radicals.[1248] The alkyl group of alkyl iodides adds to alkenes with BEt_3/O_2 as the initiator and in the presence of a tetraalkylammonium hypophosphite.[1249] α-Iodo amides add to alkenes using a water-soluble *azobis* initiator (Sec. 14.A.i) to give the iodo

[1234] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 928–929.
[1235] See Curran, D.P. *Synthesis* ***1988***, 489 (pp. 497–498).
[1236] Lo, J.C.; Kim, D.; Pan, C.-M.; Edwards, J.T.; Yabe, Y.; Gui, J.; Qin, T.; Gutiérrez, S.; Giacoboni, J.; Smith, M.W.; Holl, L.; Baran, P.S. *J. Am. Chem. Soc.* ***2017***, *139*, 2484.
[1237] Zytowski, T.; Fischer, H. *J. Am. Chem. Soc.* ***1996*** *118*, 437.
[1238] Avila, D.V.; Ingold, K.U.; Lusztyk, J.; Dolbier Jr., W.R.; Pan, H.-Q. *J. Org. Chem.* ***1996***, *61*, 2027.
[1239] Leach, A.G.; Wang, R.; Wohlhieter, G.E.; Khan, S.I.; Jung, M.E.; Houk, K.N. *J. Am. Chem. Soc.* ***2003***, *125*, 4271.
[1240] Giese, B.; Lachhein, S. *Angew. Chem. Int. Ed.* ***1982***, *21*, 768.
[1241] Dickstein, J.I.; Miller, G.I. in Patai, S. *The Chemistry of Carbon-Carbon Triple Bonds*, Vol. 2, Wiley, NY, ***1978***.
[1242] Arceo, E.; Montroni, E.; Melchiorre, P. *Angew. Chem. Int. Ed.* ***2014***, *53*, 12064.
[1243] Huo, H.; Harms, K.; Meggers, E. *J. Am. Chem Soc.* ***2016***, *138*, 6936.
[1244] Zhang, M.; Zhao, Y.; Chen, W. *Synthesis* ***2017***, *49*, 1342.
[1245] Nakajima, M.; Lefebvre, Q.; Rueping, M. *Chem. Commun.* ***2014***, *50*, 3619.
[1246] Taniguchi, T.; Zaimoku, H.; Ishibashi, H. *Chem. Eur. J.* ***2011***, *17*, 4307.
[1247] Deng, L.X.; Kutateladze, A.G. *Tetrahedron Lett.* ***1997***, *38*, 7829.
[1248] Krasna, A.I. *J. Am. Chem. Soc.* ***1961***, *83*, 289.
[1249] Jang, D.O.; Cho, D.H.; Chung, C.-M. *Synlett* ***2001***, 1923.

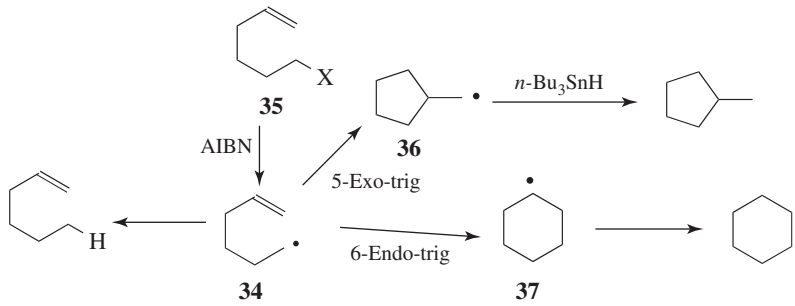
ester, which cyclizes under the reaction conditions to give a lactone.[1250] 2-Fluoropyridyl derivatives of allylic alcohols react with xanthates in the presence of lauroyl peroxide to give alkenes.[1251]

The Cu-catalyzed radical addition alkenylation reaction of alkyl bromides has been reported.[1252] Arylalkynes reacted with alkyl diacyl peroxides, catalyzed by Ni and Ru compounds under photolytic conditions, to give the hydralkylation product, the alkene, with *Z* selectivity.[1253] Thiols were converted to thiyl radicals that added to alkenes to give the corresponding sulfide.[1254]

15-26 Radical Cyclization[1255]



ω-Haloalkenes generate radicals upon treatment with radical initiator reagents such as AIBN, or under photolysis conditions,[1256] and the radical carbon adds to the alkene to form cyclic compounds.[1257] This intramolecular addition of a radical to an alkene is called *radical cyclization*. In a typical example, haloalkene **35** reacts with the radical produced by AIBN to give radical **34**. The radical can add to the more-substituted carbon to give **36** via a 5-*exo-trig* reaction (see *Baldwin rules*, Sec. 6.E).[1258] If the radical adds to the less-substituted carbon, **37** is formed via a 6-*endo-trig* reaction.[1259] In both cases, the product is another radical, which must be converted to an unreactive product.



[1250] Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 1963.
[1251] Charrier, N.; Quiclet-Sire, B.; Zard, S.Z. *J. Am. Chem. Soc.* ***2008***, *130*, 8898.
[1252] Zhang, X.; Yi, H.; Liao, Z.; Zhang, G.; Fan, C.; Qin, C.; Liu, J.; Lei, A. *Org. Biomol. Chem.* ***2014***, *12*, 6790.
[1253] Li, Y.; Ge, L.; Qian, B.; Babu, K.R.; Bao, H. *Tetrahedron Lett.* ***2016***, *57*, 5677.
[1254] Subramanian, H.; Moorthy, R.; Sibi, M.P. *Angew. Chem. Int. Ed.* ***2014***, *53*, 13660.
[1255] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 938–946. Rheault, T.R.; Sibi, M.P. *Synthesis* ***2003***, 803.
[1256] See Pandey, G.; Reddy, G.D.; Chakrabarti, D. *J. Chem. Soc., Perkin Trans. 1* ***1996***, 219.
[1257] See Jasperse, C.P.; Curran, D.P.; Fevig, T.L. *Chem. Rev.* ***1991***, *91*, 1237; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 413–418; See Majumdar, K.C.; Karunakar, G.V.; Sinha, B. *Synthesis* ***2012***, *44*, 2475; Serelis, A.K. *Aust. J. Chem.* ***2011***, *64*, 358.
[1258] Chatgilialoglu, C.; Ferreri, C.; Guerra, M.; Timokhin, V.; Froudakis, G.; Gimisis, Z.T. *J. Am. Chem. Soc.* ***2002***, *124*, 10765. See Guan, X.; Phillips, D.L.; Yang, D. *J. Org. Chem.* ***2006***, *71*, 1984.
[1259] See Ishibashi, H.; Sato, T.; Ikeda, M. *Synthesis* ***2002***, 695.

A 4-*exo-trig* radical cyclization has been studied,[1260] as has selectivity in a 7-*endo* versus 6-*exo* cyclization,[1261] and also an 8-*endo*-trig reaction.[1262]

The mechanism of this reaction has been discussed.[1263] Cyclization via 5-*endo-dig* transition states require reorientation of the radical orbital needed to reach the in-plane acetylene π orbital in the bond-forming step, with accompanying loss of conjugative stabilization and an increase in the activation energy. Therefore, many 5-*endo* cyclizations undergo H abstraction or equilibration with an isomeric radical.[1264] The issue of dissociation vs. cyclization has been discussed.[1265] Such cyclizations normally give predominant formation of five-membered rings, but large rings (11–20 members) have also been synthesized by this reaction.[1266]

This reaction is generally accomplished by adding a hydrogen-transfer agent[1267] such as tributyltin hydride (Bu_3SnH), which reacts with **36** to form methylcyclopentane and $Bu_3Sn\bullet$, or reacts with **37** to give cyclohexane. The $Bu_3Sn\bullet$ formed in both cases usually dimerizes to form $Bu_3SnSnBu_3$. Cyclization can compete with hydrogen transfer[1268] from Bu_3SnH to **34** to give the reduction product. Atom-transfer cyclization is possible with other atoms, such as halogen, catalyzed by $InCl_3$[1269] or CuBr.[1270] Tin-free radical cyclizations are known using $CpCr(CO_3H)$.[1271]

In general, formation of the five-membered ring dominates the cyclization,[1272] but if addition to the C═C unit is relatively slow, the reduction product is formed preferentially. This preference may be caused by more favorable entropy factors leading to a five-membered ring, as well as by stereoelectronic factors, but other explanations have also been offered.[1273] In each case, the smaller ring (*exo-trig* addition) is preferred to the larger (*endo-trig* addition).[1274] However, when a radical that is unsaturated in the 5,6 position contains an alkyl group in the 5 position, formation of the six-membered ring is generally favored, presumably due to unfavorable steric interactions.[1275]

Radical rearrangements can diminish the yield of the desired product.[1276] Given a choice between a larger ring and a smaller ring, radical cyclization generally gives the smaller ring,[1277] but not always.[1278] Formation of other size rings is possible of course. In radical

[1260] Jung, M.E.; Marquez, R.; Houk, K.N. *Tetrahedron Lett.* ***1999***, *40*, 2661.
[1261] Kamimura, A.; Taguchi, Y. *Tetrahedron Lett.* ***2004***, *45*, 2335.
[1262] Wang, Li.C. *J. Org. Chem.* ***2002***, *67*, 1271.
[1263] Bailey, W.F.; Carson, M.W. *Tetrahedron Lett.* ***1999***, *40*, 5433.
[1264] Alabugin, I.V.; Manoharan, M. *J. Am. Chem. Soc.* ***2005***, *127*, 9534.
[1265] McBurney, R.T.; Walton, J.C. *J. Am. Chem. Soc.* ***2013***, *135*, 7349.
[1266] See Porter, N.A.; Chang, V.H. *J. Am. Chem. Soc.* ***1987***, *109*, 4976.
[1267] See Ha, C.; Horner, J.H.; Newcomb, M.; Varick, T.R.; Arnold, B.R.; Lusztyk, J. *J. Org. Chem.* ***1993***, *58* 1194.
[1268] See Furxhi, E.; Horner, J.H.; Newcomb, M. *J. Org. Chem.* ***1999***, *64*, 4064; Tauh, P.; Fallis, A.G. *J. Org. Chem.* ***1999***, *64*, 6960.
[1269] Cook, G.R.; Hayashi, R. *Org. Lett.* ***2006***, *8*, 1045.
[1270] Clark, A.J.; Wilson, P. *Tetrahedron Lett.* ***2008***, *49*, 4848.
[1271] Smith, D.M.; Pulling, M.E.; Norton, J.R. *J. Am. Chem. Soc.* ***2007***, *129*, 770.
[1272] For an exception, see Wilt, J.W. *Tetrahedron* ***1985***, *41*, 3979.
[1273] See Beckwith, A.L.J.; Schiesser, C.H. *Tetrahedron* ***1985***, *41*, 3925; Spellmeyer, D.C.; Houk, K.N. *J. Org. Chem.* ***1987***, *52*, 959.
[1274] See Beckwith, A.L.J.; Easton, C.J.; Serelis, A.K. *J. Chem. Soc., Chem. Commun.* ***1980***, 482.
[1275] See Chuang, C.; Gallucci, J.C.; Hart, D.J.; Hoffman, C. *J. Org. Chem.* ***1988***, *53*, 3218.
[1276] Mueller, A.M.; Chen, P. *J. Org. Chem.* ***1998***, *63*, 4581.
[1277] Beckwith, A.L.J.; Ingold, K.U. in de Mayo, P. *Rearrangements in Ground States and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 162–283. Gómez, A.M.; Company, M.D.; Uriel, C.; Valverde, S.; López, J.C. *Tetrahedron Lett.* ***2002***, *43*, 4997.
[1278] Mayon, P.; Chapleur, Y. *Tetrahedron Lett.* ***1994***, *35*, 3703; Marco-Contelles, J.; Sánchez, B. *J. Org. Chem.* ***1993***, *58*, 4293.

cyclization to form large rings, 1,5- and 1,9-hydrogen atom abstractions can pose a problem[1279] The former abstraction proceeds via a six-center transition state. Ring expansion during radical cyclization is possible when the terminal intermediate is a cyclobutylcarbinyl radical.[1280]

In cases where hydrogen atom transfer gives primarily reduced products, one solution to promote cyclization generates the radical by photochemical cleavage of $Bu_3Sn{-}SnBu_3$ and the resulting carbon radical can cyclize (see **15-42**).[1281] A halogen atom transfer agent, such as iodoethane, is used rather than a hydrogen transfer agent, so the final product is an alkyl iodide. Samarium(II) has been used to initiate 5-*exo-trig* ketyl-alkene coupling, and the mechanism of the reaction has been examined.[1282] Radical cyclization has also been terminated by Ir-catalyzed hydrogen atom transfer.[1283]

Radical cyclization reactions often proceed with high diastereoselectivity[1284] and high asymmetric induction when chiral precursors are used. Internal alkynes are good substrates for radical cyclization,[1285] but terminal alkynes tend to give mixtures of *exo*/*endo-dig* products (Sec. 6.E).[1286] Radical cyclization has been used to transfer asymmetry from transient atropisomers to form lactams.[1287]

Radical cyclization is compatible with the presence of other functional groups, and heterocyclic rings may be formed via radical cyclization.[1288] Aryl radicals participate in radical cyclization reactions when the aromatic ring has an alkene or alkyne substituent. *o*-Iodo aryl allyl ethers cyclize to benzofuran derivatives, for example, when treated with AIBN, aqueous H_3PO_2, and $NaHCO_3$ in ethanol.[1289] Cyclizations of vinyl radicals[1290] and allenyl radicals[1291] are also well known. Cyclization of *N*-iodoethyl-5-vinyl-2-pyrrolidinone led to the corresponding bicyclic lactam,[1292] and there are other examples of radical cyclization with molecules containing a lactam unit[1293] or an amide unit.[1294] β-Lactams can be produced by radical cyclization, using $Mn(OAc)_3$.[1295] Primary amides with a distal (*Z*)-iodoalkene moiety cyclized to a piperidone derivative via a *6-exo* reaction of an amidyl radical when treated with lead tetraacetate and iodine under photolytic conditions.[1296]

[1279] Kraus, G.A.; Wu, Y. *J. Am. Chem. Soc.* ***1992*** *114*, 8705.
[1280] Zhang, W.; Dowd, P. *Tetrahedron Lett.* ***1995***, *36*, 8539.
[1281] For a polymer-bound Sn catalyst, see Hernán, A.G.; Kilburn, J.D. *Tetrahedron Lett.* ***2004***, *45*, 831.
[1282] Sadasivam, D.V.; Antharjanam, P.K.S.; Prasad, E.; Flowers II, R.A. *J. Am. Chem. Soc.* ***2008***, *130*, 7228.
[1283] Gansäuer, A.; Otte, M.; Shi, L. *J. Am. Chem. Soc.* ***2011***, *133*, 416.
[1284] See Bouvier, J.-P.; Jung, G.; Liu, Z.; Guérin, B.; Guindon, Y. *Org. Lett.* ***2001***, *3*, 1391; Bailey, W.F.; Longstaff, S.C. *Org. Lett.* ***2001***, *3*, 2217; Stalinski, K.; Curran, D.P. *J. Org. Chem.* ***2002***, *67*, 2982.
[1285] See Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* ***2007***, *13*, 7280. Rules for the ring closure of alkynes have been discussed: see Alabugin, I.V.; Gilmore, K.; Manoharan, M. *J. Am. Chem. Soc.* ***2011***, *133*, 12608.
[1286] Robertson, J.; Lam, H.W.; Abazi, S.; Roseblade, S.; Lush, R.K. *Tetrahedron* ***2000***, *56*, 8959.
[1287] Petit, M.; Lapierre, A.J.B.; Curran, D.P. *J. Am. Chem. Soc.* ***2005***, *127*, 14994.
[1288] Majumdar, K.C.; Basu, P.K.; Mukhopadhyay, P.P. *Tetrahedron* ***2007***, *63*, 793.
[1289] Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Chem. Lett.* ***2000***, 104.
[1290] Sha, C.-K.; Zhan, Z.-P.; Wang, F.-S. *Org. Lett.* ***2000***, *2*, 2011.
[1291] Wartenberg, F.-H.; Junga, H.; Blechert, S. *Tetrahedron Lett.* ***1993***, *34*, 5251. See Shi, J.; Zhang, M.; Fu, Y.; Liu, L.; Guo, Q.-X. *Tetrahedron* ***2007***, *63*, 12681.
[1292] Keusenkothen, P.F.; Smith, M.B. *J. Chem. Soc., Perkin Trans. 1* ***1994***, 2485.
[1293] Padwa, A.; Rashatasakhon, P.; Ozdemir, A.D.; Willis, J. *J. Org. Chem.* ***2005***, *70*, 519.
[1294] Beckwith, A.L.J.; Joseph, S.P.; Mayadunne, R.T.A. *J. Org. Chem.* ***1993***, *58*, 4198.
[1295] See Lee, E.; Kim, S.K.; Kim, J.Y.; Lim, J. *Tetrahedron Lett.* ***2000***, *41*, 5915. For a related reaction with tin hydride, see Curran, D.P.; Guthrie, D.B.; Geib, S.J. *J. Am. Chem. Soc.* ***2008***, *130*, 8437. For a discussion of mechanism, see Snider, B.B. *Tetrahedron* ***2009***, *65*, 10738.
[1296] Zhuang, S.; Liu, K.; Li, C. *J. Org. Chem.* ***2011***, *76*, 8100. See Xu, H.-C.; Campbell, J.M.; Moeller, K.D. *J. Org. Chem.* ***2014***, *79*, 379.

Radical cyclization occurs with oximes to form the corresponding heterocyclic ring.[1297] ω-Iodo acrylate esters cyclize to form lactones,[1298] and allylic acetoxy compounds of the type $C{=}C{-}C{-}O_2C{-}CH_2I$ cyclize in a similar manner to give lactones.[1299] Iodolactonization (see **15-37**) occurs under standard radical cyclization conditions using allylic acetoxy compounds[1300] and $HGaCl_2/BEt_3$ has been used to initiate the radical process.[1301] Organoborane-mediated radical cyclizations are known (Sec. 14.A.i).[1302]

A mixture of a *Grignard reagent* and $CoCl_2$ has been used to initiate aryl radical cyclizations.[1303] Transition metal catalysis is known.[1304] The influence of the halogen atom on radical cyclization has been studied.[1305]

Both phenylthio[1306] and phenylseleno groups[1307] can be used as "leaving groups" for radical cyclization, where S or Se atom transfer leads to formation of the radical. A seleno ester, $R_2N{-}CH_2C(=O)SeMe$, has also been used with $(Me_3Si)_3SiH$ [tris(trimethylsilyl)silane], TTMSS) and AIBN to generate $R_2NCH_2\bullet$.[1308] *O*-Phosphonate esters have also served as the leaving group.[1309]

Radical cyclization of iodo aldehydes or ketones, at the carbon of the carbonyl, is effectively an acyl addition reaction (**16-22**, **16-23**). This cyclization is often reversible, and there are many fewer examples of addition to an alkene or alkyne. In one example, a δ-iodo aldehyde was treated with BEt_3/O_2 to initiate formation of the radical, and, in the presence of Bu_3SnH, cyclization gave a cyclopentanol.[1310] The reaction of an aldehyde alkene with AIBN, 0.5 $PhSiH_3$ and 0.1 Bu_3SnH generated a radical from the alkene, which cyclized at the aldehyde to give cyclopentanol derivatives.[1311] Acyl radicals can be generated and they cyclize in the usual manner.[1312]

Molecular orbital calculations have shown that acyl radicals, as well as silyl radicals, simultaneously use SOMO–LUMO (Singly Occupied Molecular Orbital) and LUMO–HOMO interactions in reactions with alkenes.[1313] A polyene-cyclization reaction generated four rings, initiating the sequence by treatment of a phenylseleno ester with Bu_3SnH/AIBN to form the acyl radical, which added to the first alkene unit,[1314] and the

[1297] Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* ***2008***, *81*, 539.
[1298] Ryu, I.; Nagahara, K.; Yamazaki, H.; Tsunoi, S.; Sonoda, N. *Synlett* ***1994***, 643.
[1299] Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* ***2000***, *122*, 6496.
[1300] Ollivier, C.; Bark, T.; Renaud, P. *Synthesis* ***2000***, 1598.
[1301] Mikami, S.; Fujita, K.; Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* ***2001***, *3*, 1853.
[1302] Becattini, B.; Ollivier, C.; Renaud, P. *Synlett* ***2003***, 1485.
[1303] Clark, A.J.; Davies, D.I.; Jones, K.; Millbanks, C. *J. Chem. Soc., Chem. Commun.* ***1994***, 41.
[1304] Yamamoto, Y. *Chem. Rev.* ***2012***, *112*, 4736; Barrero, A.F.; Oltra, J.E.; Cuerva, J.M.; Rosales, A. *J. Org. Chem.* ***2002***, *67*, 2566; Molander, G.A.; St. Jean Jr., D.J. *J. Org. Chem.* ***2002***, *67*, 3861.
[1305] Tamura, O.; Matsukida, H.; Toyao, A.; Takeda, Y.; Ishibashi, H. *J. Org. Chem.* ***2002***, *67*, 5537.
[1306] See Ikeda, M.; Shikaura, J.; Maekawa, N.; Daibuzono, K.; Teranishi, H.; Teraoka, Y.; Oda, N.; Ishibashi, H. *Heterocycles* ***1999***, *50*, 31.
[1307] See Ericsson, C.; Engman, L. *Org. Lett.* ***2001***, *3*, 3459.
[1308] Quirante, J.; Vila, X.; Escolano, C.; Bonjoch, J. *J. Org. Chem.* ***2002***, *67*, 2323.
[1309] Crich, D.; Ranganathan, K.; Huang, X. *Org. Lett.* ***2001***, *3*, 1917.
[1310] Devin, P.; Fensterbank, L.; Malacria, M. *Tetrahedron Lett.* ***1999***, *40*, 5511.
[1311] Hays, D.S.; Fu, G.C. *Tetrahedron* ***1999***, *55*, 8815.
[1312] Jiaang, W.-T.; Lin, H.-C.; Tang, K.-H.; Chang, L.-B.; Tsai, Y.-M. *J. Org. Chem.* ***1999***, *64*, 618.
[1313] Schiesser, C.H.; Matsubara, H.; Ritsner, I.; Wille, U. *Chem. Commun.* ***2006***, 1067.
[1314] Pattenden, G.; Roberts, L.; Blake, A.J. *J. Chem. Soc., Perkin Trans. 1* ***1998***, 863. Also see, Pattenden, G.; Smithies, A.J.; Tapolczay, D.; Walter, D.S. *J. Chem. Soc., Perkin Trans. 1* ***1996***, 7.

newly formed carbon radical added to the next alkene, and so on. Potassium aryltrifluoroborates with an aryloxy group gave the dibenzofuran derivative when treated with $K_2S_2O_8$ and a Ag catalyst.[1315] The radical cyclization reaction of 1,6-enynes by reaction with sulfonyl hydrazides, TBHP, and iodine gave five- and six-membered ring sulfonylated products.[1316]

The attacking radical in radical cyclization reactions is not limited to a carbon, and a number of heterocycles can be prepared.[1317] Amidyl radical are known and give cyclization reactions.[1318] Alkynyl imines are cyclized to the imino carbon to form alkylidene lactams under radical conditions in the presence of CO. *N*-Chloroamine alkenes give an aminyl radical when treated with $TiCl_3$•BF_3, and cyclization give a pyrrolidine derivative with a pendant chloromethyl group.[1319] Aminyl radical cyclizations have been reported.[1320] Oxime alkenes cyclize to imines when treated with PhSSPh and TEMPO (Sec. 5.C.i).[1321] An oxygen radical can be generated under photochemical conditions, and they add to alkenes in a normal manner.[1322] Note that radical substitution occurs, and reaction of Ph_3SnH/AIBN and an *O*-amidyl compound having a phosphonate ester elsewhere in the molecule gave cyclization to a tetrahydrofuran derivative.[1323]

Vinyl ethers with a distal iodo moiety gave tetrahydropyran derivatives via radical cyclization when treated with 3 equivalents of Zn and a Ni catalyst.[1324] Isoquinolines have been prepared.[1325] Tetrahydrofuran derivatives were prepared by the photocyclization of propargylic ethers with CHRX (X = Br, I) unit, using flow conditions (Sec. 7.D).[1326]

15-27 Conjugate Addition With Heteroatom Nucleophiles

Heteroatom nucleophiles add to conjugated systems to give Michael-type products.[1327] Conjugated carbonyl compounds react via conjugate addition with amines to give β-amino derivatives (see **15-27**).[1328] Conjugate addition of nitrogen-containing compounds is often called the *aza-Michael reaction*.[1329] Amines add to conjugated systems in the presence

[1315] Lockner, J.W.; Dixon, D.D.; Risgaard, R.; Baran, P.S. *Org. Lett.* ***2011***, *13*, 5628.
[1316] Zheng, L.; Zhou, Z.-Z.; He, Y.-T.; Li, L.-H.; Ma, J.-W.; Qiu, Y.-F.; Zhou, P.-X.; Liu, X.-Y.; Xu, P.-F.; Liang, Y.-M. *J. Org. Chem.* ***2016***, *81*, 66.
[1317] See Majumdar, K.C.; Basu, P.K.; Mukhopadhyay, P.P. *Tetrahedron* ***2004***, *60*, 6239.
[1318] Clark, A.J.; Peacock, J.L. *Tetrahedron Lett.* ***1998***, *39*, 6029. See Prabhakaran, E.N.; Nugent, B.M.; Williams, A.L.; Nailor, K.E.; Johnston, J.N. *Org. Lett.* ***2002***, *4*, 4197.
[1319] Hemmerling, M.; Sjöholm, Å.; Somfai, P. *Tetrahedron: Asymmetry* ***1999***, *10*, 4091.
[1320] Martinez II, E.; Newcomb, M. *J. Org. Chem.* ***2006***, *71*, 557.
[1321] Lin, X.; Stien, D.; Weinreb, S.M. *Org. Lett.* ***1999***, *1*, 637.
[1322] For a review, see Hartung, J. *Eur. J. Org. Chem.* ***2001***, 619.
[1323] Crich, D.; Huang, X.; Newcomb, M. *Org. Lett.* ***1999***, *1*, 225.
[1324] Kim, H.; Lee, C. *Org. Lett.* ***2011***, *13*, 2050.
[1325] Zhou, W.; Ni, S.; Mei, H.; Han, J.; Pan, Y. *Org. Lett.* ***2015***, *17*, 2724.
[1326] Fukuyama, T.; Fujita, Y.; Rashid, M.A.; Ryu, I. *Org. Lett.* ***2016***, *18*, 5444.
[1327] For *N*-heterocyclic carbene-catalyzed reactions, see Hans, M.; Delaude, L.; Rodriguez, J.; Coquerel, Y. *J. Org. Chem.* ***2014***, *79*, 2758. See Han, F.; Yang, L.; Li, Z.; Xia, C. *Org. Biomol. Chem.* ***2012***, *10*, 346.
[1328] See Cossu, S.; DeLucchi, O.; Durr, R. *Synth. Commun.* ***1996***, *26*, 4597.
[1329] Yamagiwa, N.; Qin, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2005***, *127*, 13419. See Munro-Leighton, C.; Blue, E.D.; Gunnoe, T.B. *J. Am. Chem. Soc.* ***2006***, *128*, 1446.

of In,[1330] Pd,[1331] Sm,[1332] Bi,[1333] Cu,[1334] Ce,[1335] La,[1336] or Yb compounds[1337] to give β-amino derivatives. This reaction can be initiated photochemically[1338] or with microwave irradiation.[1339] A Brønsted acid-catalyzed reaction used ultrasound activation.[1340] An aza-Michael reaction has been reported in ioinic liquids.[1341] A solvent-free conjugate addition of amines occurs on alumina in the presence of a Ce catalyst.[1342] A green aza-Michael addition of amines to diethyl maleate has been reported.[1343] A lipase-catalyzed aza-Michael reaction has been reported.[1344] *N*-Heterocyclic carbenes have been used to catalyze aza-Michael addition.[1345] A catalytic amount of DBU promotes the aza-Michael reaction.[1346] Boric acid has been used as a catalyst of aza-Michael reactions in water.[1347] An intramolecular addition of an amine unit to a conjugated ketone in the presence of a Pd catalyst, or photochemically, led to cyclic amines.[1348] *N*-Phenyl amides with a distal conjugated ester moiety cyclized to the corresponding lactam in the presence of a Ti catalyst and a catalytic amount of TEMPO.[1349] A variety of heterocycles were prepared by the Cu-catalyzed conjugate addition reaction of aromatic amines and aromatic aza-heterocycles to α,β-unsaturated alkenes.[1350] Amidocuprates add to conjugated systems to give β-nitrogen compounds, and a β-silyl group has an activating effect on the amidocuprate.[1351]

There are asymmetric versions of the aza-Michael reaction.[1352] Chiral catalysts lead to enantioselective reactions[1353] and high enantioselectivity is possible using an organocatalyst.[1354] Chiral additives, such as chiral *Cinchona* alkaloids[1355] or chiral naphthol derivatives,[1356] have also been used. Chiral catalysts have been used for the conjugated addition

[1330] Loh, T.-P.; Wei, L.-L. *Synlett* ***1998***, 975.
[1331] Takasu, K.; Nishida, N.; Ihara, M. *Synlett* ***2004***, 1844.
[1332] Yadav, J.S.; Reddy, A.R.; Rao, Y.G.; Narsaiah, A.V.; Reddy, B.V.S. *Synthesis* ***2007***, 3447.
[1333] Srivastava, N.; Banik, B.K. *J. Org. Chem.* ***2003***, *68*, 2109.
[1334] Xu, L.-W.; Wei, J.-W.; Xia, C.-G.; Zhou, S.-L.; Hu, X.-X. *Synlett* ***2003***, 2425.
[1335] Bartoli, G.; Bosco, M.; Marcantoni, E.; Petrini, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* ***2001***, *66*, 9052.
[1336] Matsubara, S.; Yoshioka, M.; Utimoto, K. *Chem. Lett.* ***1994***, 827.
[1337] Jenner, G. *Tetrahedron Lett.* ***1995***, *36*, 233.
[1338] Das, S.; Kumar, J.S.D.; Shivaramayya, K.; George, M.V. *J. Chem. Soc., Perkin Trans. 1* ***1995***, 1797.
[1339] Moghaddam, F.M.; Mohammadi, M.; Hosseinnia, A. *Synth. Commun.* ***2000***, *30*, 643.
[1340] Du, X.-J.; Wang, Z.-P.; Hou, Y.-L.; Zhang, C.; Li, Z.-M.; Zhao, W.G. *Tetrahedron Lett.* ***2014***, *55*, 1002.
[1341] Ghasemi, M.H.; Kowsari, E.; Shafiee, A. *Tetrahedron Lett.* ***2016***, *57*, 1150.
[1342] Bartoli, G.; Bartolacci, M.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Torregiani, E. *J. Org. Chem.* ***2005***, *70*, 169.
[1343] Bosica, G.; Debono, A.J. *Tetrahedron* ***2014***, *70*, 6607.
[1344] Steunenberg, P.; Sijm, M.; Zuilhof, H.; Sanders, J.P.M.; Scott, E.L.; Franssen, M.C.R. *J. Org. Chem.* ***2013***, *78*, 3802.
[1345] Kang, Q.; Zhang, Y. *Org. Biomol. Chem.* ***2011***, *9*, 6715.
[1346] Yeom, C.-E.; Kim, M.J.; Kim, B.M. *Tetrahedron* ***2007***, *63*, 904. See Markó, I.E.; Chesney, A. *Synlett* ***1992***, 275.
[1347] Chaudhuri, M.K.; Hussain, S.; Kantam, M.L.; Neelima, B. *Tetrahedron Lett.* ***2005***, *46*, 8329.
[1348] Zhang, X.; Jung, Y.S.; Mariano, P.S.; Fox, M.A.; Martin, P.S.; Merkert, J. *Tetrahedron Lett.* ***1993***, *34*, 5239.
[1349] Tarantino, K.T.; Miller, D.C.; Callon, T.A.; Knowles, R.R. *J. Am. Chem. Soc.* ***2015***, *137*, 6440.
[1350] Kim, S.; Kang, S.; Kim, G.; Lee, Y. *J. Org. Chem.* ***2016***, *81*, 4048.
[1351] Bertz, S.H.; Ogle, C.A.; Rastogi, A. *J. Am. Chem. Soc.* ***2005***, *127*, 1372.
[1352] See Krishna, P.R.; Sreeshailam, A.; Srinivas, R. *Tetrahedron* ***2009***, *65*, 9657.
[1353] Sugihara, H.; Daikai, K.; Jin, X.L.; Furuno, H.; Inanaga, J. *Tetrahedron Lett.* ***2002***, *43*, 2735.
[1354] See Lu, X.; Deng, L. *Angew. Chem. Int. Ed.* ***2008***, *47*, 7710.
[1355] Jew, S.-s.; Jeong, B.S.; Yoo, M.-S.; Huh, H.; Park, H.-g. *Chem. Commun.* ***2001***, 1244.
[1356] Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2003***, *125*, 16178.

of carbamates.[1357] Indoles add to nitro alkenes in the presence of an organocatalyst.[1358] Indoline derivatives have been reported via aza-Michael addition, prepared with good enantioselectivity.[1359] The conjugate addition of pyrroles to enones was catalyzed by *Cinchona* alkaloid-derived primary amines.[1360]

Lactams have been shown to add to conjugated esters in the presence of $Si(OEt)_4$ and CsF.[1361] Amines also add in a conjugate manner to alkynyl phosphonate esters, $C{\equiv}C{-}PO(OEt)_2$, using a CuI catalyst.[1362] Trimethylsilyl azide with acetic acid reacts with conjugated ketones to give the β-azido ketone.[1363] Sodium azide adds to conjugated ketones in aqueous acetic acid and 20% PBu_3.[1364] An interesting variation involves a double Michael addition of amido amines, amido alcohols, or amido thiols to conjugated alkynes, forming pyrrolidine, oxazolidine, or thiazolidine derivatives.[1365]

The nitrogen of carbamates adds to conjugated ketones with Pt,[1366] Pd,[1367] Cu,[1368] or a bis(triflamide) organocatalyst.[1369] The amine moiety of a carbamate adds to conjugated ketones with a polymer-supported acid catalyst,[1370] or with $BF_3{\bullet}OEt_2$.[1371]

Phosphines react similarly to the reactions of amines under certain conditions. The steric and electronic effects that affect the phospha-Michael addition to activated internal alkenes have been discussed.[1372] Conjugate addition of R_2PH and a Ni catalyst give conjugate addition to α,β-unsaturated nitriles.[1373] A Pd-catalyzed addition of diarylphosphines proceeds with good enantioselectivity to give chiral phosphines.[1374] The phospha-Michael reaction with nitroalkenes has been reported.[1375] An enantioselective phospha-Michael addition of diarylphosphines to β,γ-unsaturated-α-keto esters and amides has been reported.[1376] Asymmetric phospha-Michael reactions were catalyzed by bicyclic guanidines.[1377]

Alcohols add to conjugated ketones with a PMe_3 catalyst to give the β-alkoxy ketone[1378] in what is called an *oxy-Michael reaction*.[1379] An intramolecular variation is known that

[1357] Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J.M. *J. Am. Chem. Soc.* ***2004***, *126*, 9188.
[1358] Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* ***2008***, *130*, 16464.
[1359] Miyaji, R.; Asano, K.; Matsubara, S. *Org. Lett.* ***2013***, *15*, 3658.
[1360] Hack, D.; Enders, D. *Synthesis* ***2013***, *45*, 2904.
[1361] Ahn, K.H.; Lee, S.J. *Tetrahedron Lett.* ***1994***, *35*, 1875.
[1362] Panarina, A.E.; Dogadina, A.V.; Zakharov, V.I.; Ionin, B.I. *Tetrahedron Lett.* ***2001***, *42*, 4365.
[1363] Guerin, D.J.; Horstmann, T.E.; Miller, S.J. *Org. Lett.* ***1999***, *1*, 1107.
[1364] Xu, L.-W.; Xia, C.-G.; Li, J.-W.; Zhou, S.-L. *Synlett* ***2003***, 2246.
[1365] Sriramurthy, V.; Barcan, G.A.; Kwon, O. *J. Am. Chem. Soc.* ***2007***, *129*, 12928.
[1366] Kakumoto, K.; Kobayashi, S.; Sugiura, M. *Org. Lett.* ***2002***, *4*, 1319.
[1367] Gaunt, M.J.; Spencer, J.B. *Org. Lett.* ***2001***, *3*, 25.
[1368] Wabnitz, T.C.; Spencer, J.B. *Tetrahedron Lett.* ***2002***, *43*, *3*891.
[1369] Wabnitz, T.C.; Spencer, J.B. *Org. Lett.* ***2003***, *5*, 2141.
[1370] Wabnitz, T.C.; Yu, J.-Q.; Spencer, J.B. *Synlett* ***2003***, 1070.
[1371] Xu, L.-W.; Li, L.; Xia, C.-G.; Zhou, S.-L.; Li, J.-W.; Hu, X.-X. *Synlett* ***2003***, 2337.
[1372] Lenker, H.K.; Richard, M.E.; Reese, K.P.; Carter, A.F.; Zawisky, J.D.; Winter, E.F.; Bergeron, T.W.; Guydon, K.S.; Stockland Jr., R.A. *J. Org. Chem.* ***2012***, *77*, 1378.
[1373] Sadow, A.D.; Haller, I.; Fadini, L.; Togni, A. *J. Am. Chem. Soc.* ***2004***, *126*, 14704.
[1374] Feng, J.-J.; Chen, X.-F.; Shi, M.; Duan, W.-L. *J. Am. Chem. Soc.* ***2010***, *132*, 5562. See Chen, Y.-R.; Duan, W.-L. *Org. Lett.* ***2011***, *13*, 5824.
[1375] Huang, H.; Palmas, J.; Kang, J.Y. *J. Org. Chem.* ***2016***, *81*, 11932.
[1376] Chew, R.J.; Teo, K.Y.; Huang, Y.; Li, B.-B.; Li, Y.; Pullarkat, S.A.; Leung, P.-H. *Chem. Commun.* ***2014***, *50*, 8768.
[1377] Cho B.; Tan, C.-H.; Wong, M.W. *Org. Biomol. Chem.* ***2011***, *9*, 4550.
[1378] Stewart, I.C.; Bergman, R.G.; Toste, F.D. *J. Am. Chem. Soc.* ***2003***, *125*, 8696.
[1379] Also called hydroalkoxylation. See Ramachary, D.B.; Mondal, R. *Tetrahedron Lett.* ***2006***, *47*, 7689.

produces dihydropyrones.[1380] Alcohol addition is catalyzed by *N*-heterocyclic carbenes[1381] and other organocatalysts,[1382] with good enantioselectivity.[1383] An oxa-Michael reaction was shown to be promoted by aqueous sodium carbonate.[1384] Organocatalysts have been used for the enantioselective intramolecular oxa-Michael reaction of conjugated amides and esters,[1385] and an oxa-Michael reaction with conjugated nitriles is known.[1386]

Thiols undergo conjugate addition[1387] and thiol addition is also catalyzed by iodine under solvent-free conditions.[1388] Thiols add without a catalyst in water,[1389] and enantioselectively with Sc catalysis in water,[1390] in polyethylene glycol (PEG),[1391] or in ionic liquids.[1392] Similar addition is observed with selenium compounds RSeLi.[1393] An odorless thia-Michael reaction using alkyl halides and thiourea to give the alkylthiouronium salt has been reported using a eutectic solvent (choline chloride/urea).[1394] Alkyl thiols add to conjugated carbonyl compounds with good enantioselectivity using an organocatalyst.[1395] Chiral amines catalyzed the thia-Michael reaction of α-substituted conjugated ketones with good enantioselectivity.[1396] A biocatalyzed thio-Michael reaction using chymosin and papain has been reported.[1397] Using tetrabutylammonium hydroxide, the selectivity of the thia-Michael addition was reversed.[1398]

Asymmetric thio-Michael reactions have been reported using transition metal catalysis.[1399] Thiols react with conjugated amides via 1,4-addition with the addition of 10% $Hf(OTf)_4$ or other lanthanide triflates[1400] or with conjugated ketones in ionic solvents.[1401] Iron(III)-catalyzed addition of thiols occurs under solvent-free conditions.[1402] The Re-catalyzed addition of thiols to conjugated ketones is known.[1403] Ceric ammonium nitrate

[1380] Baker-Glenn, C.; Hodnett, N.; Reiter, M.; Ropp, S.; Ancliff, R.; Gouverneur, V. *J. Am. Chem. Soc.* ***2005***, *127*, 1481.
[1381] Phillips, E.M.; Riedrich, M.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2010***, *132*, 13179.
[1382] Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron Lett.* ***2006***, *47*, 3039.
[1383] Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron* ***2007***, *63*, 8658.
[1384] Guo, S.-H.; Xing, S.-Z.; Mao, S.; Gao, Y.-R.; Chen, W.-L.; Wang, Y.-Q. *Tetrahedron Lett.* ***2014***, *55*, 6718.
[1385] Kobayashi, Y.; Taniguchi, Y.; Hayama, N.; Inokuma, T.; Takemoto, Y. *Angew. Chem. Int. Ed.* ***2013***, *52*, 11114.
[1386] Perdriau, S.; Zijlstra, D.S.; Heeres, H.J.; de Vries, J.G.; Otten, E. *Angew. Chem. Int. Ed.* ***2015***, *54*, 4236.
[1387] Kowalczyk, R.; Wierzba, A.J.; Boratyński, P.J.; Bąkowicz, J. *Tetrahedron* ***2014***, *70*, 5834.
[1388] Gao, S.; Tzeng, T.; Sastry, M.N.V.; Chu, C.-M.; Liu, J.-T.; Lin, C.; Yao, C.-F. *Tetrahedron Lett.* ***2006***, *47*, 1889.
[1389] Khatik, G.L.; Kumar, R.; Chakraborti, A.K. *Org. Lett.* ***2006***, *8*, 2433.
[1390] Bonollo, S.; Lanari, D.; Pizzo, F.; Vaccaro, L. *Org. Lett.* ***2011***, *13*, 2150; Ueno, M.; Kitanosono, T.; Sakai, M.; Kobayashi, S. *Org. Biomol. Chem.* ***2011***, *9*, 3619.
[1391] Kamal, A.; Reddy, D.R.; Rajendar *Tetrahedron Lett.* ***2005***, *46*, 7951.
[1392] Mečiarová, M.; Toma, Š.; Kotrusz, P. *Org. Biomol. Chem.* ***2006***, *4*, 1420.
[1393] Zeni, G.; Stracke, M.P.; Nogueira, C.W.; Braga, A.L.; Menezes, P.H.; Stefani, H.A. *Org. Lett.* ***2004***, *6*, 1135.
[1394] Azizi, N.; Yadollahy, Z.; Rahimzadeh-Oskooee, A. *Tetrahedron Lett.* ***2014***, *55*, 1722.
[1395] Kumar, A.; Akanksha *Tetrahedron* ***2007***, *63*, 11086; Kawazoe, S.; Yoshida, K.; Shimazaki,Y.; Oriyama, T. *Chem. Lett.* ***2014***, *43*, 1659.
[1396] Fu, N.; Zhang, L.; Luo, S.; Cheng, J.-P. *Org. Lett.* ***2014***, *16*, 4626.
[1397] Rizzo, P.V.S.; Boarin, L.A.; Freitas, I.O.M.; Gomes, R.S.; Beatriz, A.; Rinaldi, A.W.; Domingues, N.L.C. *Tetrahedron Lett.* ***2014***, *55*, 430.
[1398] Nicponski, D.R.; Marchi, J.M. *Synthesis* ***2014***, *46*, 1725.
[1399] Yuan, P.; Meng, S.; Chen, J.; Huang, Y. *Synlett* ***2016***, *27*, 1068; Ktanosono, T.; Sakai, M.; Ueno, M.; Kobayashi, S. *Org. Biomol. Chem.* ***2012***, *10*, 7134.
[1400] Kobayashi, S.; Ogawa, C.; Kawamura, M.; Sugiura, M. *Synlett* ***2001***, 983.
[1401] Yadav, J.S.; Reddy, B.V.S.; Baishya, G. *J. Org. Chem.* ***2003***, *68*, 7098.
[1402] Chu, C.-M.; Huang, W.-J.; Lu, C.; Wu, P.; Liu, J.-T.; Yao, C.-F. *Tetrahedron Lett.* ***2006***, *47*, 7375.
[1403] Peng, A.; Rosenblatt, R.; Nolinm, K. *Tetrahedron Lett.* ***2012***, *53*, 2712.

promotes the conjugate addition of thiols.[1404] Addition to conjugated lactones is possible to produce β-aryl thiolated lactones.[1405]

The reaction of dialkyl diselenides with conjugated carbonyl compounds in the presence of $NaBH_4$ gave the β-selenide product.[1406]

15-28 Acylation of Activated Double Bonds and of Triple Bonds

Under some conditions, acid derivatives add directly to activated double bonds to give the hydroacylation product. Acetic anhydride, Mg metal, and Me_3SiCl react with conjugated esters to give a γ-keto ester.[1407] Similar reaction with vinyl phosphonate esters leads to a γ-keto phosphonate ester.[1408] Thioesters undergo conjugate addition to α,β-unsaturated ketones in the presence of SmI_2.[1409] Under microwave irradiation, aldehydes add to conjugated ketones using DBU/Al_2O_3 and a thiazolium salt.[1410] The conjugate addition of acyl zirconium complexes in the presence of BF_3•OEt_2 is catalyzed by palladium acetate.[1411]

An acyl group can be introduced into the 4 position of an α,β-unsaturated ketone by treatment with an organolithium compound and nickel carbonyl[1412] to give a 1,4-diketone. The R group may be aryl or primary alkyl. The reaction can also be applied to alkynes (which need not be activated), in which case 2 molar equivalents add and the product is also a 1,4-diketone, e.g., $R'C{\equiv}CH \rightarrow RCOCHR'CH_2COR$.[1413] In a different procedure, α,β-unsaturated ketones and aldehydes are acylated by treatment at −110 °C with $R_2(CN)CuLi_2$ and CO. This method is successful for R = primary, secondary, and tertiary alkyl.[1414] For secondary and tertiary groups, R(CN)CuLi (which does not waste an R group) can be used instead.[1415]

The hydroacylation of cyclic ketene silyl acetals with acyl fluorides, catalyzed by a functionalized thiourea and 4-pyrrolidinopyridine, gave the 2-acyl butyrolactone.[1416] The hydroacylation of cyclopropane was catalyzed by *N*-heterocyclic carbenes.[1417] The Rh-catalyzed hydroformylation of alkenes has been reported.[1418] Aldehydes reacted with 1,3-dienes with a Co catalyst, and aryl aldehydes gave primarily the 1,4-alkenyl ketone

[1404] Chu, C.-M.; Gao, S.; Sastry, M.N.V.; Kuo, C.-W.; Lu, C.; Liu, J.-T.; Yao, C.-F. *Tetrahedron* ***2007***, *63*, 1863.
[1405] Nishimura, K.; Tomioka, K. *J. Org. Chem.* ***2002***, *67*, 431.
[1406] Perin, G.; Borges, E.L.; Rosa, P.C.; Carvalho, P.N.; Lenardão, E.J. *Tetrahedron Lett.* ***2013***, *54*, 1718.
[1407] Ohno, T.; Sakai, M.; Ishino, Y.; Shibata, T.; Maekawa, H.; Nishiguchi, I. *Org. Lett.* ***2001***, *3*, 3439.
[1408] Kyoda, M.; Yokoyama, T.; Maekawa, H.; Ohno, T.; Nishiguchi, I. *Synlett* ***2001***, 1535.
[1409] Blakskjær, P.; Høj, B.; Riber, D.; Skrydstrup, T. *J. Am. Chem. Soc.* ***2003***, *125*, 4030.
[1410] Yadav, J.S.; Anuradha, K.; Reddy, B.V.S.; Eeshwaraiah, B. *Tetrahedron Lett.* ***2003***, *44*, 8959.
[1411] Hanzawa, Y.; Tabuchi, N.; Narita, K.; Kakuuchi, A.; Yabe, M.; Taguchi, T. *Tetrahedron* ***2002***, *58*, 7559.
[1412] Corey, E.J.; Hegedus, L.S. *J. Am. Chem. Soc.* ***1969***, *91*, 4926.
[1413] Sawa, Y.; Hashimoto, I.; Ryang, M.; Tsutsumi, S. *J. Org. Chem.* ***1968***, *33*, 2159.
[1414] Seyferth, D.; Hui, R.C. *J. Am. Chem. Soc.* ***1985***, *107*, 4551. See also, Lipshutz, B.H.; Elworthy, T.R. *Tetrahedron Lett.* ***1990***, *31*, 477.
[1415] Seyferth, D.; Hui, R.C. *Tetrahedron Lett.* ***1986***, *27*, 1473.
[1416] Birrell, J.A.; Desrosiers, J.-N.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2011***, *133*, 13872.
[1417] Bugaut, X.; Liu, F.; Glorius, F. *J. Am. Chem. Soc.* ***2011***, *133*, 8130.
[1418] Wang, X.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2011***, *133*, 19080. For a computational study of the mechanism, see Luo, X.; Bai, R.; Liu, S.; Shan, C.; Chen, C.; Lan, Y. *J. Org. Chem.* ***2016***, *81*, 2320.

(the β,γ-derivative), whereas aliphatic aldehydes gave primarily the 1,2-alkenyl ketone (the γ,δ−derivative).[1419] The Pd-catalyzed hydroacylation of allenes uses acid chlorides and hydrosilanes.[1420]

The reaction of acyl chlorides with alkynes, with an Ir catalyst, gave the β-chloro-α,β-unsaturated ketone.[1421] The hydroacylation of alkynes gave the conjugated carbonyl, and choice of the Ru catalyst allowed switching the regioselectivity.[1422] Allenes reacted with acyl chlorides in the presence of $HSi(O\textit{i}\text{-}Pr)_3$ and with a Pd catalyst to give conjugated ketones.[1423]

The reaction of an aldehyde and cyanide ion (see **16-51**) in a polar aprotic solvent (e.g., DMF or DMSO) leads to a cyanohydrin, which generates a diketone via loss of HCN.[1424] This method has been applied to α,β-unsaturated ketones, esters, and nitriles to give the corresponding 1,4-diketones, γ-keto esters, and γ-keto nitriles, respectively (see also, **16-54**).

OS **VI**, 866; **VIII**, 620.

15-29 Addition of Alcohols, Amines, Carboxylic Esters, Aldehydes, and so on

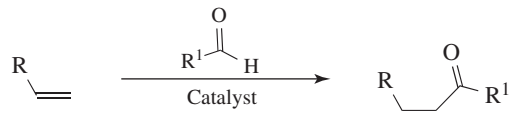
Formates, primary and secondary alcohols, amines, ethers, alkyl halides, compounds of the type $Z{-}CH_2{-}Z'$, and a few other compounds add to double bonds in the presence of free-radical initiators.[1425] Alcohols, ethers, amines, and alkyl halides add via the OH-bearing carbon. Compounds with an active hydrogen such as ZCH_2Z' react with alkenes.[1426] Similar additions have been successfully carried out with carboxylic acids, anhydrides,[1427] acyl halides, carboxylic esters, nitriles, and other types of compounds.[1428]

Similar reactions have been carried out on acetylene.[1429] Aldehydes add to alkynes in the presence of a Rh catalyst to give conjugated ketones.[1430] In a cyclic version of the addition of aldehydes, penten-4-al was converted to cyclopentanone with a Rh complex catalyst.[1431] An intramolecular acyl addition to an alkyne was reported using silyl ketones, acetic acid, and a Rh catalyst.[1432] Formamides add to alkynes in the presence of a Pd catalyst to form conjugated amides.[1433]

OS **IV**, 430; **V**, 93; **VI**, 587, 615.

[1419] Chen, Q.-A.; Kim, D.K.; Dong, Vy.M. *J. Am. Chem. Soc.* ***2014***, *136*, 3772.
[1420] Fujihara, T.; Tatsumi, K.; Terao, J.; Tsuji, Y. *Org. Lett.* ***2013***, *15*, 2286.
[1421] Iwai, T.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* ***2012***, *134*, 1268.
[1422] Chen, Q.-A.; Cruz, F.A.; Dong, Vy.M. *J. Am. Chem. Soc.* ***2015***, *137*, 3157.
[1423] Fujihara, T.; Tatsumi, K.; Terao, J.; Tsuji, Y. *Org. Lett.* ***2013***, *15*, 2286.
[1424] See Stetter, H.; Kuhlmann, H. *Org. React.* ***1991***, *40*, 407–496; Stetter, H.; Kuhlmann, H.; Haese, W. *Org. Synth., 65*, 26.
[1425] See Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***, pp. 69–77; Vogel, H. *Synthesis* ***1970***, 99; Dang, H.-S.; Roberts, B.P. *Chem. Commun.* ***1996***, 2201.
[1426] See Hájek, M.; Málek, J. *Coll. Czech. Chem. Commun.* ***1979***, *44*, 3695.
[1427] de Klein, W.J. *Recl. Trav. Chim. Pays-Bas* ***1975***, *94*, 48.
[1428] Cadogan, J.I.G. *Pure Appl. Chem.* ***1967***, *15*, 153 (pp. 153–158). See also, Giese, B.; Zwick, W. *Chem. Ber.* ***1982***, *115*, 2526; Giese, B.; Erfort, U. *Chem. Ber.* ***1983***, *116*, 1240.
[1429] See DiPietro, J.; Roberts, W.J. *Angew. Chem. Int. Ed.* ***1966***, *5*, 415.
[1430] Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* ***1997***, *62*, 4564.
[1431] Fairlie, D.P.; Bosnich, B. *Organometallics* ***1988***, *7*, 936, 946. Also see, Barnhart, R.W.; Wang, X.; Noheda, P.; Bergens, S.H.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* ***1994***, *116*, 1821.
[1432] Yamane, M.; Amemiya, T.; Narasaka, K. *Chem. Lett.* ***2001***, 1210.
[1433] Fujihara, T.; Katafuchi, Y.; Iwai, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* ***2010***, *132*, 2094.

15-30 Addition of Aldehydes



In the presence of metal catalysts such as Rh[1434] or Yb[1435], aldehydes can add directly to alkenes to form ketones. Additives play an important role in such reactions.[1436] The reaction of ω-alkenyl aldehydes with a Rh catalyst leads to cyclic ketones,[1437] with high enantioselectivity if chiral ligands are employed. A carbene organocatalyst was used for an enantioselective intramolecular reaction.[1438] β,γ-Unsaturated ketones are prepared by the Rh-catalyzed addition of aldehydes to dienes.[1439] The addition of aldehydes to activated double bonds, mediated by a catalytic amount of thiazolium salt in the presence of a weak base, is called the *Stetter reaction*.[1440] An internal addition of an alkynyl aldehyde, catalyzed by a Rh complex, led to a cyclopentenone derivative.[1441] These reactions are not successful when the alkene contains electron-withdrawing groups, such as halo or carbonyl groups. A free-radical initiator is required,[1442] usually peroxides or UV light. The aldehyde is first converted to an acyl radical, which adds to an alkene to give a new radical. This radical deprotonates another molecule of the aldehyde in a chain-carrying step to give the acylated product and another acyl radical. In the presence of BF_3 and a Ag salt, aldehydes add to alkynes to give the corresponding conjugated ketone,[1443] but polymers are often side products. Photochemical addition of aldehydes to conjugated C═C units can be efficient when a triplet sensitizer (Sec. 7.A.vi, category 5) such as benzophenone is used.[1444]

N-Heterocyclic carbene-catalyzed C—C bond cleavage of carbohydrates via a retro-benzoin-type reaction generated the acyl anion intermediates that were formaldehyde equivalents for a *Stetter reaction* with conjugated ketones, and the product was a β-formyl ketone.[1445] The Stetter reaction is the 1,4-addition of a nucleophile.[1446] Other organocatalysts have been used for an intermolecular and enantioselective Stetter reaction.[1447] Apart

[1434] See Imai, M.; Tanaka, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *J. Org. Chem.* ***2007***, *72*, 2543. For a discussion of the mechanism, see Roy, A.H.; Lenges, C.P.; Brookhart, M. *J. Am. Chem. Soc.* ***2007***, *129*, 2082.

[1435] Curini, M.; Epifano, F.; Maltese, F.; Rosati, O. *Synlett* ***2003***, 552.

[1436] See Jo, E.-A.; Jun, C.-H. *Tetrahedron Lett.* ***2009***, *50*, 3338.

[1437] Barnhart, R.W.; McMorran, D.A.; Bosnich, B. *Chem. Commun.* ***1997***, 589.

[1438] See Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* ***2006***, *128*, 2552; Enders, D.; Han, J.; Henseler, A. *Chem. Commun.* ***2008***, 3989.

[1439] Omura, S.; Fukuyama, T.; Horiguchi, J.; Murakami, Y.; Ryu, I. *J. Am. Chem. Soc.* ***2008***, *130*, 14094. For a related reaction, see Shibahara, F.; Bower, J.F.; Krische, M.J. *J. Am. Chem. Soc.* ***2008***, *130*, 14120.

[1440] Stetter, H.; Kuhlmann, H. *Org. React.* ***1991***, *40*, 407; See Yetra, S.R.; Patra, A.; Biju, A.T. *Synthesis* ***2015***, *47*, 1357. See also, Mattson, A.E.; Bharadwaj, A.R.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2004***, *126*, 2314.

[1441] Tanaka, K.; Fu, G.C. *J. Am. Chem. Soc.* ***2002***, *124*, 10296.

[1442] See Lee, E.; Tae, J.S.; Chong, Y.H.; Park, Y.C.; Yun, M.; Kim, S. *Tetrahedron Lett.* ***1994***, *35*, 129 for an example.

[1443] Rhee, J.U.; Krische, M.J. *Org. Lett.* ***2005***, *7*, 2493.

[1444] Kraus, G.A.; Liu, P. *Tetrahedron Lett.* ***1994***, *35*, 7723.

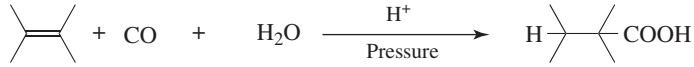
[1445] Zhang, J.; Xing, C.; Tiwari, B.; Chi, Y.R. *J. Am. Chem. Soc.* ***2013***, *135*, 8113.

[1446] See Stetter, H. *Angew. Chem. Int. Ed.* ***1976***, *15*, 639.

[1447] Sánchez-Larios, E.; Thai, K.; Bilodeau, F.; Gravel, M. *Org. Lett.* ***2011***, *13*, 4942.

from the formation of keto esters,[1448] the Stetter reaction has been applied to conjugated sulfones[1449] and nitrostyrenes.[1450]

15-31 Hydrocarboxylation



The acid-catalyzed hydrocarboxylation of alkenes (the *Koch reaction*) can be performed in a number of ways.[1451] In one method, the alkene is treated with carbon monoxide and water at 100–350 °C and 500–1000 atm pressure with a mineral acid catalyst. However, the reaction can also be performed under milder conditions. If the alkene is first treated with CO and catalyst and then water added, the reaction can be accomplished at 0–50 °C and 1–100 atm. If formic acid is used as the source of both the CO and the water, the reaction can be carried out at room temperature and atmospheric pressure.[1452] The formic acid procedure is called the *Koch-Haaf reaction* (the Koch-Haaf reaction can also be applied to alcohols, see **10-78**). Nearly all alkenes can be hydrocarboxylated by one of these procedures. However, conjugated dienes are polymerized under these conditions. Hydrocarboxylation can also be accomplished under mild conditions (160 °C and 50 atm) by the use of $Ni(CO)_4$ as catalyst. Acid catalysts are used along with the $Ni(CO)_4$, but basic catalysts can also be employed.[1453] The $Ni(CO)_4$-catalyzed oxidative carbonylation with CO and water as a nucleophile is often called *Reppe carbonylation*.[1454] The toxic nature of $Ni(CO)_4$ has led to development of other catalysts.[1455] Indeed, variations in the reaction procedure include the use of Pd,[1456] Pt,[1457] and Rh[1458] catalysts. This reaction carboxylates alkenes, alkynes, and dienes and is tolerant of a wide variety of functional groups. When the additive is alcohol or acid, the products are saturated or unsaturated acids, esters, or anhydrides (see **15-32**). The transition metal-catalyzed carbonylation has been done enantioselectively, with moderate to high optical yields, by the use of an optically active Pd complex catalyst.[1459]

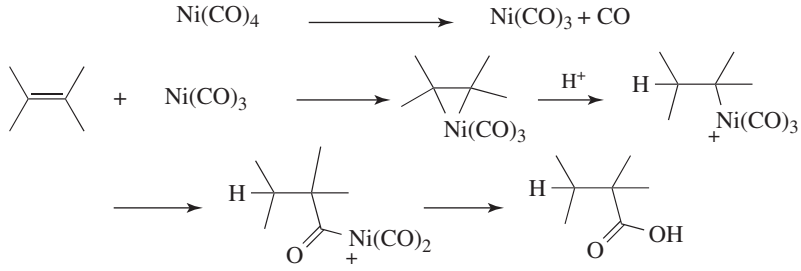
[1448] Wurz, N.E.; Daniliuc, C.G.; Glorius, F. *Chem. Eur. J.* ***2012***, *18*, 16297.
[1449] Bhunia, A.; Yetra, S.R.; Bhojgude, S.S.; Biju, A.T. *Org. Lett.* ***2012***, *14*, 2830.
[1450] DiRocco, D.A.; Noey, E.L.; Houk, K.N.; Rovis, T. *Angew. Chem. Int. Ed.* ***2012***, *51*, 2391.
[1451] See Lapidus, A.L.; Pirozhkov, S.D. *Russ. Chem. Rev.* ***1989***, *58*, 117; Anderson, G.K.; Davies, J.A. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 3, Wiley, NY, ***1985***, pp. 335–359 (pp. 335–348). In Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, see the articles by Mullen, A. pp. 243–308; and by Bahrmann, H. pp. 372–413. Falbe, J. *Carbon Monoxide in Organic Synthesis*, Springer, Berlin, ***1970***, pp. 78–174.
[1452] Haaf, W. *Chem. Ber.* ***1966***, *99*, 1149; Christol, H.; Solladié, G. *Bull. Soc. Chim. Fr.* ***1966***, 1307.
[1453] Sternberg, H.W.; Markby, R.; Wender, P. *J. Am. Chem. Soc.* ***1960***, *82*, 3638.
[1454] Tsuji, J. *Palladium Reagents and Catalysts*, Wiley, NY, ***1999***; Beller, M.; Tafesh, A.M. in *Applied Homogeneous Catalysis with Organometallic Compounds*, Vol. 1, VCH, NY, ***1996***, p. 187; Drent, E.; Jager, W.W.; Keijsper, J.J.; Niele, F.G.M. in *Applied Homogeneous Catalysis with Organometallic Compounds*, Vol. 1, VCH, NY, ***1996***, p 1119; Bertoux, F.; Monflier, E.; Castanet, Y.; Mortreux, A. *J. Mol. Catal. A: Chem.* ***1999***, *143*, 11; Milstein, D. *Acc. Chem. Res.* ***1988***, *21*, 428.
[1455] For a review, see Kiss, G. *Chem. Rev.* ***2001***, *101*, 3435.
[1456] See Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 381–395; See Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* ***2008***, *130*, 15254.
[1457] Xu, Q.; Fujiwara, M.; Tanaka, M.; Souma, Y. *J. Org. Chem.* ***2000***, *65*, 8105.
[1458] Xu, Q.; Nakatani, H.; Souma, Y. *J. Org. Chem.* ***2000***, *65*, 1540.
[1459] Alper, H.; Hamel, N. *J. Am. Chem. Soc.* ***1990***, *112*, 2803.

Alkenes also react with $Fe(CO)_5$ and CO to give carboxylic acids.[1460] Electrochemical carboxylation procedures have been developed, including the conversion of alkenes to 1,4-butanedicarboxylic acids.[1461] A reductive carboxylation of alkenes with CO and cesium carbonate has been reported.[1462]

When applied to triple bonds, hydrocarboxylation gives α,β-unsaturated acids under very mild conditions. Triple bonds give unsaturated acids and saturated dicarboxylic acids when treated with carbon dioxide and an electrically reduced nickel complex catalyst.[1463] A related reaction with CO and Pd catalysts in the presence of $SnCl_2$ leads to conjugated acid derivatives.[1464] Terminal alkynes react with CO_2 and $Ni(cod)_2$, and subsequent treatment with DBU gives the α,β-unsaturated carboxylic acid.[1465]

When acid catalysts are employed, in the absence of nickel carbonyl, the mechanism[1466] involves (i) initial attack on a proton to give a carbocation, followed by (ii) attack by carbon monoxide on the resulting carbocation on to give an acyl cation, and (iii) subsequent reaction with water gives the product, the carboxylic acid. *Markovnikov's rule* is followed, and carbon skeleton rearrangements and double bond isomerizations (prior to attack by CO) are frequent.

For the transition metal-catalyzed reactions, the nickel carbonyl reaction has been well studied and the addition is *syn* for both alkenes and alkynes.[1467] The accepted mechanism[1467] involves formation of $Ni(CO)_3$ from $Ni(CO)_4$, which reacts with the alkene to give a bridged Ni complex. Subsequent treatment with H^+ opens the three-membered ring and a rearrangement gives the acyl Ni complex, which leads to the carboxylic acid.



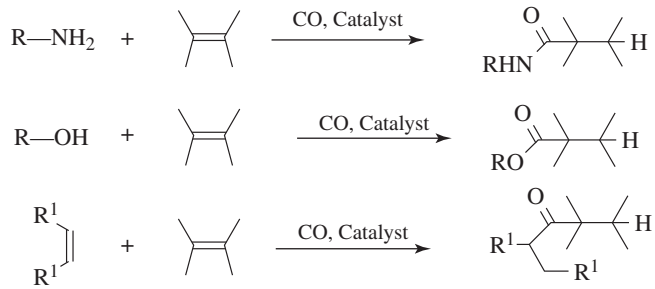
Hydrocarboxylation was reported via the Fe-catalyzed reaction of aryl alkenes with CO_2 and methylmagnesium bromide to give α-aryl carboxylic acids.[1468] Vinyl triflates or aryl triflates were converted to the corresponding carboxylic acids via reaction with CO_2, mediated by Mn, catalyzed by a Co or a Ni catalyst.[1469] The Co-catalyzed allylic carboxylation with CO_2 was reported.[1470] The reaction of CO_2 with 1,3-dienes via Pd-catalyzed

[1460] Brunet, J.-J.; Neibecker, D.; Srivastava, R.S. *Tetrahedron Lett.* ***1993***, *34*, 2759.
[1461] Senboku, H.; Komatsu, H.; Fujimura, Y.; Tokuda, M. *Synlett* ***2001***, 418.
[1462] Williams, C.M.; Johnson, J.B.; Rovis, T. *J. Am. Chem. Soc.* ***2008***, *130*, 14936.
[1463] Duñach, E.; Dérien, S.; Périchon, J. *J. Organomet. Chem.* ***1989***, *364*, C33.
[1464] Takeuchi, R.; Sugiura, M. *J. Chem. Soc., Perkin Trans. 1* ***1993***, 1031.
[1465] Saito, S.; Nakagawa, S.; Koizumi, T.; Hirayama, K.; Yamamoto, Y. *J. Org. Chem.* ***1999***, *64*, 3975. See also, Takimoto, M.; Shimizu, K.; Mori, M. *Org. Lett.* ***2001***, *3*, 3345.
[1466] See Hogeveen, H. *Adv. Phys. Org. Chem.* ***1973***, *10*, 29.
[1467] Bird, C.W.; Cookson, R.C.; Hudec, J.; Williams, R.O. *J. Chem. Soc.* ***1963***, 410.
[1468] Greenhalgh, M.D.; Thomas, S.P. *J. Am. Chem. Soc.* ***2012***, *134*, 11900.
[1469] Nogi, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Org. Chem.* ***2015***, *80*, 11618.
[1470] Michigami, K.; Mita, T.; Sato, Y.; *J. Am. Chem. Soc.* ***2017***, *139*, 6094.

hydrocarboxylation, mediated by $AlEt_n(OEt)_{3-n}$, gave the β,γ-unsaturated carboxylic acid.[1471] The hydrocarboxylation of styrenes with CO_2 was accomplished using continuous flow techniques (Sec. 7.D).[1472]

The alkoxycarbonylation of 1-alkenes used a Lewis acid and a Pd catalyst to give the carboxylic ester.[1473] The Ni-catalyzed double carboxylation of alkynes with CO_2 and 3 equivalents of Zn powder and 2 equivalents of $MgBr_2$ gave the maleic anhydride derivative.[1474] The Pd-catalyzed hydrocarboxylation of alkenes with phenyl formate and formic acid gave the carboxylic acid.[1475]

15-32 Carbonylation, Alkoxycarbonylation, and Aminocarbonylation Of Double And Triple Bonds



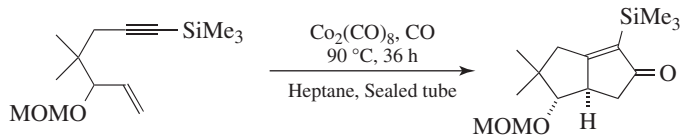
In the presence of certain metal catalysts, alkenes and alkynes can be carbonylated or converted to give an amide or an ester.[1476] There are several variations.[1477] The reaction of an alkyl iodide and a conjugated ester with CO, $(Me_3Si)_3SiH$, and AIBN in supercritical CO_2 (Sec. 9.D.ii) gave a γ-keto ester.[1478] Conjugated dienes react with thiophenol, CO, and $Pd(OAc)_2$ to give the β,γ-unsaturated thioester.[1479] Alkynes react with thiophenol and CO with a Pd[1480] or Pt[1481] catalyst to give a conjugated thioester. Terminal alkynes react with CO and methanol, using a combination of a Pd and a Cu catalyst, to give a conjugated diester, $MeO_2C{-}C{\equiv}C{-}CO_2Me$.[1482] A similar reaction with alkenes using a combination of a Pd and a Mo catalyst led to a saturated diester, $MeO_2C{-}C{-}C{-}CO_2Me$.[1483] Note that alkenes are converted to primarily the *anti-Markovnikov* ester upon treatment with arylmethyl formate esters ($ArCH_2OCHO$) and a Ru catalyst.[1484]

[1471] Takaya, J.; Sasano, K.; Iwasawa, N. *Org. Lett.* ***2011***, *13*, 1698.
[1472] Seo, H.; Liu, A.; Jamison, T.F. *J. Am. Chem. Soc.* ***2017***, *139*, 13969.
[1473] Amézquita-Valencia, M.; Achonduh, G.; Alper, H. *J. Org. Chem.* ***2015***, *80*, 6419.
[1474] Fujihara, T.; Horimoto, Y.; Mizoe, T.; Sayyed, F.B.; Tani, Y.; Terao, J.; Sakaki, S.; Tsuji, Y. *Org. Lett.* ***2014***, *16*, 4960.
[1475] Wang, Y.; Ren, W.; Li, J.; Wang, H.; Shi, Y. *Org. Lett.* ***2014***, *16*, 5960.
[1476] See Fallis, A.G.; Forgione, P. *Tetrahedron* ***2001***, *57*, 5899.
[1477] Wu, X.-F.; Fang, X.; Wu, L.; Jackstell, R.; Neumann, H.; Beller, M. *Acc. Chem. Res.* ***2014***, *47*, 1041.
[1478] Kishimoto, Y.; Ikariya, T. *J. Org. Chem.* ***2000***, *65*, 7656.
[1479] Xiao, W.-J.; Alper, H. *J. Org. Chem.* ***2001***, *66*, 6229.
[1480] Xiao, W.-J.; Vasapollo, G.; Alper, H. *J. Org. Chem.* ***1999***, *64*, 2080.
[1481] Kawakami, J.-i.; Mihara, M.; Kamiya, I.; Takeba, M.; Ogawa, A.; Sonoda, N. *Tetrahedron* ***2003***, *59*, 3521.
[1482] Li, J.; Jiang, H.; Chen, M. *Synth. Commun.* ***2001***, *31*, 3131; El Ali, B.; Tijani, J.; El-Ghanam, A.; Fettouhi, M. *Tetrahedron Lett.* ***2001***, *42*, 1567.
[1483] Yokota, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2002***, *67*, 5005.
[1484] Ko, S.; Na, Y.; Chang, S. *J. Am. Chem. Soc.* ***2002***, *124*, 750.

A bicyclic ketone was generated when 1,2-diphenylethyne was heated with CO, methanol, and a dirhodium catalyst.[1485] Another variation reacted a conjugated allene alkene with 5 atmospheres of CO and a Rh catalyst to give a bicyclic ketone.[1486] An intermolecular version of this reaction is known using a Co catalyst, giving a cyclopentenone[1487] in a reaction related to the *Pauson-Khand reaction* (see below). The reaction of a conjugated diene having a distal alkene unit and CO with a Rh catalyst led to a bicyclic conjugated ketone.[1488] Alkynes were converted to cyclobutenones using $Fe_3(CO)_{12}$ to form an initial complex, followed by reaction with copper(II) chloride.[1489] Bicyclic fused cyclopentenes were prepared from *Baylis-Hillman* acetates (**16-27**) of acetylenic aldehydes.[1490] Aliphatic alkynes are also substrates.[1491] The reaction of allylic alcohols used a Rh catalyst with CO/H_2, followed by $NaClO_2$, NaH_2PO_4, and 2-methylbut-2-ene to give the carboxylic acid.[1492] The reaction of alkenes with aniline derivatives, in the presence of Pd catalyst and CO/H_2, gave hydroaminocarbonylation and the corresponding amide.[1493] Heating alkenes with benzylamine•HCl, CO, and a Pd catalyst gave the amide.[1494]

The reactions of dienes, diynes, or enynes with transition metals[1495] (usually Co)[1496] form organometallic coordination complexes. Rhodium,[1497] Ti,[1498] Mo,[1499] and W[1500] complexes have been used for this reaction. In the presence of CO, the metal complexes derived primarily from enynes (alkene alkynes) generate cyclopentenone derivatives in what is known as the *Pauson-Khand reaction*.[1501] This reaction involves formation of a hexacarbonyldicobalt alkyne complex and subsequent decomposition of the complex in the presence of an alkene.[1502] A typical example is the preparation of **38**.[1503] An yne diene can also be used for the Pauson-Khand reaction.[1504] A psuedo-Pauson-Khand reaction has been reported that gave cyclopentenones.[1505]

[1485] Yoneda, E.; Kaneko, T.; Zhang, S.-W.; Onitsuka, K.; Takahashi, S. *Tetrahedron Lett.* ***1999***, *40*, 7811.
[1486] Murakami, M.; Itami, K.; Ito, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 4130.
[1487] Jeong, N.; Hwang, S.H. *Angew. Chem. Int. Ed.* ***2000***, *39*, 636.
[1488] Lee, S.I.; Park, J.H.; Chung, Y.K.; Lee, S.-G. *J. Am. Chem. Soc.* ***2004***, *126*, 2714.
[1489] Rameshkumar, C.; Periasamy, M. *Tetrahedron Lett.* ***2000***, *41*, 2719.
[1490] Reddy, C.R.; Kumaraswamy, P.; Singarapu, K.K. *J. Org. Chem.* ***2014***, *79*, 7880.
[1491] Fager-Jokela, E.; Muuronen, M.; Khaizourane, H.; Vázquez-Romero, A.; Verdaguer, X.; Riera, A.; Helaja, J. *J. Org. Chem.* ***2014***, *79*, 10999.
[1492] Lightburn, T.E.; De Paolis, O.A.; Cheng, Ka.H.; Tan, K.L. *Org. Lett.* ***2011***, *13*, 2686.
[1493] Fang, X.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed.* ***2013***, *52*, 14089.
[1494] Liu, J.; Li, H.; Spannenberg, A.; Franke, R.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed.* ***2016***, *55*, 13544.
[1495] Krafft, M.E.; Hirosawa, C.; Bonaga, L.V.R. *Tetrahedron Lett.* ***1999***, *40*, 9177.
[1496] Krafft, M.E.; Boñaga, L.V.R.; Hirosawa, C. *J. Org. Chem.* ***2001***, *66*, 3004.
[1497] Koga, Y.; Kobayashi, T.; Narasaka, K. *Chem. Lett.* ***1998***, 249. An entrapped Rh catalyst has been used: Park, K.H.; Son, S.U.; Chung, Y.K. *Tetrahedron Lett.* ***2003***, *44*, 2827.
[1498] Hicks, F.A.; Kablaoui, N.M.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1999***, *121*, 5881.
[1499] Adrio, J.; Carretero, J.C. *J. Am. Chem. Soc.* ***2007***, *129*, 778.
[1500] Hoye, T.R.; Suriano, J.A. *J. Am. Chem. Soc.* ***1993***, *115*, 1154.
[1501] Khand, I.U.; Pauson, P.L.; Habib, M.J. *J. Chem. Res. (S)* ***1978***, 348; Lee, H.-W.; Kwong, F.-Y. *Eur. J. Org. Chem.* ***2010***, 789; *The Pauson–Khand Reaction. Scope, Variations and Applications*, Torres, R.R. (Ed.), Wiley, Hoboken, ***2012***.
[1502] See de Bruin, T.J.M.; Milet, A.; Greene, A.E.; Gimbert, Y. *J. Org. Chem.* ***2004***, *69*, 1075. See also, Rivero, M.R.; Adrio, J.; Carretero, J.C. *Eur. J. Org. Chem.* ***2002***, 2881.
[1503] Magnus, P.; Principe, L.M. *Tetrahedron Lett.* ***1985***, *26*, 4851.
[1504] Wender, P.A; Deschamps, N.M.; Gamber, G.G. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1853.
[1505] Barluenga, J.; Álvarez-Fernández, A.; Suárez-Sobrino, Á.L.; Tomás, M. *Angew. Chem. Int. Ed.* ***2012***, *51*, 183.



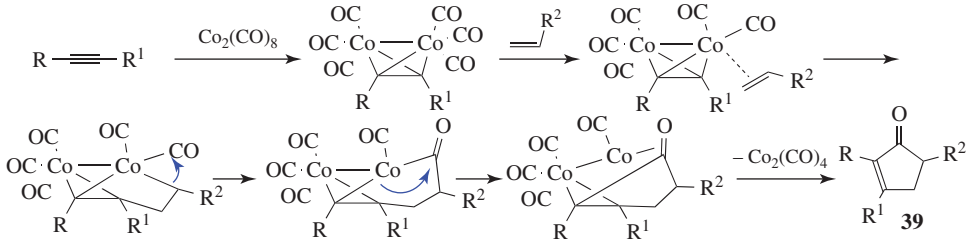
38

The reaction can be promoted photochemically[1506] and the rate is enhanced by the presence of primary amines.[1507] Coordinating ligands also accelerate the reaction.[1508] There are many possible variations in reaction conditions.[1509] The Pauson-Khand reaction has been carried out under heterogeneous reaction conditions,[1510] in water,[1511] with ultrasound promotion,[1512] and with microwave promotion.[1513] The Pauson-Khand reaction has been reported using flow conditions (Sec. 7.D).[1514] Asymmetric Pauson-Khand reactions are known.[1515]

The Pauson-Khand reaction is compatible with other groups or heteroatoms elsewhere in the molecule. These include ethers,[1516] aryl halides,[1516] esters,[1517] amides,[1518] alcohols,[1519] diols,[1520] and an indole unit.[1521] Allenes are reaction partners in the Pauson-Khand reaction.[1522] A double Pauson-Khand process was reported.[1523] Intramolecular Pauson-Khand reactions are known, catalyzed by oxime-derived palladacycles,[1524] or the Rh-catalyzed reactions of 1,4-enynes.[1525] A silicon-tethered Pauson-Khand reaction is known.[1526] This type of reaction can be extended to form six-membered rings using a Ru catalyst.[1527] Polycyclic compounds (tricyclic and higher) are prepared in a relatively straightforward manner

[1506] Pagenkopf, B.L.; Livinghouse, T. *J. Am. Chem. Soc.* ***1996***, *118*, 2285.
[1507] Sugihara, T.; Yamada, M.; Ban, H.; Yamaguchi, M.; Kaneko, C. *Angew. Chem. Int. Ed.* ***1997***, *36*, 2801.
[1508] Krafft, M.E.; Scott, I.L.; Romero, R.H. *Tetrahedron Lett.* ***1992***, *33*, 3829.
[1509] Krafft, M.E.; Boñaga, L.V.R.; Wright, J.A.; Hirosawa, C. *J. Org. Chem.* ***2002***, *67*, 1233; Blanco-Urgoiti, J.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett.* ***2002***, *43*, 5763. In aqueous media, see: Krafft, M.E.; Wright, J.A.; Boñaga, L.V.R. *Tetrahedron Lett.* ***2003***, *44*, 3417.
[1510] Kim, S.-W.; Son, S.U.; Lee, S.I.; Hyeon, T.; Chung, Y.K. *J. Am. Chem. Soc.* ***2000***, *122*, 1550.
[1511] Krafft, M.E.; Wright, J.A.; Llorente, V.R.; Boñaga, L.V.R. *Can. J. Chem.* ***2005***, *83*, 1006.
[1512] Ford, J.G.; Kerr, W.J.; Kirk, G.G.; Lindsay, D.M.; Middlemiss, D. *Synlett* ***2000***, 1415.
[1513] Iqbal, M.; Vyse, N.; Dauvergne, J.; Evans, P. *Tetrahedron Lett.* ***2002***, *43*, 7859.
[1514] Garcia-Lacuna, J.; Doninguez, G.; Blanco-Urgoiti, J.; Pérez-Castells, J. *Chem. Commun.* ***2017***, *53*, 4014.
[1515] Konya, D.; Robert, F.; Gimbert, Y.; Greene, A.E. *Tetrahedron Lett.* ***2004***, *45*, 6975; Orgué, S.; León, T.; Riera, A.; Verdaguer, X. *Org. Lett.* ***2015***, *17*, 250.
[1516] For a review, see Suh. W.H.; Choi, M.; Lee, S.I.; Chung, Y.K. *Synthesis* ***2003***, 2169.
[1517] Krafft, M.E.; Boñaga, L.V.R. *Angew. Chem. Int. Ed.* ***2000***, *39*, 3676, and references cited therein; Sturla, S.J.; Buchwald, S.L. *J. Org. Chem.* ***2002***, *67*, 3398.
[1518] Comely, A.C.; Gibson, S.E.; Stevenazzi, A.; Hales, N.J. *Tetrahedron Lett.* ***2001***, *42*, 1183.
[1519] Blanco-Urgoiti, J.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett.* ***2001***, *42*, 3315.
[1520] Mukai, C.; Kim, J.S.; Sonobe, H.; Hanaoka, M. *J. Org. Chem.* ***1999***, *64*, 6822.
[1521] Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *J. Org. Chem.* ***2004***, *69*, 5413.
[1522] Brummond, K.M.; Chen, H.; Fisher, K.D.; Kerekes, A.D.; Rickards, B.; Sill, P.C.; Geib, A.D. *Org. Lett.* ***2002***, *4*, 1931. See Shibata, T.; Kadowaki, S.; Hirase, M.; Takagi, K. *Synlett* ***2003***, 573.
[1523] Rausch, B.J.; Gleiter, R. *Tetrahedron Lett.* ***2001***, *42*, 1651.
[1524] Wang, X.-R.; Lu, F.-H.; Song, Y.; Lu, Z.-L. *Tetrahedron Lett.* ***2012***, *53*, 589.
[1525] Chen, G.-Q.; Shi, M. *Chem. Commun.* ***2013***, *49*, 698.
[1526] Brummond, K.M.; Sill, P.C.; Rickards, B.; Geib, S.J. *Tetrahedron Lett.* ***2002***, *43*, 3735; Reichwein, J.F.; Iacono, S.T.; Patel, U.C.; Pagenkopf, B.L. *Tetrahedron Lett.* ***2002***, *43*, 3739.
[1527] Trost, B.M.; Brown, R.E.; Toste, F.D. *J. Am. Chem. Soc.* ***2000***, *122*, 5877.

using this reaction.[1528] Heating an alkenyl aldehyde with a Rh catalyst gave cyclopentanone derivatives.[1529]



The accepted mechanism was proposed by Magnus,[1530] and is shown for the formation of **39**.[1531] This is supported by Krafft's work.[1532] Mechanistic work continues.[1533] It has been shown that CO is lost from the Pauson-Khand complex prior to alkene coordination and insertion.[1534] Calculations led to the conclusion that the LUMO of the coordinated alkene plays a crucial role in alkene reactivity by determining the degree of back donation in the complex.[1535]

The Pd-catalyzed alkoxycarbonylation of allenes with aliphatic alcohols and CO gave α,β- and β,γ-unsaturated esters[1536] Alkenes reacted with CO_2 with a Ti catalyst; alkyl alkenes gave the terminal carboxylic acid whereas aryl alkenes gave the benzylic carboxylic acid.[1537] The hydroesterification reaction of alkenes was reported by heating sodium formate and alcohols with a Ru catalyst and a catalytic amount of 2-pyridinemethanol to 170 °C.[1538] The Pd-catalyzed, photolytic reaction of alkenes, CO, alcohols, and alkyl iodides gave the corresponding ester.[1539] The reaction of alkenyl amines with benzylic formates and a Ru catalyst gave the corresponding δ-amino ester.[1540]

The reaction of cyclic alkenes with an *O*-carbamate unit gave the oxazolidone compound upon photolysis with an Ir catalyst and a phosphate base.[1541] The intramolecular oxidative carbonylation of enamides with CO used a Pd and photoredox catalysis, with oxygen as the oxidant, to give 1,3-oxazin-6-ones.[1542] The reaction of an alkene with an alcohol, 20% of

[1528] Ishizaki, M.; Iwahara, K.; Niimi, Y.; Satoh, H.; Hoshino, O. *Tetrahedron* ***2001***, *57*, 2729; Son, S.U.; Yoon, Y.A.; Choi, D.S.; Park, J.K.; Kim, B.M.; Chung, Y.K. *Org. Lett.* ***2001***, *3*, 1065.

[1529] Murphy, S.K.; Dong, Vy.M. *Chem. Commun.* ***2013***, *49*, 698. See Hooper, J.F.; Young, R.D.; Weller, A.S.; Willis, M.C. *Chem. Eur. J.* ***2013***, *19*, 3125.

[1530] Magnus, P.; Principe, L.M. *Tetrahedron Lett.* ***1985***, *26*, 4851.

[1531] For a review, see Brummond, K.M.; Kent, J.L. *Tetrahedron* ***2000***, *56*, 3263.

[1532] Krafft, M.E. *Tetrahedron Lett.* ***1988***, *29*, 999.

[1533] Lesage, D.; Milet, A.; Memboeuf, A.; Blu, J.; Greene, A.E.; Tabet, J.-C.; Gimbert, Y. *Angew. Chem. Int. Ed.* ***2014***, *53*, 1939.

[1534] Gimbert, Y.; Lesage, D.; Milet, A.; Fournier, F.; Greene, A.E.; Tabet, J.-C. *Org. Lett.* ***2003***, *5*, 4073. See Robert, F.; Milet, A.; Gimbert, Y.; Konya, D.; Greene, A.E. *J. Am. Chem. Soc.* ***2001***, *123*, 5396.

[1535] de Bruin, T.J.M.; Milet, A.; Greene, A.E.; Gimbert, Y. *J. Org. Chem.,* ***2004*** *69*, 1075.

[1536] Liu, J.; Liu, Q.; Franke, R.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* ***2015***, *137*, 8556.

[1537] Shao, P.; Wang, S.; Chen, C.; Xi, C. *Org. Lett.* ***2016***, *18*, 2050.

[1538] Kim, D.-S.; Park, W.-J.; Lee, C.-H.; Jun, C.-H. *J. Org. Chem.* ***2014***, *79*, 12191.

[1539] Fusano, A.; Sumino, S.; Fukuyama, T.; Ryu, I. *Org. Lett.* ***2011***, *13*, 2114.

[1540] Armanino, N.; Lafrance, M.; Carreira, E.M. *Org. Lett.* ***2014***, *16*, 572.

[1541] Choi, G.J.; Knowles, R.R. *J. Am. Chem. Soc.* ***2015***, *137*, 9226.

[1542] Liu, K.; Zou, M.; Lei, A. *J. Org. Chem.* ***2016***, *81*, 7088.

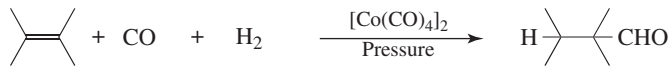
PTSA, and a dipalladium catalyst gave the corresponding ester, with high regioselectivity and good enantioselectivity.[1543]

The reaction of terminal alkynes with CO_2, AgI, and Cs_2CO_3 gave the propiolic acid derivative.[1544] The reaction of diynes with CO_2, 3 equivalents of Et_2Zn, and a Ni catalyst gave 2,4-alkadienoic acids,[1545] and a similar reaction with alkynes gave the conjugated carboxylic acid.[1546] The Cu-catalyzed hydrocarboxylation of alkynes using carbon dioxide gave conjugated carboxylic acids in the presence of a hydrosilane.[1547]

Other carbonylation methods are available. Carbonylation occurs with conjugated ketones to give 1,4-diketones, using phenylboronic acid (see **13-11**), CO, and a Rh catalyst.[1548] A noncarbonylation route treated a conjugated diene with an excess of *tert*-butyllithium, and quenching with carbon dioxide led to a cyclopentadienone.[1549] When quenched with CO rather than CO_2, a nonconjugated cyclopentenone was formed.[1550] It is noted that a carbonylation reaction with CO, a diyne, and an Ir catalyst[1551] or a Co catalyst[1552] provided similar molecules.

With any method, if the alkene contains a functional group such as OH, NH_2, or $CONH_2$, the corresponding lactone (**16-62**),[1553] lactam (**16-73**), or cyclic imide may be the product.[1554] Titanium,[1555] Pd,[1556] Ru,[1557] and Rh[1558] catalysts have been used to generate lactones. Larger-ring conjugated lactones can also be formed by this route using the appropriate allenic alcohol.[1559] Propargylic alcohols lead to β-lactones[1560] or to butenolides with CO/H_2O and a Rh catalyst.[1561] Conjugated imines are converted to similar products with CO, ethylene, and a Ru catalyst.[1562] Amines add to allenes, in the presence of CO and a Pd catalyst, to form conjugated amides.[1563]

15-33 Hydroformylation



[1543] Konrad, T.M.; Durrani, J.T.; Cobley, C.J.; Clarke, M.L. *Chem. Commun.* ***2013***, *49*, 698.
[1544] Zhang, X.; Zhang, W.-Z.; Ren, X.; Zhang, L.-L.; Lu, X.-B. *Org. Lett.* ***2011***, *13*, 2402.
[1545] Cao, T.; Ma, S. *Org. Lett.* ***2016***, *18*, 1510.
[1546] Li, S.; Yuan, W.; Ma, S. *Angew. Chem. Int. Ed.* ***2011***, *50*, 2578.
[1547] Fujihara, T.; Xu, T.; Semba, K.; Terao J.; Tsuji, Y. *Angew. Chem. Int. Ed.* ***2011***, *50*, 523.
[1548] Sauthier, M.; Castanet, Y.; Mortreux, A. *Chem. Commun.* ***2004***, 1520.
[1549] Xi, Z.; Song, Q. *J. Org. Chem.* ***2000***, *65*, 9157.
[1550] Song, Q.; Li, Z.; Chen, J.; Wang, C.; Xi, Z. *Org. Lett.* ***2002***, *4*, 4627.
[1551] Shibata, T.; Yamashita, K.; Katayama, E.; Takagi, K. *Tetrahedron* ***2002***, *58*, 8661.
[1552] Sugihara, T.; Wakabayashi, A.; Takao, H.; Imagawa, H.; Nishizawa, M. *Chem. Commun.* ***2001***, 2456.
[1553] Dong, C.; Alper, H. *J. Org. Chem.* ***2004***, *69*, 5011.
[1554] See Ohshiro, Y.; Hirao, T. *Heterocycles* ***1984***, *22*, 859; Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, pp. 147–174. See Krafft, M.E.; Wilson, L.J.; Onan, K.D. *Tetrahedron Lett.* ***1989***, *30*, 539.
[1555] Kablaoui, N.M.; Hicks, F.A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1997***, *119*, 4424.
[1556] El Ali, B.; Okuro, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc.* ***1996***, *118*, 4264. Also see, Brunner, M.; Alper, H. *J. Org. Chem.* ***1997***, *62*, 7565.
[1557] Kondo, T.; Kodoi, K.; Mitsudo, T.-a.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* ***1994***, 755.
[1558] Yoneda, E.; Kaneko, T.; Zhang, S.-W.; Takahashi, S. *Tetrahedron Lett.* ***1998***, *39*, 5061.
[1559] Yoneda, E.; Zhang, S.-W.; Onitsuka, K.; Takahashi, S. *Tetrahedron Lett.* ***2001***, *42*, 5459.
[1560] Ma, S.; Wu, B.; Zhao, S. *Org. Lett.* ***2003***, *5*, 4429.
[1561] Fukuta, Y.; Matsuda, I.; Itoh, K. *Tetrahedron Lett.* ***2001***, *42*, 1301.
[1562] Chatani, N.; Kamitani, A.; Murai, S. *J. Org. Chem.* ***2002***, *67*, 7014.
[1563] Grigg, R.; Monteith, M.; Sridharan, V.; Terrier, C. *Tetrahedron* ***1998***, *54*, 3885.

Alkenes can be hydroformylated[1564] by treatment with CO and hydrogen over a catalyst. The catalyst is usually a Co carbonyl or a Rh complex,[1565] but other transition metal compounds have also been used,[1566] including Ir[1567] and Os.[1568] Cobalt catalysts[1569] are less active than the Rh type, and catalysts of other metals are generally less active.[1570] Commercially, this is called the *oxo process*, but it can be carried out in the laboratory in an ordinary hydrogenation apparatus. The order of reactivity is straight-chain terminal alkenes > straight-chain internal alkenes > branched-chain alkenes. With terminal alkenes, for example, the aldehyde unit is formed on both the primary and secondary carbon, but proper choice of catalyst and additive leads to selectivity for the secondary product[1571] or primary product.[1572] Alkylidene cyclopropane derivatives undergo hydroformylation to give aldehydes with a quaternary center.[1573] A retro-hydroformylation reaction has been reported.[1574] Hydroformylation has been done using flow conditions (Sec. 7.D).[1575]

Good yields for hydroformylation have been reported using Rh catalysts in the presence of certain other additives.[1576] Among the side reactions are the *aldol reaction* (**16-34**), acetal formation, the *Tishchenko reaction* (**19-86**), and polymerization. Conjugated dienes give dialdehydes when rhodium catalysts are used[1577] but saturated monoaldehydes with cobalt carbonyls (the second double bond is reduced). Both 1,4- and 1,5-dienes may give cyclic ketones.[1578]

The Pd-catalyzed hydroformylation of alkenes used formic acid.[1579] Hydroformylation using a Rh catalyst has been reported in supercritical CO_2.[1580] Formaldehyde has been used for hydroformylation, using a Rh catalyst. The Rh-catalyzed hydroformylation of 1,3-dienes with chiral ligands gave β,γ-unsaturated aldehydes.[1581] The hydroformylation of styrenes with diethoxyacetic acid as the formylation reagent and a photocatalytic dye to give

[1564] See Kalck, P.; Peres, Y.; Jenck, J. *Adv. Organomet. Chem.* ***1991***, *32*, 121; Falbe, J. *Carbon Monoxide in Organic Synthesis*, Springer, NY, ***1980***, pp. 3–77. See Börner, A.; Franke, R. *Hydroformylation. Fundamentals, Processes, and Applications in Organic Synthesis*, Wiley-VCH, Weinheim, ***2016***; Franke, R.; Selent, D.; Börner, A. *Chem. Rev.* ***2012***, *112*, 5675.

[1565] See Gadzikwa, T.; Bellini, R.; Dekker, H.L.; Reek, J.N.H. *J. Am. Chem. Soc.* ***2012***, *134*, 2860.

[1566] See Pospech, J.; Fleischer, I.; Franke, R.; Buchholz, S.; Beller, M. *Angew. Chem. Int. Ed.* ***2013***, *52*, 2852.

[1567] Piras, I.; Jennerjahn, R.; Jackstell, R.; Spannenberg, A.; Franke, R.; Beller, M. *Angew. Chem. Int. Ed.* ***2011***, *50*, 280.

[1568] Wu, L.; Liu, Q.; Spannenberg, A.; Jackstell, R.; Beller, M. *Chem. Commun.* ***2015***, *51*, 3080.

[1569] Achonduh, G.; Yang, Q.; Alper, H. *Tetrahedron* ***2015***, *71*, 1241.

[1570] Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA, ***1987***, p. 630. See Brezny, A.C.; Landis, C.R. *J. Am. Chem. Soc.* ***2017***, *139*, 2778.

[1571] Chan, A.S.C.; Pai, C.-C.; Yang, T.-K.; Chen, S.M. *J. Chem. Soc., Chem. Commun.* ***1995***, 2031.

[1572] Breit, B.; Seiche, W. *J. Am. Chem. Soc.* ***2003***, *125*, 6608.

[1573] Simaan, S.; Marek, I. *J. Am. Chem. Soc.* ***2010***, *132*, 4066.

[1574] Kusumoto, S.; Tatsuki, T.; Nozaki, K. *Angew. Chem. Int. Ed.* ***2015***, *54*, 8458.

[1575] Kasinathan, S.; Bourne, S.L.; Tolstoy, P.; Koos, P.; O'Brien, M.; Bates, R.W.; Baxendale, I.R.; Ley, S.V. *Synlett* ***2011***, *22*, 2548.

[1576] Johnson, J.R.; Cuny, G.D.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***1995***, *34*, 1760.

[1577] Fell, B.; Rupilius, W. *Tetrahedron Lett.* ***1969***, 2721.

[1578] See Mullen, A. in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, pp. 414–439. See also, Eilbracht, P.; Hüttmann, G.; Deussen, R. *Chem. Ber.* ***1990***, *123*, 1063, and other papers in this series.

[1579] Ren, W.; Chang,W.; Dai, J.; Shi, Y.; Li, J.; Shi, Y. *J. Am. Chem. Soc.* ***2016***, *138*, 14864.

[1580] Lyubimov, S.E.; Rastorguev, E.A.; Lubentsova, K.I.; Korlyukov, A.A.; Davankov, V.A. *Tetrahedron Lett.* ***2013***, *54*, 1116.

[1581] Watkins, A.L.; Landis, C.R. *Org. Lett.* ***2011***, *13*, 164.

the aldehyde was shown to follow a radical pathway.[1582] Hydroformylation of heterocyclic alkenes is known, using a Rh catalyst.[1583]

Hydroformylation of triple bonds proceeds very slowly,[1584] but the Rh-[1585] or Pd-catalyzed[1586] reaction gave conjugated aldehydes. In the presence of a Rh catalyst, the triple bond of a conjugated enyne is formylated.[1587] The Rh-catalyzed reaction can be regioselective.[1588] Many functional groups, such as OH, CHO, CO_2R,[1589] and CN, can be present in the molecule, although halogens usually interfere. Stereoselective *syn* addition has been reported,[1590] and also stereoselective *anti* addition.[1591]

Asymmetric hydroformylation of alkenes has been accomplished with a chiral catalyst.[1592] The choice of ligand is important in such reactions.[1593] Cyclization to prolinal derivatives has been reported with allylic amines.[1594]

When dicobalt octacarbonyl, $[Co(CO)_4]_2$, is the catalyst, the species that actually adds to the double bond is tricarbonylhydrocobalt $HCo(CO)_3$.[1595] Carbonylation $RCo(CO)_3 + CO \rightarrow RCo(CO)_4$ takes place, followed by a rearrangement and a reduction of the C—Co bond. The reducing agent in the reduction step is tetracarbonylhydrocobalt $HCo(CO)_4$,[1596] or, under some conditions, H_2.[1597] When $HCo(CO)_4$ was the agent used to hydroformylate styrene, the observation of CIDNP (Sec. 5.C.i) indicated that the mechanism is different, and involves free radicals.[1598] Key intermediates have been detected in the Co-catalyzed hydroformylation reaction.[1599] Alcohols can be obtained by allowing the reduction to continue after all the carbon monoxide is used up.

OS **VI**, 338.

[1582] Huang, H.; Yu, C.; Zhang, Y.; Zhang, Y.; Mariano, P.S.; Wang, W. *J. Am. Chem. Soc.* ***2017***, *139*, 9799.

[1583] Chikkali, S.H.; Bellini, R.; de Bruin, B.; van der Vlugt, J.I.; Reek, J.N.H. *J. Am. Chem. Soc.* ***2012***, *134*, 6607.

[1584] See Botteghi, C.; Salomon, C. *Tetrahedron Lett.* ***1974***, 4285. For an indirect method, see Campi, E.; Fitzmaurice, N.J.; Jackson, W.R.; Perlmutter, P.; Smallridge, A.J. *Synthesis* ***1987***, 1032.

[1585] Zhang, Z.; Wang, Q.; Chen, C.; Han, Z.; Dong, X.-Q.; Zhang, X. *Org. Lett.* ***2016***, *18*, 3290.

[1586] Fang, X.; Zhang, M.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed.* ***2013***, *52*, 4645.

[1587] van den Hoven, B.G.; Alper, H. *J. Org. Chem.* ***1999***, *64*, 3964.

[1588] Kuil, M.; Soltner, T.; van Leeuwen, P.W.N.M.; Reek, J.N.H. *J. Am. Chem. Soc.* ***2006***, *128*, 11344. See Dydio, P.; Detz, R.J.; Reek, J.N.H. *J. Am. Chem. Soc.* ***2013***, *135*, 10817.

[1589] See Hu, Y.; Chen, W.; Osuna, A.M.B.; Stuart, A.M.; Hope, E.G.; Xiao, J. *Chem. Commun.* ***2001***, 725.

[1590] See Haelg, P.; Consiglio, G.; Pino, P. *Helv. Chim. Acta* ***1981***, *64*, 1865.

[1591] Krauss, I.J.; Wang, C.C.-Y.; Leighton, J.L. *J. Am. Chem. Soc.* ***2001***, *123*, 11514.

[1592] Ojima, I.; Hirai, K. in Morrison, J.D. *Organic Synthesis*, Vol. 5, Wiley, NY, ***1985***, pp. 103–145 (pp. 125–139); Noonan, G.M.; Fuentes, J.A.; Cobley, C.J.; Clarke, M.L. *Angew. Chem. Int. Ed.* ***2012***, *51*, 2477; Vautravers, N.R.; Regent, D.D.; Breit, B. *Chem. Commun.* ***2011***, *47*, 6635. See Neves, Â.C.B.; Calvete, M.F.; Pinho e Melo, T.M.V.D.; Pereira, M.M. *Eur. J. Org. Chem.* ***2012***, 6309.

[1593] Adint, T.T.; Landis, C.R. *J. Am. Chem. Soc.* ***2014***, *136*, 7943; García-Simón, C.; Gramage-Doria, R.; Raoufmoghaddam, S.; Parella, T.; Costas, M.; Ribas, X.; Reek, J.N.H. *J. Am. Chem. Soc.* ***2015***, *137*, 2680; Yu, Z.; Eno, M.S.; Annis, A.H.; Morken, J.P. *Org. Lett.* ***2015***, *17*, 3264; Tan, R.; Zheng, X.; Qu, B.; Sader, C.A.; Fandrick, K.R.; Senanayake, C.H.; Zhang, X. *Org. Lett.* ***2016***, *18*, 3346; Yeung, C.S.; Dong, Vy.M. *Angew. Chem. Int. Ed.* ***2011***, *50*, 809; Mon, I.; Jose, D.A.; Vidal-Ferran, A. *Chem. Eur. J.* ***2013***, *19*, 2720.

[1594] Anastasiou, D.; Campi, E.M.; Chaouk, H.; Jackson, W.R.; McCubbin, Q.J. *Tetrahedron Lett.* ***1992***, *33*, 2211.

[1595] Mirbach, M.F. *J. Organomet. Chem.* ***1984***, *265*, 205. For the mechanism see Orchin, M. *Acc. Chem. Res.* ***1981***, *14*, 259; Versluis, L.; Ziegler, T.; Baerends, E.J.; Ravenek, W. *J. Am. Chem. Soc.* ***1989***, *111*, 2018.

[1596] Ungváry, F.; Markó, L. *Organometallics* ***1982***, *1*, 1120.

[1597] See Kovács, I.; Ungváry, F.; Markó, L. *Organometallics* ***1986***, *5*, 209.

[1598] Bockman, T.M.; Garst, J.F.; King, R.B.; Markó, L.; Ungváry, F. *J. Organomet. Chem.* ***1985***, *279*, 165.

[1599] Godard, C.; Duckett, S.B.; Polas, S.; Tooze, R.; Whitwood, A.C. *J. Am. Chem. Soc.* ***2005***, *127*, 4994.

15-34 Hydrocyanation of Alkenes or Alkynes

Ordinary alkenes do not react with HCN, but polyhalo alkenes and alkenes of the form C═C─Z add HCN to give nitriles, where Z is an electron-withdrawing group.[1600] The reaction is therefore a nucleophilic addition and is base catalyzed. Hydrogen cyanide can be added to ordinary alkenes in the presence of dicobalt octacarbonyl[1601] or certain other transition metal compounds.[1602] When Z is COR or, more especially, CHO, 1,2-addition (**16-52**) is an important competing reaction and may be the only reaction. An acid-catalyzed hydrocyanation is also known.[1603] Triple bonds react very well when catalyzed by an aqueous solution of CuCl, NH_4Cl, and HCl or by Ni or Pd compounds.[1604] The HCN can be generated *in situ* from acetone cyanohydrin (**16-51**), avoiding the use of the poisonous HCN.[1605] Alkenes react with HCN via this procedure to give a nitrile in the presence of a Ni complex.[1606]

α,β-Unsaturated sulfones undergo conjugate addition of a cyano group using Et_2AlCN.[1607] Trimethylsilyl enol ethers reacted with 3 equivalents of TMSCN in the presence of PhIO and BF_3•OEt_2 to give the α-cyano ketone.[1608] Conjugated *N*-acylpyrroles reacted with HCN in the presence of ruthenium catalyst to give the β-cyano ketone.[1609]

The reaction of alkenes with cyanohydrins gave the corresponding nitrile using a Ni catalyst and 10–30% Zn.[1610] Conjugate addition of the cyano group gave the β-cyano ketone, using cyanohydrins and a phase-transfer catalyst.[1611] Magnesium complexes have been used to catalyze the conjugate cyanation of conjugate amides and ketones.[1612]

Alkylaluminum cyanides (Et_2AlCN), or mixtures of HCN and trialkylalanes R_3Al, are especially good reagents for conjugate addition of HCN[1613] to α,β-unsaturated ketones and α,β-unsaturated acyl halides. *tert*-Butyl isocyanide and $TiCl_4$ have been used to add HCN to C═C─Z alkenes.[1614] Pretreatment with NaI/Me_3SiCl followed by CuCN converts alkynes

[1600] See Friedrich, K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1983***, pp. 1345–1390; Nagata, W.; Yoshioka, M. *Org. React.* ***1977***, *25*, 255.
[1601] Arthur Jr., P.; England, D.C.; Pratt, B.C.; Whitman, G.M. *J. Am. Chem. Soc.* ***1954***, *76*, 5364.
[1602] See Brown, E.S. in Wender, P.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 658–667. For studies of the mechanism, see McKinney, R.J.; Roe, D.C. *J. Am. Chem. Soc.* ***1986***, *108*, 5167; Funabiki, T.; Tatsami, K.; Yoshida, S. *J. Organomet. Chem.* ***1990***, *384*, 199. See also, Bini, L.; Müller, C.; Vogt, D. *Chem. Commun.* ***2010***, 8325.
[1603] Yanagisawa, A.; Nezu, T.; Mohri, S.-i. *Org. Lett.* ***2009***, *11*, 5286.
[1604] Jackson, W.R.; Lovel, C.G. *Aust. J. Chem.* ***1983***, *36*, 1975.
[1605] Jackson, W.R.; Perlmutter, P. *Chem. Br.* ***1986***, 338.
[1606] Yan, M.; Xu, Q.-Y.; Chan, A.S.C. *Tetrahedron: Asymmetry* ***2000***, *11*, 845.
[1607] Ruano, J.L.G.; García, M.C.; Laso, N.M.; Castro, A.M.M.; Ramos, J.H.R. *Angew. Chem. Int. Ed.* ***2001***, *40*, 2507.
[1608] Shen, H.; Li, J.; Liu, Q.; Pan, J.; Huang, R.; Xiong, Y. *J. Org. Chem.* ***2015***, *80*, 7212.
[1609] Sakaguchi, Y.; Kurono, N.; Yamauchi, K.; Ohkuma, T. *Org. Lett.* ***2014***, *16*, 808.
[1610] Nemoto, K.; Nagafuchi, T.; Tominaga, K.; Sato, K. *Tetrahedron Lett.* ***2016***, *57*, 3199.
[1611] Provencher, B.A.; Bartelson, K.J.; Liu, Y.; Foxman, B.M.; Deng, L. *Angew. Chem. Int. Ed.* ***2011***, *50*, 10565.
[1612] Zhang, J.; Liu, X.; Wang, R. *Chem. Eur. J.* ***2014***, *20*, 4911.
[1613] See Nagata, W.; Yoshioka, M. *Org. React.* ***1977***, *25*, 255.
[1614] Ito, Y.; Kato, H.; Imai, H.; Saegusa, T. *J. Am. Chem. Soc.* ***1982***, *104*, 6449.

to vinyl nitriles.[1615] Enantioselective cyanation using TMSCN and HCN, and a Gd catalyst, leads to β-cyano amides.[1616]

OS **I**, 451; **II**, 498; **III**, 615; **IV**, 392, 393, 804; **V**, 239, 572; **VI**, 14.

15.C.iii. Reactions in Which Hydrogen Adds to Neither Side

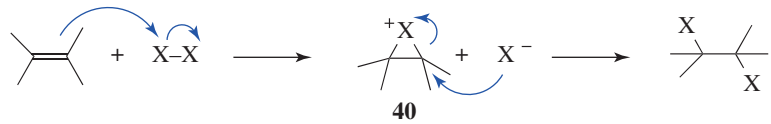
Some of these reactions are *cycloadditions* (reactions **15-46**, **15-58**, **15-50**, and **15-53** to **15-62**). In such cases, addition to the multiple bond closes a ring.

A. Halogen on One or Both Sides

15-35 Halogenation of Double and Triple Bonds (Addition of Halogen, Halogen)

Most double bonds are easily halogenated[1617] with bromine, chlorine, or inter-halogen compounds.[1618] Substitution can compete with addition in some cases.[1619] Iodination has also been accomplished, but the reaction is slower.[1620] Under free-radical conditions, iodination proceeds more easily.[1621] However, *vic*-diiodides are generally unstable and tend to revert to iodine and the alkene.

The mechanism is usually electrophilic and involves formation of an halonium ion (**40**),[1622] followed by nucleophilic ring opening to give the *vic*-dihalide. When an alkene attacks (donates two electrons to) Br^+ (or Br_2) to give **40**, the addition is *anti*, so the reaction is diastereospecific.



40

Nucleophilic attack occurs with selectivity for the less-substituted carbon. Similar results are found when the reaction is carried out in the presence of water[1623] (**15-36**) or in the presence of other nucleophiles.[1624] *Ab initio* molecular orbital studies show that **40** is more

[1615] Luo, F.-T.; Ko, S.-L.; Chao, D.-Y. *Tetrahedron Lett.* ***1997***, *38*, 8061.

[1616] Mita, T.; Kazuki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2005***, *127*, 514.

[1617] Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 629–632. Chen, J.; Zhou, L. *Synthesis* ***2014***, *46*, 586. See Castellanos, A.; Fletcher, S.P. *Chem. Eur. J.* ***2011***, *17*, 5766.

[1618] de la Mare, P.B.D. *Electrophilic Halogenation*, Cambridge University Press, Cambridge, ***1976***; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 422–431.

[1619] McMillen, D.W.; Grutzner, J.B. *J. Org. Chem.* ***1994***, *59*, 4516.

[1620] Zanger, M.; Rabinowitz, J.L. *J. Org. Chem.* ***1975***, *40*, 248.

[1621] Ayres, R.L.; Michejda, C.J.; Rack, E.P. *J. Am. Chem. Soc.* ***1971***, *93*, 1389.

[1622] See Lenoir, D.; Chiappe, C. *Chem. Eur. J.* ***2003***, *9*, 1037; Ashikari, Y.; Shimizu, A.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* ***2013***, *135*, 16070. For a theoretical study of these intermediates, see Okazaki, T.; Laali, K.K. *J. Org. Chem.* ***2005***, *70*, 9139. Also see Zabalov, M.V.; Karlov, S.S.; Lemenovskii, D.A.; Zaitseva, G.S. *J. Org. Chem.* ***2005***, *70*, 9175.

[1623] See Butler, R.N.; Coyne, A.G. *J. Org. Chem.* ***2015***, *80*, 1809.

[1624] See Zefirov, N.S.; Koz'min, A.S.; Dan'kov, Yu.V.; Zhdankin, V.V.; Kirin, V.N. *J. Org. Chem. USSR* ***1984***, *20*, 205.

stable than its open isomer **1** (Y = Br),[1625] and there is evidence that the formation of **40** is reversible.[1626] It is noted that theoretical and experimental studies have shown that in nonpolar solvents the bromination of acetylene via a covalent tribromide adduct is strongly favored over the textbook mechanism via a bridged bromonium ion.

Where electrophilic addition involves bridged-ion intermediates, those arising from triple bonds (**41**) are more strained than the corresponding **42**. This fact may be a reason why electrophilic addition by such electrophiles as Br, I, SR, and so on, is slower for triple bonds than for double bonds.[1627] As might be expected, triple bonds connected to a Z group (C≡C—Z) undergo nucleophilic addition especially well.[73] Markovnikov's rule is also followed where bromonium ions or other three-membered rings intermediates are formed in protic solvents such as methanol.[1628]

41

42

A number of examples have been found where addition of bromine is not stereospecifically *anti*. For example, the addition of Br_2 to *cis*- and *trans*-1-phenylpropenes in CCl_4 was not stereospecific.[1629] Furthermore, the stereospecificity of bromine addition to stilbene depends on the dielectric constant of the solvent.[1630] Likewise in the case of triple bonds, stereoselective *anti* addition was found in bromination of hex-3-yne, but both *cis* and *trans* products were obtained in bromination of phenylacetylene.[1631] These results indicate that a bromonium ion is not formed when the open cation can be stabilized in other ways.[1632] Previously seen cases (Sec. 10.C.i, category 4) showed that cations require more stabilization from outside sources as they become intrinsically less stable themselves.[1633]

When the π bond of an alkene attacks Cl^+,[1634] I^+,[1635] or RS^+,[1636] the result is similar to that when the electrophile is Br^+; there is a spectrum of mechanisms between cyclic intermediates and open cations. As might be expected from the discussion in Sec. 10.C, iodonium ions compete with open carbocations more effectively than bromonium ions, while chloronium ions compete less effectively. There is kinetic and spectral evidence that at least in some cases, the electrophile forms a π complex with the alkene before a covalent bond

[1625] Hamilton, T.P.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1990***, *112*, 8260.

[1626] See Bennet, A.J.; Brown, R.S.; McClung, R.E.D.; Klobukowski, M.; Aarts, G.H.M.; Santarsiero, B.D.; Bellucci, G.; Bianchini, R. *J. Am. Chem. Soc.* ***1991***, *113*, 8532.

[1627] See Schmid, G.H.; Modro, A.; Lenz, F.; Garratt, D.G.; Yates, K. *J. Org. Chem.* ***1976***, *41*, 2331.

[1628] See Dubois, J.E.; Chrétien, J.R. *J. Am. Chem. Soc.* ***1978***, *100*, 3506.

[1629] Fahey, R.C.; Schneider, H. *J. Am. Chem. Soc.* ***1968***, *90*, 4429. See also, Rolston, J.H.; Yates, K. *J. Am. Chem. Soc.* ***1969***, *91*, 1469, 1477, 1483.

[1630] Bellucci, G.; Bianchini, R.; Chiappe, C.; Marioni, F. *J. Org. Chem.* ***1990***, *55*, 4094.

[1631] Pincock, J.A.; Yates, K. *Can. J. Chem.* ***1970***, *48*, 3332.

[1632] For a review, see Ruasse, M. *Acc. Chem. Res.* ***1990***, *23*, 87.

[1633] See Naae, D.G. *J. Org. Chem.* ***1980***, *45*, 1394.

[1634] Fahey, R.C. *Top. Stereochem.* ***1968***, *3*, 237 (pp. 273–277).

[1635] Hassner, A.; Boerwinkle, F.; Levy, A.B. *J. Am. Chem. Soc.* ***1970***, *92*, 4879.

[1636] Capozzi, G.; Modena, G. in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, ***1985***, pp. 246–298. The specific nature of the 3-membered sulfur-containing ring is in dispute; see Smit, W.A.; Zefirov, N.S.; Bodrikov, I.V.; Krimer, M.Z. *Acc. Chem. Res.* ***1979***, *12*, 282; Schmid, G.H.; Strukelj, M.; Dalipi, S. *Can. J. Chem.* ***1987***, *65*, 1945.

is formed.[1637] There is evidence for β-chloro- and β-bromocarbenium ions in some reactions.[1638] Iodine monochloride cyclization reactions are known.[1639]

Under ordinary conditions, fluorine itself is too reactive to give simple addition and mixtures are obtained.[1640] However, F_2 has been successfully added to certain double bonds in an inert solvent at low temperatures (−78 °C), usually by diluting the F_2 gas with Ar or N_2.[1641] The Au-catalyzed reaction of Et_3N/HF with alkynes gives vinyl fluorides.[1642]

The reaction with bromine is very rapid and is easily carried out at room temperature,[1643] although the reaction is reversible under some conditions.[1644] In the case of bromine, an alkene•Br_2 complex has been detected in at least one case.[1645] Bromine is often used as a qualitative or quantitative test for unsaturation[1646] because the vast majority of double bonds can be successfully brominated. Bromination has been carried out in an ionic liquid.[1647] Alkenes were converted to vicinal dichlorides by reaction with NH_4Cl and Oxone®.[1648] The dichlorination of alkenes was reported using NCS and PPh_3.[1649]

Several reagents other than chlorine gas add Cl_2 to double bonds, among them Me_3SiCl/MnO_2,[1650] $BnNEt_3MnO_4/Me_3SiCl$,[1651] and $KMnO_4$-oxalyl chloride.[1652] A convenient reagent for the addition of Br_2 to a double bond on a small scale is the commercially available pyridinium bromide perbromide $C_5H_5NH^+Br_3^-$.[1653] Potassium bromide with ceric ammonium nitrate, in water/dichloromethane, gives the dibromide.[1654] A combination of KBr and Selectfluor also gives the dibromide.[1655] A combination of $CuBr_2$ in aq. THF and a chiral ligand led to the dibromide with good enantioselectivity.[1656]

Catalytic, enantioselective halogenation of alkenes has been reviewed.[1657] Allylic alcohols are dichlorinated with good enantioselectivity using aryl iododichlorides, catalyzed by dimeric *Cinchona* alkaloid derivatives.[1658] The enantioselective dibromination of allylic alcohols was reported using dibromomalonate as the bromine source and a Ti catalyst.[1659]

[1637] See Bellucci, G.; Bianchini, R.; Chiappe, C.; Marioni, F.; Ambrosetti, R.; Brown, R.S.; Slebocka-Tilk, H. *J. Am. Chem. Soc.* ***1989***, *111*, 2640.
[1638] Ohta, B.K.; Hough, R.E.; Jeffrey W.; Schubert, J.W. *Org. Lett.* ***2007***, *9*, 2317.
[1639] Singh, S.; Chimni, S.S. *Synthesis* ***2015***, *47*, 1961.
[1640] See Fuller, G.; Stacey, F.W.; Tatlow, J.C.; Thomas, C.R. *Tetrahedron* ***1962***, *18*, 123.
[1641] Rozen, S.; Brand, M. *J. Org. Chem.* ***1986***, *51*, 3607.
[1642] Akana, J.A.; Bhattacharyya, K.X.; Müller, P.; Sadighi, J.P. *J. Am. Chem. Soc.* ***2007***, *129*, 7736.
[1643] See Bellucci, G.; Chiappe, C. *J. Org. Chem.* ***1993***, *58*, 7120.
[1644] Zheng, C.Y.; Slebocka-Tilk, H.; Nagorski, R.W.; Alvarado, L.; Brown, R.S. *J. Org. Chem.* ***1993***, *58*, 2122.
[1645] Bellucci, G.; Chiappe, C.; Bianchini, R.; Lenoir, D.; Herges, R. *J. Am. Chem. Soc.* ***1995***, *117*, 12001.
[1646] See Kuchar, E.J. in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 273–280.
[1647] Chiappe, C.; Capraro, D.; Conte, V.; Picraccini, D. *Org. Lett.* ***2001***, *3*, 1061.
[1648] Swamy, P.; Reddy, M.M.; Kumar, M.A.; Naresh, M.; Narender, N. *Synthesis* ***2014***, *46*, 251.
[1649] Kamada, Y.; Kitamura, Y.; Tanaka, T.; Yoshimitsu, T. *Org. Biomol. Chem.* ***2013***, *11*, 1598.
[1650] Bellesia, F.; Ghelfi, F.; Pagnoni, U.M.; Pinetti, A. *J. Chem. Res. (S)* ***1989***, *108*, 360.
[1651] Markó, I.E.; Richardson, P.R.; Bailey, M.; Maguire, A.R.; Coughlan, N. *Tetrahedron Lett.* ***1997***, *38*, 2339.
[1652] Markó, I.E.; Richardson, P.F. *Tetrahedron Lett.* ***1991***, *32*, 1831.
[1653] Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 1, Wiley, NY, ***1967***, pp. 967–970. For a mechansitic discussion, Bellucci, G.; Bianchini, R.; Vecchiani, S. *J. Org. Chem.* ***1986***, *51*, 4224.
[1654] Nair, V.; Panicker, S.B.; Augstine, A.; George, T.G.; Thomas, S.; Vairamani, M. *Tetrahedron* ***2001***, *57*, 7417.
[1655] Ye, C.; Shreeve, J.M. *J. Org. Chem.* ***2004***, *69*, 8561.
[1656] El-Quisairi, A.K.; Qaseer, H.A.; Katsigras, G.; Lorenzi, P.; Tribedi, U.; Tracz, S.; Hartman, A.; Miller, J.A.; Henry, P.M. *Org. Lett.* ***2003***, *5*, 439.
[1657] Hennecke, U. *Chem. Asian J.* ***2012***, *7*, 456.
[1658] Nicolaou, K.C.; Simmons, N.L.; Ying, Y.; Heretsch, P.M.; Chen, J.S. *J. Am. Chem. Soc.* ***2011***, *133*, 8134.
[1659] Hu, D.X.; Shibuya, G.M.; Burns, N.Z. *J. Am. Chem. Soc.* ***2013***, *135*, 12960.

Alkenes reacted with Selectfluor and Pyr•$(HF)_x$ in the presence of $ArIF_2$ to give the vicinal difluoride.[1660]

Mixed halogenations have also been achieved, and the order of activity for some of the reagents is BrCl > ICl[1661] > Br_2 > IBr > I_2.[1662] Mixtures of Br_2 and Cl_2 have been used to give bromochlorination,[1663] as has tetrabutylammonium dichlorobromate, Bu_4NBrCl_2.[1664] Iodochlorination has been achieved with $KICl_2$,[1665] $CuCl_2$, and one of I_2, HI, or CdI_2; iodofluorination[1666] has been achieved with mixtures of AgF and I_2;[1667] and mixtures of *N*-bromo amides in anhydrous HF give bromofluorination.[1668] Bromo-, iodo-, and chlorofluorination have also been achieved by treatment of the substrate with a solution of Br_2, I_2, or an *N*-halo amide in polyhydrogen fluoride/pyridine;[1669] while addition of I along with Br, Cl, or F has been accomplished with the reagent bis(pyridine)iodo(I) tetrafluoroborate $[I(Py)_2BF_4]$ and Br^-, Cl^-, or F^-, respectively.[1670] This reaction (which is also successful for triple bonds[1671]) can be extended to the addition of I^- and other nucleophiles.[1671]

The addition of Br and Cl across an alkene π bond was promoted by a Schiff base catalyst in the presence of NBS and $ClTi(O\textit{i}\text{-}Pr)_3$.[1672] The reaction of 1-trimethylsilylalkynes and ICl[1673] gave the (*Z*)-1-iodo-2-chloroalkene.[1674] Iodofluorination of alkynes gave the iodofluoroalkene using IF_5•pyridine•HF.[1675] The reaction of alkynes with IBr, generated by sequential reaction with TMSBr and then NIS, gave the (*E*)-bromoiodoalkene.[1676]

When free-radical initiators (or UV light) are present, addition can occur by a free-radical mechanism.[1677] Once Br• or Cl• radicals are formed, however, substitution may compete (**14-1** and **14-3**). This competition is especially important when the alkene has allylic or benzylic hydrogen atoms. Under free-radical conditions (UV light), bromine or chlorine adds to a benzene substituent to give, respectively, hexabromo- or hexachlorocyclohexane. These are mixtures of stereoisomers (Sec. 4.K.ii).[1678]

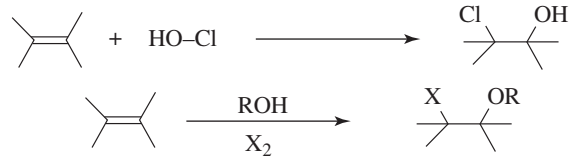
Triple bonds add bromine, although generally more slowly than double bonds (Sec. 15.B.i). Molecules that contain both double and triple bonds are preferentially

[1660] Molnár, I.G.; Gilmour, R. *J. Am. Chem. Soc.* ***2016***, *138*, 5004.
[1661] See McCleland, C.W. in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 85–164.
[1662] White, E.P.; Robertson, P.W. *J. Chem. Soc.* ***1939***, 1509.
[1663] Buckles, R.E.; Forrester, J.L.; Burham, R.L.; McGee, T.W. *J. Org. Chem.* ***1960***, *25*, 24.
[1664] Negoro, T.; Ikeda, Y. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 3519.
[1665] Zefirov, N.S.; Sereda, G.A.; Sosounk, S.E.; Zyk, N.V.; Likhomanova, T.I. *Synthesis* ***1995***, 1359.
[1666] See Sharts, C.M.; Sheppard, W.A. *Org. React.* ***1974***, *21*, 125 (see pp. 137–157); Boguslavskaya. L.S. *Russ. Chem. Rev.* ***1984***, *53*, 1178.
[1667] Evans, R.D.; Schauble, J.H. *Synthesis* ***1987***, 551; Kuroboshi, M.; Hiyama, T. *Synlett* ***1991***, 185.
[1668] Pattison, F.L.M.; Peters, D.A.V.; Dean, F.H. *Can. J. Chem.* ***1965***, *43*, 1689. For other methods, see Shimizu, M.; Nakahara, Y.; Yoshioka, H. *J. Chem. Soc., Chem. Commun.* ***1989***, 1881.
[1669] Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979***, *44*, 3872. See Camps, F.; Chamorro, E.; Gasol, V.; Guerrero, A. *J. Org. Chem.* ***1989***, *54*, 4294; Ichihara, J.; Funabiki, K.; Hanafusa, T. *Tetrahedron Lett.* ***1990***, *31*, 3167.
[1670] Barluenga, J.; González, J.M.; Campos, P.J.; Asensio, G. *Angew. Chem. Int. Ed.* ***1985***, *24*, 319.
[1671] Barluenga, J.; Rodríguez, M.A.; González, J.M.; Campos, P.J.; Asensio, G. *Tetrahedron Lett.* ***1986***, *27*, 3303.
[1672] Hu, D.X.; Seidl, F.J.; Bucher, C.; Burns, N.Z. *J. Am. Chem. Soc.* ***2015***, *137*, 3795.
[1673] See Singh, S.; Chimni, S.S. *Synthesis* ***2015***, *47*, 1961; Alikarami, M.; Farhadi, M. *Helv. Chim. Acta* ***2015***, *98*, 1302.
[1674] Sproul, K.C.; Chalifoux, W.A. *Org. Lett.* ***2015***, *17*, 3334.
[1675] Ukigai, H.; Hara, S. *Tetrahedron Lett.* ***2016***, *57*, 1379; Yano, S.; Hara, S. *Synthesis* ***2015***, *47*, 2839.
[1676] Ide, M.; Yauchi, Y.; Shiogai, R.; Iwasawa, T. *Tetrahedron* ***2014***, *70*, 8532.
[1677] See Dessau, R.M. *J. Am. Chem. Soc.* ***1979***, *101*, 1344.
[1678] See Cais, M. in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 993.

attacked at the double bond. Addition of 2 molar equivalents of bromine to triple bonds gives tetrabromo products. There is evidence that the addition of the first molar equivalent of bromine to a triple bond may take place by a nucleophilic mechanism.[1679] Alkynes reacted with $CuBr_2$ in the presence of MS 4Å to give the (*E*)-vinyldibromide.[1680] Molecular diiodine on Al_2O_3 adds to triple bonds to give good yields of 1,2-diiodoalkenes.[1681] Interestingly, 1,1-diiodoalkenes are prepared from an alkynyltin compound, via initial treatment with $Cp_2Zr(H)Cl$, and then 2.15 equivalents of iodine.[1682] A mixture of $NaBO_3$ and NaBr adds two bromine atoms across a triple bond.[1683] With allenes it is easy to stop the reaction after only 1 equivalent has added, to give X–C–CX=C.[1684]

OS **I**, 205, 521; **II**, 171, 177, 270, 408; **III**, 105, 123, 127, 209, 350, 526, 531, 731, 785; **IV**, 130, 195, 748, 851, 969; **V**, 136, 370, 403, 467; **VI**, 210, 422, 675, 862, 954; **IX**, 117; **76**, 159.

15-36 Addition of Hypohalous Acids and Hypohalites (Addition of Halogen, Oxygen)[1685]



Hypohalous acids (HOCl, HOBr, and HOI) react with alkenes[1686] to produce halohydrins.[1687] Both HOBr and HOCl can be generated *in situ* by the reaction between water and Br_2 or Cl_2, respectively. HOI, generated from I_2 and H_2O, also adds to double bonds, if the reaction is carried out in tetramethylene sulfone/$CHCl_3$[1688] or if an oxidizing agent, such as HIO_3, is present.[1689] Iodine and cerium sulfate in aqueous acetonitrile generates iodohydrins,[1690] as do iodine and ammonium acetate in acetic acid,[1691] or $NaIO_4$ with sodium bisulfite.[1692] The impact of water on the reaction has been studied, and "the reaction between ClOH and the $H_2O\cdots HO$ complex is slower, but it is up to 2.2 times faster than the reaction without water."[1693] In addition, "a three-body interchange reaction that can occur,"[1693] is

$$HOCl + HO\cdots H_2O \rightarrow HOCl\cdots H_2O + OH$$

[1679] Sinn, H.; Hopperdietzel, S.; Sauermann, D. *Monatsh. Chem.* ***1965***, *96*, 1036.
[1680] Xiang, J.; Yuan, R.; Wang, R.; Yi, N.; Lu, L.; Zou, H.; He, W. *J. Org. Chem.* ***2014***, *79*, 11378.
[1681] Hondrogiannis, G.; Lee, L.C.; Kabalka, G.W.; Pagni, R.M. *Tetrahedron Lett.* ***1989***, *30*, 2069.
[1682] Dabdoub, M.J.; Dabdoub, V.B.; Baroni, A.C.M. *J. Am. Chem. Soc.* ***2001***, *123*, 9694.
[1683] Kabalka, G.W.; Yang, K. *Synth. Commun.* ***1998***, *28*, 3807.
[1684] See Jacobs, T.L. in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, pp. 466–483.
[1685] Addends are listed in order of priority in the Cahn-Ingold-Prelog system (Sec. 4.E.i).
[1686] Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 638–642.
[1687] See Boguslavskaya, L.S. *Russ. Chem. Rev.* ***1972***, *41*, 740.
[1688] Cambie, R.C.; Noall, W.I.; Potter, G.J.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc., Perkin Trans. 1* ***1977***, 266.
[1689] See Antonioletti, R.; D'Auria, M.; De Mico, A.; Piancatelli, G.; Scettri, A. *Tetrahedron* ***1983***, *39*, 1765.
[1690] Horiuchi, C.A.; Ikeda, A.; Kanamori, M.; Hosokawa, H.; Sugiyama, T.; Takahashi, T.T. *J. Chem. Res. (S)* ***1997***, 60.
[1691] Myint, Y.Y.; Pasha, M.A. *Synth. Commun.* ***2004***, *34*, 4477.
[1692] Masuda, H.; Takase, K.; Nishio, M.; Hasegawa, A.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* ***1994***, *59*, 5550.
[1693] Gonzalez, J.; Anglada, J.M.; Buszek, R.J.; Francisco, J.S. *J. Am. Chem. Soc.* ***2011***, *133*, 3345.

Alkenes reacted with Chloramine-T trihydrate, 1,3-dichloro-5,5-dimethylhydantoin, or *N*-bromoacetamide and *N*-tosyl-L-threonine to give the chlorohydrin.[1694] The ring openings of *meso*-epoxides, catalyzed by chiral phosphine oxides, gave chiral 1,2-chlorohydrins.[1695]

The HOBr can be conveniently used in a reaction using a *N*-bromo amide (e.g., NBS or *N*-bromoacetamide) and a small amount of water in a solvent such as DMSO or dioxane.[1696] *N*-Iodosuccinimide (NIS) in aqueous dimethoxyethane leads to the iodohydrin.[1697] An especially powerful reagent for HOCl addition is *tert*-butyl hydroperoxide (or di-*tert*-butyl peroxide) along with $TiCl_4$.[1698] Chlorohydrins were formed by the reaction of alkenes with $ClCH_nMgCl{\bullet}LiCl$.[1699] The compound HOI can be added by treatment of alkenes with periodic acid and $NaHSO_3$.[1700] There are Se-catalyzed iodohydrin-forming reactions.[1701] Hypervalent iodine compounds react with an alkene and iodine in aqueous media to give the iodohydrin.[1702] Halohydrins are produced in ionic liquids.[1703] *N*-Bromo and *N*-iodosaccharin have been used to prepare the corresponding halohydrins.[1704] Alkenes were converted to chlorohydrins by a Ru-based artificial enzyme.[1705] The compound HOF has also been used, but this reagent is difficult to prepare in a pure state and *explosions have occurred.*[1706] Fluorohydrins have been prepared by the fluorination of allylsilanes by reaction with Selectfluor.[1707]

The mechanism of HOX addition is electrophilic, with initial attack by the alkene on the positive halogen end of the HOX dipole. Following *Markovnikov's rule*, the positive halogen goes to the side of the double bond that has more hydrogen atoms (forming a more stable carbocation). This carbocation (or bromonium or iodonium ion in the absence of an aqueous solvent) reacts with ^-OH or H_2O to give the product. If the substrate is treated with Br_2 or Cl_2 (or another source of positive halogen such as NBS) in an alcohol or a carboxylic acid solvent, it is possible to obtain C—C—C—OR or X—C—C—OCOR, respectively, directly (see also, **15-44**).[1708] There is evidence that the mechanism with Cl_2 and H_2O is different from that with HOCl.[1709] HOCl and HOBr can be added to triple bonds to give dihalo carbonyl compounds $-CX_2-CO-$.

Alcohols and halogens react with alkenes to form halo ethers.[1710] When a homoallylic alcohol is treated with bromine, cyclization occurs to give a 3-bromotetrahydrofuran

[1694] Zhang, J.; Wang, J.; Qiu, Z.; Wang, Y. *Tetrahedron* ***2011***, *67*, 6859.
[1695] Kotani, S.; Furusho, H.; Sugiura, M.; Nakajima, M. *Tetrahedron* ***2013***, *69*, 3075.
[1696] See Dalton, D.R.; Dutta, V.P. *J. Chem. Soc. B* ***1971***, 85; Sisti, A.J. *J. Org. Chem.* ***1970***, *35*, 2670.
[1697] Smietana, M.; Gouverneur, V.; Mioskowski, C. *Tetahedron Lett.* ***2000***, *41*, 193.
[1698] Klunder, J.M.; Caron M.; Uchiyama, M.; Sharpless, K.B. *J. Org. Chem.* ***1985***, *50*, 912.
[1699] Nishimura, R.H.V.; Toledo, F.T.; Lopes, J.L.C.; Clososki, G.C. *Tetrahedron Lett.* ***2013***, *54*, 287.
[1700] Ohta, M.; Sakata, Y.; Takeuchi, T.; Ishii, Y. *Chem. Lett.* ***1990***, 733.
[1701] Carrera, I.; Brovetto, M.C.; Seoane, G.A. *Tetrahedron Lett.* ***2006***, *47*, 7849.
[1702] DeCorso, A.R.; Panunzi, B.; Tingoli, M. *Tetrahedron Lett.* ***2001***, *42*, 7245.
[1703] Yadav, J.S.; Reddy, B.V.S.; Baishya, G.; Harshavardhan, S.J.; Chary, Ch.J.; Gupta, M.K. *Tetrahedron Lett.* ***2005***, *46*, 3569.
[1704] Urankar, D.; Rutar, I.; Modec, B.; Dolenc, D. *Eur. J. Org. Chem.* ***2005***, 2349.
[1705] Lopez, S.; Rondot, L.; Cavazza, C.; Iannello, M.; Boeri-Erba, E.; Buzlaff, N.; Strinitz, F.; Jorge-Robin, A.; Marchi-Delapierre, C.; Ménage, S. *Chem. Commun.* ***2017***, *53*, 3579.
[1706] Migliorese, K.G.; Appelman, E.H.; Tsangaris, M.N. *J. Org. Chem.* ***1979***, *44*, 1711.
[1707] Wang, W.; Xu, B.; Hammond, G.B. *Synthesis* ***2011***, *43*, 2383.
[1708] Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 642–643.
[1709] Buss, E.; Rockstuhl, A.; Schnurpfeil, D. *J. Prakt. Chem.* ***1982***, *324*, 197.
[1710] For an enantioselective reaction, see Müller, C.H.; Rösner, C.; Hennecke, U. *Chem. Asian J.* ***2014***, *9*, 2162.

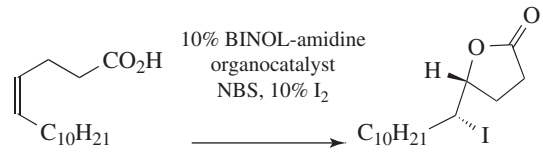
derivative.[1711] *tert*-Butyl hypochlorite (Me_3COCl), hypobromite, and hypoiodite[1712] add to double bonds to give halogenated *tert*-butyl ethers, X—C—C—$OCMe_3$. This approach is a convenient method for the preparation of tertiary ethers. Iodine and ethanol convert some alkenes to iodo ethers.[1713] Iodine, alcohol, and a $Ce(OTf)_2$ catalyst also generate the iodo ether.[1714] When Me_3COCl or Me_3COBr is added to alkenes in the presence of excess ROH, the ether X—C—C—OR is produced.[1715] Vinylic ethers give β-halo acetals.[1716] The Au-catalyzed iodoalkoxylation of alkenes has been reported.[1717] The alkoxybromination of alkenes was reported using ammonium bromide and Oxone.[1718] The bromohydroxylation of allenes was reported by the reaction of allenes and NBS.[1719]

OS **I**, 158; **IV**, 130, 157; **VI**, 184, 361, 560; **VII**, 164; **VIII**, 5, 9.

15-37 Halolactonization

Halo esters can be formed by addition of halogen atoms and ester groups to an alkene. Alkene carboxylic acids give a tandem reaction of formation of a halonium ion followed by intramolecular displacement of the carboxylic group to give a halo lactone. This tandem addition of X and OCOR to form a lactone is called *halolactonization*.[1720]

The most common version of this reaction is known as *iodolactonization,*[1721] and an enantioselective example is the conversion of **43** to **44** in Martin and Klosowski's synthesis of (+)-disparlure.[1722]



43 **44**

Bromo lactones and, to a lesser extent, chloro lactones have also been prepared. In general, addition of the halogen to an alkenyl acid, as shown, leads to the halo lactone. Other reagents include $I^+(collidine)_2\ PF_6^-$,[1723] NIS,[1724] KI/sodium persulfate,[1725] and

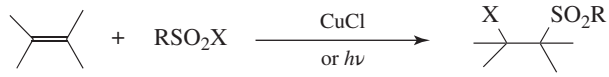
[1711] Chirskaya, M.V.; Vasil'ev, A.A.; Sergovskaya, N.L.; Shovshinev, S.V.; Sviridov, S.I. *Tetrahedron Lett.* ***2004***, *45*, 8811.
[1712] Glover, S.A.; Goosen, A. *Tetrahedron Lett.* ***1980***, *21*, 2005.
[1713] Sanseverino, A.M.; de Mattos, M.C.S. *Synthesis* ***1998***, 1584. See Horiuchi, C.A.; Hosokawa, H.; Kanamori, M.; Muramatsu, Y.; Ochiai, K.; Takahashi, E. *Chem. Lett.* ***1995***, 13.
[1714] Iranpoor, N.; Shekarriz, M. *Tetrahedron* ***2000***, *56*, 5209.
[1715] Bresson, A.; Dauphin, G.; Geneste, J.; Kergomard, A.; Lacourt, A. *Bull. Soc. Chim. Fr.* ***1970***, 2432; ***1971***, 1080.
[1716] Weissermel, K.; Lederer, M. *Chem. Ber.* ***1963***, *96*, 77.
[1717] Heuer-Jungemann, A.; McLaren, R.G.; Hadfield, M.S.; Lee, A.-L. *Tetrahedron* ***2011***, *67*, 1609.
[1718] Kumar, M.A.; Naresh, M.; Rohitha, C.N.; Narender, N. *Synth. Commun.* ***2013***, *43*, 3121.
[1719] Kong, W.; Guo, B.; Fu, C.; Ma, S. *Eur. J. Org. Chem.* ***2011***, 2278.
[1720] See Cardillo, G.; Orena, M. *Tetrahedron* ***1990***, *46*, 3321; Dowle, M.D.; Davies, D.I. *Chem. Soc. Rev.* ***1979***, *8*, 171. For a list of reagents that accomplish this, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1870–1876.
[1721] Corey, E.J.; Albonico, S.M.; Koelliker, V.; Schaaf, T.K.; Varma, R.K. *J. Am. Chem. Soc.* ***1971***, *93*, 1491.
[1722] Klosowski, D.W.; Martin, S.F. *Org. Lett.* ***2018***, *20*, 1269.
[1723] Homsi, F.; Rousseau, G. *J. Org. Chem.* ***1998***, *63*, 5255.
[1724] Reddy, A.R.; Sangwan, P.L.; Chinthakindi, P.K.; Farooq, S.; Siddaiah, V.; Surrinder Koul, S. *Helv. Chim. Acta* ***2013***, *96*, 1313.
[1725] Royer, A.C.; Mebane, R.C.; Swafford, A.M. *Synlett* ***1993***, 899.

Tl[1726] and Y[1727] reagents, along with the halogen, have also been used. There is a *gem-dimethyl effect* that favors formation of 7 to 11-membered ring lactones by this procedure.[1728] *N*-Iodosuccimide has been used for the iodoesterification of alkenes.[1729]

New catalyst systems have been developed that promote halolactonization.[1730] Enantioselective halolactonization reactions have been developed (see **44**).[1731] An enantioselective 5-*endo*-halolactonization procedure has been reported using systems such as $I^+(collidine)_2\ PF_6^-$ or $AgSbF_6$ followed by iodine.[1732] Organocatalysts have also been used to mediate asymmetric halolactonization reactions.[1733,1734] Enantioselective iodolactonization of allenoic acids has been reported.[1735] The reaction of alkenyl carboxylic acids with a chiral proton catalyst/*N*-iodosuccinimide reagent led to enantioselective halolactonizations and it was observed that modulating the achiral counterion optimized the enantioselectivity.[1736] The V-catalyzed bromolactonization of alkenoic acids has been reported.[1737] Selenolactonization reactions of unsaturated acids has been reported using ammonium iodide.[1738] Fluorolactonization has been reported.[1739]

OS **IX**, 516.

15-38 Addition of Sulfur Compounds (Addition of Halogen, Sulfur)



Sulfonyl halides add to double bonds to give β-halo sulfones in the presence of free-radical initiators or UV light. A particularly good catalyst is cuprous chloride.[1740] In the presence of TsCl, AIBN, and a Ru catalyst, β-chloro sulfones are generated from alkenes.[1741] A combination of the anion $ArSO_2Na$, NaI, and ceric ammonium nitrate converts alkenes

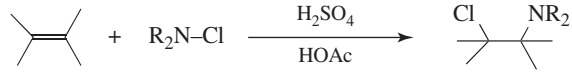
[1726] See Cambie, R.C.; Rutledge, P.S.; Somerville, R.F.; Woodgate, P.D. *Synthesis* ***1988***, 1009, and references cited therein.
[1727] Genovese, S.; Epifano, F.; Pelucchini, C.; Procopio, A.; Curini, M. *Tetrahedron Lett.* ***2010***, *51*, 5992.
[1728] Simonot, B.; Rousseau, G. *Tetrahedron Lett.* ***1993***, *34*, 4527.
[1729] Reddy, A.R.; Sangwan, P.L.; Chinthakindi, P.K.; Farooq, S.; Siddaiah, V.; Koul, S. *Helv. Chim. Acta* ***2013***, *96*, 1313.
[1730] Paull, D.H.; Fang, C.; Donald, J.R.; Pansick, A.D.; Martin, S.F. *J. Am. Chem. Soc.* ***2012***, *134*, 11128; Cheng, Y.A.; Chen, T.; Tan, C.K.; Heng, J.J.; Yeung, Y.-Y. *J. Am. Chem. Soc.* ***2012***, *134*, 16492; Denmark, S.E.; Ryabchuk, P.; Burk, M.T.; Gilbert, B.B. *J. Org. Chem.* ***2016***, *81*, 10411; Jiang, X.; Tan, C.K.; Zhou, L.; Yeung, Y.-Y. *Angew. Chem. Int. Ed.* ***2012***, *51*, 7771.
[1731] Ning, Z.; Jin, R.; Ding, J.; Gao, L. *Synlett* ***2009***, 2291; Aursnes, M.; Tungen, J.E.; Hansen, T.V. *J. Org. Chem.* ***2016***, *81*, 8287; Armstrong, A.; Braddock, D.C.; Jones, A.X.; Clark, S. *Tetrahedron Lett.* ***2013***, *54*, 7004.
[1732] Garnier, J.M.; Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* ***2007***, 3281.
[1733] Tan, C.K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* ***2010***, *132*, 15474; Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem. Int. Ed.* ***2010***, *49*, 9174.
[1734] Tan, C.K.; Zhou, L.; Yeung, Y.-Y. *Synlett* ***2011***, *22*, 1335.
[1735] Kristianslund, R.; Aursnes, M.; Tungen, J.E.; Hansen, T.V. *Tetrahedron Lett.* ***2016***, *57*, 5232; Murai, K.; Shimizu, N.; Fujioka, H. *Chem. Commun.* ***2014***, *50*, 12530.
[1736] Dobish, M.C.; Johnston, J.N. *J. Am. Chem. Soc.* ***2012***, *134*, 6068.
[1737] Campbell, M.L.; Rackley, S.A.; Giambalvo, L.N.; Whitehead, D.C. *Tetrahedron* ***2015***, *71*, 3895.
[1738] Shi, H.; Yu, C.; Zhu, M.; Yan, J. *Synthesis* ***2016***, *48*, 57.
[1739] Egami, H; Asada, J.; Sato, K.; Hashizume, D.; Kawato, Y.; Hamashima, Y. *J. Am. Chem. Soc.* ***2015***, *137*, 10132; Woerly, E.M.; Banik, S.M.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2016***, *138*, 13858.
[1740] Sinnreich, J.; Asscher, M. *J. Chem. Soc., Perkin Trans. 1* ***1972***, 1543.
[1741] Quebatte, L.; Thommes, K.; Severin, K. *J. Am. Chem. Soc.* ***2006***, *128*, 7440.

to vinyl sulfones.[1742] Triple bonds behave similarly, to give β-halo-α,β-unsaturated sulfones.[1743] In a similar reaction, sulfenyl chlorides, RSCl, give β-halo thioethers.[1744] The latter may be free-radical or electrophilic additions, depending on conditions. The addition of MeS and Cl has also been accomplished by treating the alkene with Me_3SiCl and Me_2SO.[1745] The use of Me_3SiBr and Me_2SO does not give this result; dibromides (**15-35**) are formed instead. Allylic sulfones were formed by the Rh-catalyzed reaction of terminal alkynes and sulfonyl hydrazides.[1746] Bromosulfones have been prepared from alkenes by reaction with sulfinic acids and NBS.[1747] Halosulfonation used an Fe catalyst for reaction of terminal alkynes,[1748] and iodothiolation reactions are known.[1749]

Bromothiocyanation can be accomplished with Br_2 and thallium(I) thiocyanate.[1750] Such compounds were also prepared from alkenes using KSCN and $FeCl_3$[1751] or using iodine thiocyanate.[1752] β-Halo disulfides, formed by addition of arenethiosulfenyl chlorides to double bond compounds, are easily converted to thiiranes by treatment with sodium amide or sodium sulfide.[1753]

OS **VIII**, 212. See also, OS **VII**, 251.

15-39 Addition of Halogen and a Nitrogen Group (Addition of Halogen, Nitrogen; Halolactamization)



The groups R_2N and Cl can be added directly to alkenes, allenes, conjugated dienes, and alkynes by treatment with dialkyl-*N*-chloroamines and acids.[1754] *N*-Halo amides RCONHX add RCONH and X to double bonds under the influence of UV light or chromous chloride.[1755] *N*-Bromo amides add to alkenes in the presence of a transition metal catalysts such as $SnCl_4$ to give the corresponding β-bromo amide.[1756] The reaction of $TsNCl_2$ and a $ZnCl_2$ catalyst gave the chloro tosylamine.[1757] Aminochlorination of alkenes occurs in

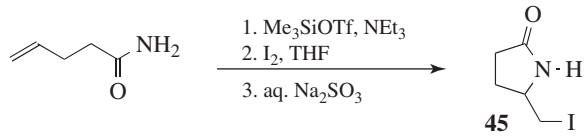
[1742] Nair, V.; Augustine, A.; George, T.G.; Nair, L.G. *Tetrahedron Lett.* ***2001***, *42*, 6763.
[1743] See Amiel, Y. *J. Org. Chem.* ***1974***, *39*, 3867.
[1744] See Rasteikiene, L.; Greiciute, D.; Lin'kova, M.G.; Knunyants, I.L. *Russ. Chem. Rev.* ***1977***, *46*, 548; Kühle, E. *Synthesis* ***1971***, 563.
[1745] Bellesia, F.; Ghelfi, F.; Pagnoni, U.M.; Pinetti, A. *J. Chem. Res. (S)* ***1987***, 238. See also, Liu, H.; Nyangulu, J.M. *Tetrahedron Lett.* ***1988***, *29*, 5467.
[1746] Xu, K.; Khakyzadeh, V.; Bury, T.; Breit, B. *J. Am. Chem. Soc.* ***2014***, *136*, 16124.
[1747] Wei, W.; Liu, X.; Yang, D.; Dong, R.; Cui, Y.; Yuan, F.; Wang, H. *Tetrahedron Lett.* ***2015***, *56*, 1808.
[1748] Li, X.; Shi, X.; Fang, M.; Xu, X. *J. Org. Chem.* ***2013***, *78*, 9499; Zeng, X.; Ilies, L.; Nakamura, E. *Org. Lett.* ***2012***, *14*, 954.
[1749] Lin, Y.-m.; Lu, G.-p.; Cai, C.; Yi, W.-b. *Org. Lett.* ***2015***, *17*, 3310.
[1750] Cambie, R.C.; Larsen, D.S.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc., Perkin Trans. 1* ***1981***, 58.
[1751] Yadav, J.S.; Reddy, B.V.S.; Gupta, M.K. *Synthesis* ***2004***, 1983.
[1752] For a discsssion of substituent effects, see Brammer, C.N.; Nelson, D.J.; Li, R. *Tetrahedron Lett.* ***2007***, *48*, 3237.
[1753] See Capozzi, F.; Capozzi, G.; Menichetti, S. *Tetrahedron Lett.* ***1988***, *29*, 4177.
[1754] See Mirskova, A.N.; Drozdova, T.I.; Levkovskaya, G.G.; Voronkov, M.G. *Russ. Chem. Rev.* ***1989***, *58*, 250; Neale, R.S. *Synthesis* ***1971***, 1.
[1755] For a review, see Labeish, N.N.; Petrov, A.A. *Russ. Chem. Rev.* ***1989***, *58*, 1048.
[1756] Yeung, Y.-Y.; Gao, X.; Corey, E.J. *J. Am. Chem. Soc.* ***2006***, *128*, 9644.
[1757] Wei, H.-X.; Ki, S.H.; Li, G. *Tetrahedron* ***2001***, *57*, 3869.

a CO_2-promoted reaction with Chloramine-T ($TolSO_2N^-$—Cl).[1758] These are free-radical additions, with initial attack by the $R_2NH^{\bullet+}$ radical ion.[1759] Amines add to allenes in the presence of a Pd catalyst.[1760] Iodoamination of alkenes has been reviewed.[1761]

Bromoamidation of alkenes was accomplished using a NBS/sulfonamide protocol.[1762] The chloroamidation (the acetamide derivative) of alkenes occurs by reaction with NCS with 20% of Ph_2Se in aqueous acetonitrile.[1763] The Ag or Ag/In-catalyzed haloamidation of alkenes was accomplished using *N*-halophthalimides as both the source of nitrogen and the halogen. The iodoamidation of alkenes in aqueous media used chloramine salts and iodine.[1764] The intramolecular iodoamination of alkenes used MnI_2 as a catalyst.[1765]

The intramolecular aminobromination of alkenes was Fe catalyzed.[1766] The enantioselective bromination of allylic alcohols used *Cinchona*-derived thiourea as the catalyst and *N*,*N*-dibromo-4-nitrobenzenesulfonamide as a bromine and amine source.[1767] The choroamination of alkenes used *N*-chlorosulfonamide as the source of both N and Cl, and was promoted by visible light.[1768]

Formation of halo lactams by a procedure similar to halolactonization is difficult, but the problems have been overcome. Formation of a triflate from pent-4-enamide followed by treatment with iodine leads to the iodolactam, **45**.[1769]



45

A related cyclization of *N*-sulfonyl amino alkenes and NBS gave the bromolactam,[1770] and a dichloro-*N*,*N*-bis(allyl amide) was converted to a dichlorolactam with $FeCl_2$.[1771] It is noted that lactone formation is possible from unsaturated amides.

15-40 Addition of NOX and NO_2X (Addition of Halogen, Nitrogen)

There are three possible products when NOCl is added to alkenes: (i) a β-halo nitroso compound, (ii) an oxime, or (iii) a β-halo nitro compound.[1772] The initial product is always the

[1758] Minakata, S.; Yoneda, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* ***2006***, *8*, 967.
[1759] See Chow, Y.L.; Danen, W.C.; Nelson, S.F.; Rosenblatt, D.H. *Chem. Rev.* ***1978***, *78*, 243.
[1760] Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett.* ***1995***, *36*, 3857.
[1761] Mizar, P.; Wirth, T. *Synthesis* ***2017***, *49*, 981.
[1762] Yu, W.Z.; Chen, F.; Cheng, Y.A.; Yeung, Y.-Y. *J. Org. Chem.* ***2015***, *80*, 2815.
[1763] Tay, D.W.; Tsoi, I.T.; Er, J.C.; Yiu, G.; Leung, C.; Yeung, Y.-Y. *Org. Lett.* ***2013***, *15*, 1310.
[1764] Minakata, S.; Hayakawa, J. *Chem. Commun.* ***2011***, *47*, 1905.
[1765] Sun, H.; Cui, B.; Liu, G.-Q.; Li, Y.-M. *Tetrahedron* ***2016***, *72*, 7170.
[1766] Tian, J.-S.; Zhu, C.-L.; Chen, Y.-R.; Xu, H. *Synthesis* ***2015***, *47*, 1709.
[1767] Qi, J.; Fan, G.-T.; Chen, J.; Sun, M.-H.; Dong, Y.-T.; Zhou, L. *Chem. Commun.* ***2014***, *50*, 13841.
[1768] Qin, Q.; Ren, D.; Yu, S. *Org. Biomol. Chem.* ***2015***, *13*, 10295.
[1769] Knapp, S.; Rodriques, K.E. *Tetrahedron Lett.* ***1985***, *26*, 1803.
[1770] Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Tetrahedron Lett.* ***1984***, *25*, 1063. See Cheng, Y.A.; Yu, W.Z.; Yeung, Y.-Y. *J. Org. Chem.* ***2016***, *81*, 545.
[1771] Tseng, C.K.; Teach, E.G.; Simons, R.W. *Synth. Commun.* ***1984***, *14*, 1027.
[1772] See Kadzyauskas, P.P.; Zefirov, N.S. *Russ. Chem. Rev.* ***1968***, *37*, 543.

β-halo nitroso compound,[1773] but these are stable only if the carbon bearing the nitrogen has no hydrogen. If it has, the nitroso compound tautomerizes to the oxime:

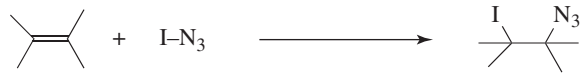
$$H{-}C{-}N{=}O \rightarrow C{=}N{-}OH$$

With some alkenes, the initial β-halo nitroso compound is oxidized by the NOCl to a β-halo nitro compound.[1774] The mechanism in most cases is probably simple electrophilic addition, and the addition is usually *anti*, although *syn* addition has been reported in some cases.[1775] *Markovnikov's rule* is followed, the positive NO going to the carbon that has more hydrogen atoms. The nitration of alkenes was reported using silver nitrate and TEMPO.[1776] Nitroalkenes were formed by the reaction of *t*-BuONO and TEMPO.[1777]

Nitryl chloride (NO_2Cl) also adds to alkenes, to give β-halo nitro compounds, but this is a free-radical process. The NO_2 goes to the less-substituted carbon.[1778] Nitryl chloride also adds to triple bonds to give the expected 1-nitro-2-chloro alkenes.[1779] The compound FNO_2 can be added to alkenes[1780] by treatment with HF in HNO_3.[1781]

OS **IV**, 711; **V**, 266, 863.

15-41 Addition of XN_3 (Addition of Halogen, Nitrogen)



The addition of iodine azide to double bonds gives β-iodo azides.[1782] The reagent can be prepared *in situ* from KI/NaN_3 in the presence of Oxone/wet alumina.[1783] The addition is stereospecific and *anti*, suggesting that the mechanism involves a cyclic iodonium ion intermediate.[1784] The reaction has been performed on many double bond compounds, including allenes[1785] and α,β-unsaturated ketones. Similar reactions can be performed with BrN_3[1786] and ClN_3. 1,4-addition has been found with acyclic conjugated dienes.[1787] In the case of BrN_3, both electrophilic and free-radical mechanisms are important,[1788] while with ClN_3

[1773] See Gowenlock, B.G.; Richter-Addo, G.B. *Chem. Rev.* ***2004***, *104*, 3315.
[1774] Shvekhgeimer, G.A.; Smirnyagin, V.A.; Sadykov, R.A.; Novikov, S.S. *Russ. Chem. Rev.* ***1968***, *37*, 351.
[1775] See Meinwald, J.; Meinwald, Y.C.; Baker III, T.N. *J. Am. Chem. Soc.* ***1964***, *86*, 4074.
[1776] Maity, S.; Naveen, T.; Sharma, U.; Maiti, D. *Synlett* ***2014***, *25*, 603.
[1777] Maity, S.; Naveen, T.; Sharma, U.; Maiti, D. *Org. Lett.* ***2013***, *15*, 3384.
[1778] Shechter, H. *Rec. Chem. Prog.* ***1964***, *25*, 55–76.
[1779] Schlubach, H.H.; Braun, A. *Liebigs Ann. Chem.* ***1959***, *627*, 28.
[1780] Sharts, C.M.; Sheppard, W.A. *Org. React.* ***1974***, *21*, 125–406 (pp. 236–243).
[1781] Knunyants, I.L.; German, L.S.; Rozhkov, I.N. *Bull Acad. Sci. USSR Div. Chem. Sci.* ***1963***, 1794.
[1782] Dehnicke, K. *Angew. Chem. Int. Ed.* ***1979***, *18*, 507; Hassner, A. *Acc. Chem. Res.* ***1971***, *4*, 9. See Nair, V.; George, T.G.; Sheeba, V.; Augustine, A.; Balagopal, L.; Nair, L.G. *Synlett* ***2000***, 1597.
[1783] Curini, M.; Epifano, F.; Marcotullio, M.C.; Rosati, O. *Tetrahedron Lett.* ***2002***, *43*, 1201.
[1784] See, however, Cambie, R.C.; Hayward, R.C.; Rutledge, P.S.; Smith-Palmer, T.; Swedlund, B.E.; Woodgate, P.D. *J. Chem. Soc., Perkin Trans. 1* ***1979***, 180.
[1785] Hassner, A.; Keogh, J. *J. Org. Chem.* ***1986***, *51*, 2767.
[1786] Olah, G.A.; Wang, Q.; Li, X.; Prakash, G.K.S. *Synlett* ***1990***, 487.
[1787] Hassner, A.; Keogh, J. *Tetrahedron Lett.* ***1975***, 1575.
[1788] Hassner, A.; Teeter, J.S. *J. Org. Chem.* ***1971***, *36*, 2176.

the additions are chiefly free radical.[1789] Iodine azide (IN_3) also adds to triple bonds to give β-iodo-α,β-unsaturated azides.[1790]

β-Iodo azides can be reduced to aziridines with $LiAlH_4$[1791] or converted to *N*-alkyl- or *N*-aryl aziridines by treatment with an alkyl- or aryldichloroborane followed by a base.[1792] In both cases the azide is first reduced to the corresponding amine (primary or secondary, respectively) and ring closure (**10-30**) follows. With Chloramine T ($TsNCl^- Na^+$) and 10% of pyridinium bromide perbromide, however, the reaction with alkenes give an *N*-tosyl aziridine directly.[1793]

OS **VI**, 893.

15-42 Addition of Alkyl Halides (Addition of Halogen, Carbon)[1074]

The difunctionalization of compounds with multiple bonds is known.[1794] Alkyl halides can be added to alkenes in the presence of a *Friedel-Crafts catalyst*, most often $AlCl_3$.[1795] The yields are best for tertiary R. Secondary R can also be used, but primary R give rearrangement products (as with **11-11**). The reactive species is the carbocation formed from the alkyl halide and the catalyst.[1796] The reaction with an alkene follows *Markovnikov's rule*, and generates the more stable carbocation from the alkene after reaction with the carbocation. Methyl and ethyl halides, which cannot rearrange to a more stable secondary or tertiary carbocation, give no reaction at all. When R^+ reacts with an alkene, a new carbocation is the product. Subsequent reaction with a nucleophile gives the substitution product whereas loss of a proton leads to the alkene. Triple bonds also undergo the reaction, to give vinylic halides.[1797] Conjugated dienes give 1,4-addition.[1798]

The Pd-catalyzed intramolecular carboiodination reaction was reported by heating *ortho*-iodoarenes that have an alkenyl unit to give the iodomethylbenzofuran or indoline derivative.[1799] The Pd-catalyzed reaction of styrenes with Selectfluor and an arylboronic acid added fluorine and the aryl group across the C=C unit.[1800] The Ir-photocatalyzed reaction of alkynes with CF_3SO_2Cl gave the chloro trifluoromethyl alkene.[1801] Alkynes reacted with allylic alcohols with an In catalyst to give halogen-substituted 1,4-dienes.[1802] The

[1789] See Cambie, R.C.; Jurlina, J.L.; Rutledge, P.S.; Swedlund, B.E.; Woodgate, P.D. *J. Chem. Soc., Perkin Trans. 1* ***1982***, 327. Also see Hassner, A. *Intra-Sci. Chem. Rep.* ***1970***, *4*, 109.
[1790] Hassner, A.; Isbister, R.J.; Friederang, A. *Tetrahedron Lett.* ***1969***, 2939.
[1791] Hassner, A.; Matthews, G.J.; Fowler, F.W. *J. Am. Chem. Soc.* ***1969***, *91*, 5046.
[1792] Levy, A.B.; Brown, H.C. *J. Am. Chem. Soc.* ***1973***, *95*, 4067.
[1793] Ali, S.I.; Nikalje, M.D.; Sudalai, A. *Org. Lett.* ***1999***, *1*, 705.
[1794] Shimizu, Y.; Kanai, M. *Tetrahedron Lett.* ***2014***, *55*, 3727.
[1795] Schmerling, L. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, pp. 1133–1174; Mayr, H.; Schade, C.; Rubow, M.; Schneider, R. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1029.
[1796] See Pock, R.; Mayr, H.; Rubow, M.; Wilhelm, E. *J. Am. Chem. Soc.* ***1986***, *108*, 7767.
[1797] See Maroni, R.; Melloni, G.; Modena, G. *J. Chem. Soc., Perkin Trans. 1* ***1973***, 2491; ***1974***, 353.
[1798] Kolyaskina, Z.N.; Petrov, A.A. *J. Gen. Chem. USSR* ***1962***, *32*, 1067.
[1799] Newman, S.G.; Lautens, M. *J. Am. Chem. Soc.* ***2011***, *133*, 1778.
[1800] Talbot, E.P.A.; de A. Fernandes, T.; McKenna, J.M.; Toste, F.D. *J. Am. Chem. Soc.* ***2014***, *136*, 4101.
[1801] Han, H.S.; Lee, Y.J.; Jung, Y.-S.; Han, S.B. *Org. Lett.* ***2017***, *19*, 1962.
[1802] Yue, H.-L.; Ma, L.; Ji, J.-X. *Synth. Commun.* ***2013***, *43*, 600.

Pd-catalyzed reaction of an alkyne with $CuBr_2$ and an allylic alcohol gave δ-bromo-γ,δ-unsaturated carbonyls in the presence of oxygen.[1803]

The cyclization reaction of $(NH_4)_2S_2O_8$ and *N*-aryl acrylamides proceeded by halocarbocyclization to the alkene moiety to give the oxindole.[1804] 1-Halo-1,4-dienes are prepared by the Pd-catalyzed reaction of alkynes and allylic alcohols in the presence of CuX_2.[1805] The Fe-catalyzed reaction of terminal alkynes and benzylic hydrocarbons with NCS and DDQ gave chlorobenzylation and formation of the vicinal chloro benzylic alkenes.[1806] Allenes reacted with allyl bromides and AIBN via bromoallylation to give the 2-bromo-1,5-diene.[1807]

Simple polyhalo alkanes, such as CCl_4, $BrCCl_3$, ICF_3, and related molecules, add to alkenes in good yield.[1808] These are free-radical additions and require initiation, for example,[1809] by peroxides, metal halides (e.g., $FeCl_2$, CuCl),[1810] Ru catalysts,[1811] or UV light. The initial reaction generates the more stable radical intermediate, as in most free-radical reactions with alkenes. Polyhalo alkanes add to halogenated alkenes in the presence of $AlCl_3$ by an electrophilic mechanism. This has been called the *Prins reaction* (not to be confused with the reaction most identified as the *Prins reaction*, **16-53**).[1812] α-Iodo lactones add to alkenes in the presence of BEt_3/O_2 to give the addition product.[1813] Other α-iodo esters add under similar conditions to give the lactone.[1814] Iodo esters also add to alkenes in the presence of BEt_3 to give iodo esters that have not cyclized.[1815]

OS **II**, 312; **IV**, 727; **V**, 1076; **VI**, 21; **VII**, 290.

15-43 Addition of Acyl Halides (Addition of Halogen, Carbon)

Acyl halides add to many alkenes using *Friedel-Crafts* catalysts, although polymerization is a problem. The reaction has been applied to straight-chain, branched, and cyclic alkenes, but to very few alkenes that contain functional groups, other than halogens.[1816] The mechanism is similar to that of **15-42**, and, as in that case, substitution competes

[1803] Wen, Y.; Huang, L.; Jiang, H.; Chen, H. *J. Org. Chem.* ***2012***, *77*, 2029.
[1804] Zhang, M.-Z.; Sheng, W.-B.; Jiang, Q.; Tian, M.; Yin, Y.; Guo, C.-C. *J. Org. Chem.* ***2014***, *79*, 10829.
[1805] Wen, Y.; Jiang, H. *Tetrahedron Lett.* ***2013***, *54*, 4034.
[1806] Shi, J.-L.; Zhang, J.-C.; Wang, B.-Q.; Hu, P.; Zhao, K.-Q.; Shi, Z.-J. *Org. Lett.* ***2016***, *18*, 1238.
[1807] Kippo, T.; Fukuyama, T.; Ryu, I. *Org. Lett.* ***2011***, *13*, 3864.
[1808] See Freidlina, R.Kh.; Velichko, F.K. *Synthesis* ***1977***, 145; Freidlina, R.Kh.; Chukovskaya, E.C. *Synthesis* ***1974***, 477.
[1809] For other initiators, see Tsuji, J.; Sato, K.; Nagashima, H. *Tetrahedron* ***1985***, *41*, 393; Phelps, J.C.; Bergbreiter, D.E.; Lee, G.M.; Villani, R.; Weinreb, S.M. *Tetrahedron Lett.* ***1989***, *30*, 3915.
[1810] See Martin, P.; Steiner, E.; Streith, J.; Winkler, T.; Bellus, D. *Tetrahedron* ***1985***, *41*, 4057. Also see Mitani, M.; Nakayama, M.; Koyama, K. *Tetrahedron Lett.* ***1980***, *21*, 4457.
[1811] Simal, F.; Wlodarczak, L.; Demonceau, A.; Noels, A.F. *Eur. J. Org. Chem.* ***2001***, 2689.
[1812] For a review with respect to fluoroalkenes, see Paleta, O. *Fluorine Chem. Rev.* ***1977***, *8*, 39.
[1813] Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* ***1998***, 1351.
[1814] Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* ***1998***, *63*, 8604.
[1815] Baciocchi, E.; Muraglia, E. *Tetrahedron Lett.* ***1994***, *35*, 2763.
[1816] See Groves, J.K. *Chem. Soc. Rev.* ***1972***, *1*, 73; Nenitzescu, C.D.; Balaban, A.T. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1033–1152.

(**12-16**). Increasing temperature favors substitution,[1817] but good yields of addition products can be achieved if the temperature is kept under 0 °C. The reaction usually fails with conjugated dienes, since polymerization predominates.[1818] Iodo acetates have been formed from alkenes using iodine and $Pb(OAc)_2$ in acetic acid.[1819] Rhodium-catalyzed variations are known.[1820] The reaction can be performed on triple bond compounds, producing compounds of the form RCO—C═C—Cl.[1821] A formyl group and a halogen can be added to triple bonds by treatment with *N*,*N*-disubstituted formamides and $POCl_3$ (*Vilsmeier conditions*, **11-18**).[1822] Chloroformates add to allenes in the presence of a Rh catalyst to give a β-chloro-β,γ-unsaturated ester.[1823]

OS **IV**, 186; **VI**, 883; **VIII**, 254.

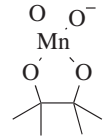
B. Oxygen, Nitrogen, or Sulfur on One or Both Sides

15-44 Dihydroxylation and Dialkoxylation (Addition of Oxygen, Oxygen)[1824]

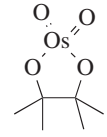
There are many reagents that add two OH groups to a double bond (dihydroxylation).[1825] The most common are OsO_4,[1826] first used by Criegee in 1936,[1827] and alkaline $KMnO_4$.[1828] Less-substituted double bonds are oxidized more rapidly than more-substituted alkenes.[1829] Both give *syn* addition from the less-hindered side of the double bond. Permanganate adds to alkenes to form an intermediate manganate ester (**46**), which is decomposed under alkaline conditions via coordination of the base and **46**.[1830] Transition state structures and the energetics of the permanganate oxidation of alkenes has been studied using molecular mechanics.[1831] Note that there are alternative Mn complexes that may be used for *cis*-dihydroxylation of alkenes.[1832] Osmium tetroxide reacts rather slowly but almost

[1817] Jones, N.; Taylor, H.T.; Rudd, E. *J. Chem. Soc.* ***1961***, 1342.
[1818] See Melikyan, G.G.; Babayan, E.V.; Atanesyan, K.A.; Badanyan, Sh.O. *J. Org. Chem. USSR* ***1984***, *20*, 1884.
[1819] Bedekar, A.V.; Nair, K.B.; Soman, R. *Synth. Commun.* ***1994***, *24*, 2299.
[1820] Hua, R.; Onozawa, S.-y.; Tanaka, M. *Chem. Eur. J.* ***2005***, *11*, 3621.
[1821] See Brownstein, S.; Morrison, A.; Tan, L.K. *J. Org. Chem.* ***1985***, *50*, 2796.
[1822] Yen, V.Q. *Ann. Chim. (Paris)* ***1962***, *[13] 7*, 785.
[1823] Hua, R.; Tanaka, M. *Tetrahedron Lett.* ***2004***, *45*, 2367.
[1824] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 266–277.
[1825] See Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, ***1990***, pp. 67–73; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1985***, pp. 73–98, 278–294. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 996–1003.
[1826] See Schröder, M. *Chem. Rev.* ***1980***, *80*, 187. Also see, Norrby, P.-O.; Gable, K.P. *J. Chem. Soc., Perkin Trans. 2* ***1996***, 171.
[1827] Criegee, R. *Liebigs Ann. Chem.* ***1936***, *522*, 75.
[1828] See Wang, C.; Zong, L.; Tan, C.-H. *J. Am. Chem. Soc.* ***2015***, *137*, 10677; Luo, Z.-b.; Zhao, C.; Xie, J.; Lu, H.-f. *Synthesis* ***2016***, *48*, 3696.
[1829] Crispino, G.A.; Jeong, K.-S.; Kolb, H.C.; Wang, Z.-M.; Xu, D.; Sharpless, K.B. *J. Org. Chem.* ***1993***, *58*, 3785.
[1830] See Chow, T.W.-S.; Liu, Y.; Che, C.-M. *Chem. Commun.* ***2011***, *47*, 11204.
[1831] Wiberg, K.B.; Wang, Y.-g.; Sklenak, S.; Deutsch, C.; Trucks, G. *J. Am. Chem. Soc.* ***2006***, *128*, 11537.
[1832] de Boer, J.W.; Brinksma, J.; Browne, W.R.; Meetsma, A.; Alsters, P.L.; Hage, R.; Feringa, B.L. *J. Am. Chem. Soc.* ***2005***, *127*, 7990.

quantitatively to form a cyclic osmate ester such as **47** as an intermediate,[1833] which may be isolated in some cases, but is usually decomposed in solution with sodium sulfite (Na_2SO_3) in ethanol or other reagents.[1834]



46



47

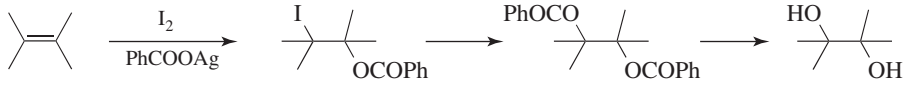
The chief drawbacks to the use of OsO_4 are expense and toxicity, but the reaction is made catalytic in OsO_4 by using *N*-methylmorpholine-*N*-oxide (NMO),[1835] *tert*-butyl hydroperoxide in alkaline solution,[1836] H_2O_2,[1837] or peroxyacid.[1838] Polymer-bound OsO_4[1839] and encapsulated OsO_4 have been shown to give the diol in the presence of NMO.[1840] Dihydroxylation has also been reported in ionic liquids.[1841] Other metals have been used to catalyze dihydroxylation, including Fe,[1842] Ir,[1843] or Ru[1844] with hydrogen peroxide.

The end product of the reaction is a 1,2-diol, but potassium permanganate is a strong oxidizing agent that can oxidize the glycol product[1845] (see **19-7** and **19-10**). In acidic and neutral solution oxidation almost always occurs so diols must be prepared with alkaline permanganate,[1846] but the conditions must be mild. Even so, yields are seldom >50%, although they can be improved with phase-transfer catalysis[1847] or increased stirring.[1848] The use of ultrasound with permanganate has resulted in good yields of the diol.[1849] This reaction is the basis of the *Baeyer test* for the presence of double bonds.

Anti hydroxylation can be achieved by treatment with H_2O_2 and formic acid. In this case, epoxidation (**15-46**) occurs first, followed by an S_N2 reaction, which results in overall *anti* addition. The same result can be achieved in one step with *m*-chloroperoxybenzoic acid (mcpba) and water,[1850] and cyclobutane malonoyl peroxide has been used.[1851] Overall *anti* addition can also be achieved by the method of Prévost (the *Prévost reaction*). In this

[1833] See Jørgensen, K.A.; Hoffmann, R. *J. Am. Chem. Soc.* ***1986***, *108*, 1867.
[1834] See Ogino, T.; Hasegawa, K.; Hoshino, E. *J. Org. Chem.* ***1990***, *55*, 2653. See, however, Freeman, F.; Kappos, J.C. *J. Org. Chem.* ***1989***, *54*, 2730, and other papers in this series.
[1835] Iwasawa, N.; Kato, T.; Narasaka, K. *Chem. Lett.* ***1988***, 1721. See also, Ray, R.; Matteson, D.S. *Tetrahedron Lett.* ***1980***, 449.
[1836] Akashi, K.; Palermo, R.E.; Sharpless, K.B. *J. Org. Chem.* ***1978***, *43*, 2063.
[1837] See Usui, Y.; Sato, K.; Tanaka, M. *Angew. Chem. Int. Ed.* ***2003***, *42*, 5623.
[1838] Bergstad, K.; Piet, J.J.N.; Bäckvall, J.-E. *J. Org. Chem.* ***1999***, *64*, 2545.
[1839] Ley, S.V.; Ramarao, C.; Lee, A.-L.; Ostergaard, N.; Smith, S.C.; Shirley, I.M. *Org. Lett.* ***2003***, *5*, 185.
[1840] Nagayama, S.; Endo, M.; Kobayashi, S. *J. Org. Chem.* ***1998***, *63*, 6094.
[1841] Branco, L.C.; Serbanovic, A.; da Ponte, M.N.; Afonso, C.A.M. *Chem. Commun.* ***2005***, 107.
[1842] Oldenburg, P.D.; Shteinman, A.A.; Que Jr., L. *J. Am. Chem. Soc.* ***2005***, *127*, *15*672.
[1843] Gärtner, M.; Mader, S.; Seehafer, K.; Helmchen, G. *J. Am. Chem. Soc.* ***2011***, *133*, 2072.
[1844] Yip, W.-P.; Ho, C.-M.; Zhu, N.; Lau, T.-C.; Che, C.-M. *Chem. Asian J.* ***2008***, *3*, 70.
[1845] See Wolfe, S.; Ingold, C.F. *J. Am. Chem. Soc.* ***1981***, *103*, 940. Also see, Lohray, B.B.; Bhushan, V.; Kumar, R.K. *J. Org. Chem.* ***1994***, *59*, 1375.
[1846] See Taylor, J.E.; Green, R. *Can. J. Chem.* ***1985***, *63*, 2777.
[1847] See Ogino, T.; Mochizuki, K. *Chem. Lett.* ***1979***, 443.
[1848] Taylor, J.E. *Can. J. Chem.* ***1984***, *62*, 2641.
[1849] Varma, R.S.; Naicker, K.P. *Tetrahedron Lett.* ***1998***, *39*, 7463.
[1850] Fringuelli, F.; Germani, R.; Pizzo, F.; Savelli, G. *Synth. Commun.* ***1989***, *19*, 1939.
[1851] Alamillo-Ferrer, C.; Davidson, S.C.; Rawling, M.J.; Theodoulou, N.H.; Campbell, M.; Humphreys, P.G.; Kennedy, A.R.; Tomkinson, N.C.O. *Org. Lett.* ***2015***, *17*, 5132.

method, the alkene is treated with iodine and silver benzoate in a 1:2 molar ratio. The initial addition is *anti* and results in a β-halo benzoate, as shown, which can be isolated.



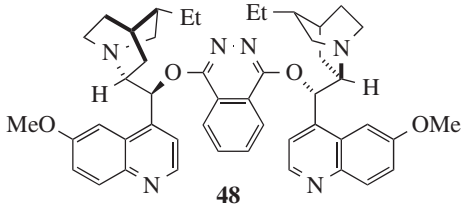
However, under the normal reaction conditions, the iodine is replaced by a second PhCOO group. This is a nucleophilic substitution reaction via the neighboring-group mechanism (Sec. 10.C), so the groups are still *anti*. Hydrolysis of the ester does not change the configuration. An enantioselective version of these reactions has been developed.[1852]

The *Woodward modification* of the Prévost reaction is similar, but results in overall *syn* hydroxylation.[1853] In this procedure, the alkene is treated with iodine and silver acetate in a 1:1 molar ratio in acetic acid containing water. Here again, the initial product is a β-halo ester; the addition is *anti* and a nucleophilic replacement of the iodine occurs. However, in the presence of water, neighboring-group participation is prevented or greatly decreased by solvation of the ester function, and the mechanism is the normal S_N2 process,[1854] so the monoacetate is *syn* and hydrolysis gives the diol as the product, with overall *syn* addition. Although the Woodward method results in overall *syn* addition, the product may be different from that with OsO_4 or $KMnO_4$, since the overall *syn* process is from the *more-hindered side* of the alkene.[1855] Both the Prévost and the Woodward methods[1856] have been carried out in high yields with thallium(I) acetate and thallium(I) benzoate instead of the silver carboxylates.[1857] Note that cyclic sulfates can be prepared from alkenes by reaction with PhIO and SO_3•DMF.[1858] Diacetates have been prepared from alkenes using a Cu-catalyzed reaction with $PhI(OAc)_2$ as the oxidizing agent.[1859] A similar Pd/Cu-catalyzed reaction is known using O_2 as the oxidant.[1860] Organocatalysts have been used,[1861] as well as a microchemical system,[1862] and a chiral iodine(III) derivative.[1863]

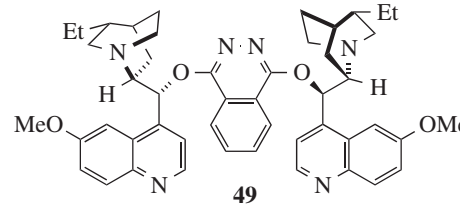
1,2-Diols are also generated from terminal alkynes by two sequential reactions with a Pt catalyst and then a Pd catalyst, both with $HSiCl_3$, and a final oxidation with H_2O_2/KF.[1864] The dihydroxylation of a vinyl ether, derived from an alkyne, leads to α-hydroxy aldehydes.[1865] Dihydroxylation of alkenes has been reported using a lipase and hydrogen peroxide, under microwave irradiation.[1866] A Pd-catalyzed diacetoxylation is also known.[1867]

[1852] Fujita, M.; Wakita, M.; Sugimura, T. *Chem. Commun.* ***2011***, *47*, 3983.
[1853] See Brimble, M.A.; Nairn, M.R. *J. Org. Chem.* ***1996***, *61*, 4801.
[1854] For another mechanism: Woodward, R.B.; Brutcher Jr., F.V. *J. Am. Chem. Soc.* ***1958***, *80*, 209.
[1855] Also see Corey, E.J.; Das, J. *Tetrahedron Lett.* ***1982***, *23*, 4217.
[1856] See Horiuchi, C.A.; Satoh, J.Y. *Chem. Lett.* ***1988***, 1209; Campi, E.M.; Deacon, G.B.; Edwards, G.L.; Fitzroy, M.D.; Giunta, N.; Jackson, W.R.; Trainor, R. *J. Chem. Soc., Chem. Commun.* ***1989***, 407.
[1857] Cambie, R.C.; Hayward, R.C.; Roberts, J.L.; Rutledge, P.S. *J. Chem. Soc., Perkin Trans. 1* ***1974***, 1858, 1864; Cambie, R.C.; Rutledge, P.S. *Org. Synth.* ***VI***, 348.
[1858] Robinson, R.I.; Woodward, S. *Tetrahedron Lett.* ***2003***, *44*, 1655.
[1859] Seayad, J.; Seayad, A.M.; Chai, C.L.L. *Org. Lett.* ***2010***, *12*, 1412.
[1860] Schultz, M.J.; Sigman, M.S. *J. Am. Chem. Soc.* ***2006***, *128*, 1460.
[1861] Zhong, W.; Liu, S.; Yang, J.; Meng, X.; Li, Z. *Org. Lett.* ***2012***, *14*, 3336. See Schwarz, M.; Reiser, O. *Angew. Chem. Int. Ed.* ***2011***, *50*, 10495; Larsen, A.T.; May, E.M.; Auclair, K. *J. Am. Chem. Soc.* ***2011***, *133*, 7853.
[1862] Park, J.H.; Park, C.Y; Song, H.S.; Huh, Y.S.; Kim, G.H.; Park, C.P. *Org. Lett.* ***2013***, *15*, 752.
[1863] Wöste, T.H.; Muñiz, K. *Synthesis* ***2016***, *48*, 816.
[1864] Shimada, T.; Mukaide, K.; Shinohara, A.; Han, J.W.; Hayashi, T. *J. Am. Chem. Soc.* ***2004***, *124*, 1584.
[1865] DeBergh, J.R.; Spivey, K.M.; Ready, J.M. *J. Am. Chem. Soc.* ***2008***, *130*, 7828.
[1866] Sarma, K.; Borthakur, N.; Goswami, A. *Tetrahedron Lett.* ***2007***, *48*, 6776.
[1867] Wang, A.; Jiang, H.; Chen, H. *J. Am. Chem. Soc.* ***2009***, *131*, 3846.

Dihydroxylation to alkenes of the form $RCH{=}CH_2$ has been made enantioselective, and addition to $RCH{=}CHR'$ both diastereoselective[1868] and enantioselective,[1869] using chiral additives or chiral catalysts[1870] that are derivatives of the naturally occurring quinine and quinuclidine,[1871] along with OsO_4,[1872] in what is called *Sharpless asymmetric dihydroxylation*.[1873] Other chiral ligands[1874] have also been used, as well as polymer-bound[1875] and silica-bound[1876] *Cinchona* alkaloids. These amines bind to the OsO_4 *in situ* as chiral ligands, causing it to add asymmetrically.[1877] Osmium tetroxide and Streptavidin has been developed as a tunable catalyst.[1878] Magnetically recoverable osmium catalysts have been developed.[1879] This asymmetric reaction has been done both with the stoichiometric method and with the catalytic method.[1880] The catalytic method has been extended to conjugated ketones[1881] and to conjugated dienes, which give tetrahydroxy products diastereoselectively.[1882] Asymmetric dihydroxylation has also been reported with chiral alkenes.[1883]



48



49

Two phthalazine derivatives,[1884] $(DHQD)_2PHAL$ (**48**) and $(DHQ)_2PHAL$ (**49**), are used in conjunction with an Os reagent to improve the efficiency and ease of use, and are

[1868] See Vedejs, E.; McClure, C.K. *J. Am. Chem. Soc.* ***1986***, *108*, 1094; Evans, D.A.; Kaldor, S.W. *J. Org. Chem.* ***1990***, *55*, 1698. See Park, J.K.; McQuade, D.T. *Angew. Chem. Int. Ed.* ***2012***, *51*, 2717.

[1869] Zaitsev, A.B.; Adolfsson, H. *Synthesis* ***2006***, 1725; Kaur, A.; Singh, V. *Synlett* ***2015***, *26*, 1191.

[1870] McNamara, C.A.; King, F.; Bradley, M. *Tetrahedron Lett.* ***2004***, *45*, 8527; Jiang, R.; Kuang, Y.; Sun, X.; Zhang, S. *Tetrahedron: Asymmetry* ***2004***, *15*, 743.

[1871] Sharpless, K.B.; Amberg, W.; Beller, M.; Chens, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* ***1991***, *56*, 4585.

[1872] Monguchi, Y.; Wakayama, F.; Takada, H.; Sawama, Y.; Sajiki, H. *Synlett* ***2015***, *26*, 700.

[1873] Kolb, H.C.; van Nieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.* ***1994***, *94*, 2483. Also see, Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 271–273. For a discussion of the existing mechanism, see Burghart-Stoll, H.; Böhnke, O.; Brückner, R. *Org. Lett.* ***2011***, *13*, 1020.

[1874] Rosini, C.; Tanturli, R.; Pertici, P.; Salvadori, P. *Tetrahedron: Asymmetry* ***1996***, *7*, 2971; Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* ***1992***, *57*, 2768.

[1875] See Karjalainen, J.K.; Hormi, O.E.O.; Sherrington, D.C. *Tetrahedron: Asymmetry* ***1998***, *9*, 1563.

[1876] Song, C.E.; Yang, J.W.; Ha, H.-J. *Tetrahedron: Asymmetry* ***1997***, *8*, 841.

[1877] See Corey, E.J.; Noe, M.C. *J. Am. Chem. Soc.* ***1996***, *118*, 319. Also see Nelson, D.W.; Gypser, A.; Ho, P.T.; Kolb, H.C.; Kondo, T.; Kwong, H.-L.; McGrath, D.V.; Rubin, A.E.; Norrby, P.-O.; Gable, K.P.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1997***, *119*, 1840.

[1878] Köhler, V.; Mao, J.; Heinisch, T.; Pordea, A.; Sardo, A.; Wilson, Y.M.; Knörr, L.; Creus, M.; Prost, J.-C.; Schirmer, T.; Ward, T.R. *Angew. Chem. Int. Ed.* ***2011***, *50*, 10863.

[1879] Fujita, K.-i.; Umeki, S.; Yasuda, H. *Synlett* ***2013***, *24*, 947.

[1880] See Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Stefanelli, S. *Tetrahedron Lett.* ***1987***, *28*, 3139; Hirama, M.; Oishi, T.; Itô, S. *J. Chem. Soc., Chem. Commun.* ***1989***, 665.

[1881] Walsh, P.J.; Sharpless, K.B. *Synlett* ***1993***, 605.

[1882] Park, C.Y.; Kim, B.M.; Sharpless, K.B. *Tetrahedron Lett.* ***1991***, *32*, 1003.

[1883] Oishi, T.; Iida, K.; Hirama, M. *Tetrahedron Lett.* ***1993***, *34*, 3573.

[1884] Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* ***1992***, *57*, 2768.

commercially available as AD-mix-β (using **48**) and AD-mix-α (using **49**).[1885] These catalysts lead to diol formation with the opposite enantioselectivity. Styrene, for example, gave the (*R*)-diol with **48**, and the (*S*)-diol with **49**.[1886] Catalyst **48** is prepared from dihydroquinidine (DHQD) and 1,4-dichlorophthalazine (PHAL), and **49** is prepared from dihydroquinine (DHQ) and PHAL. The actual oxidation using AD-mix-α or AD-mix-β uses **49** or **48**, respectively, mixed with potassium osmate [$K_2OsO_2(OH)_6$], powdered $K_3Fe(CN)_6$, and powdered K_2CO_3 in an aqueous solvent mixture.[1884] One study showed that osymylation does not always occur preferentially on the most electron-rich double bond,[1887] and there are examples of the less-rich double bond reacting preferentially, and such preferences may be amplified using AD-type reagents, as they add significant steric hindrance to the overall system.[1888] Note that ionic liquids have been used in asymmetric dihydroxylation.[1889]

These additives have been used in conjunction with microencapsulated OsO_4,[1890] and polymer bound **48** has been used.[1891] An asymmetric dihydroxylation was reported catalyzed by ionic polymer-supported OsO_4.[1892] Both **48**[1893] and **49**[1894] have been used to generate diols with high enantioselectivity. Oxidation of a terminal alkene with AD-mix and then oxidation with TEMPO/NaOCl/$NaOCl_2$ leads to α-hydroxyl carboxylic acids with high enantioselectivity.[1895]

Enantioselective addition and diastereoselective addition have also been achieved by using preformed derivatives of OsO_4 already containing chiral ligands[1896] and by the use of OsO_4 on alkenes that have a chiral group elsewhere in the molecule.[1897] A Rh-catalyzed diboration of alkenes in the presence of a chiral ligand, leads to the corresponding diol with good enantioselectivity after oxidation.[1898]

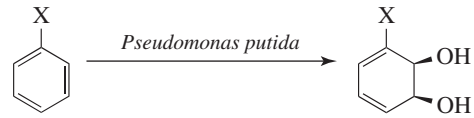
Dialkoxylation reactions are possible. The reaction of an aryl alkene with methanol, O_2, and a Pd catalyst leads to the dimethoxy compound with moderate enantioselectivity if a chiral ligand is used.[1899] 3-Methoxy tetrahydrofuran derivatives were prepared from 1-allylcyclopentan-1-ol derivatives by reaction with iodine and [hydroxy(tosyloxy)iodo]benzene (HTIB).[1900] A BF_3•OEt_2-promoted diacetoxylation of alkenes used $PhI(OAc)_2$.[1901] Oxidizing agents, such as benzoquinone, MnO_2, or O_2, along

[1885] See Jacobsen, E.N.; Marko, I.; France, M.B.; Svendsen, J.S.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1989***, *111*, 737.
[1886] Jacobsen, E.N.; Marko, I.; Mungall, W.S.; Schröder, G.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1988***, *110*, 1968.
[1887] Han, P.; Wang, R.; Wang, D.Z. *Tetrahedron* ***2011***, *67*, 8873.
[1888] For a review, see Français, A.; Bedel, O.; Haudrechy, A. *Tetrahedron* ***2008***, *64*, 2495.
[1889] See Branco, L.C.; Afonso, C.A.M. *J. Org. Chem.* ***2004***, *69*, 4381.
[1890] Kobayashi, S.; Ishida, T.; Akiyama, R. *Org. Lett.* ***2001***, *3*, 2649.
[1891] Kuang, Y.-Q.; Zhang, S.-Y.; Wei, L.-L. *Tetrahedron Lett.* ***2001***, *42*, 5925.
[1892] Lee, B.S.; Mahajan, S.; Janda, K.D. *Tetrahedron Lett.* ***2005***, *46*, 4491.
[1893] Krief, A.; Colaux-Castillo, C. *Tetrahedron Lett.* ***1999***, *40*, 4189.
[1894] Junttila, M.H.; Hormi, O.E.O. *J. Org. Chem.* ***2004***, *69*, 4816.
[1895] Aladro, F.J.; Guerra, I.M.; Moreno-Dorado, F.J.; Bustamante, J.M.; Jorge, Z.D.; Massanet, G.M. *Tetrahedron Lett.* ***2000***, *41*, 3209.
[1896] Kokubo, T.; Sugimoto, T.; Uchida, T.; Tanimoto, S.; Okano, M. *J. Chem. Soc., Chem. Commun.* ***1983***, 769.
[1897] Hauser, F.M.; Ellenberger, S.R.; Clardy, J.C.; Bass, L.S. *J. Am. Chem. Soc.* ***1984***, *106*, 2458; Johnson, C.R.; Barbachyn, M.R. *J. Am. Chem. Soc.* ***1984***, *106*, 2459.
[1898] Trudeau, S.; Morgan, J.B.; Shrestha, M.; Morken, J.P. *J. Org. Chem.* ***2005***, *70*, 9538.
[1899] Zhang, Y.; Sigman, M.S. *J. Am. Chem. Soc.* ***2007***, *129*, 3076.
[1900] Vasconcelos, R.S.; Silva Jr., L.F.; Giannis, A. *J. Org. Chem.* ***2011***, *76*, 1499.
[1901] Zhong, W.; Yang, J.; Meng, X.; Li, Z. *J. Org. Chem.* ***2011***, *76*, 9997.

with palladium acetate, have been used to convert conjugated dienes to 1,4-diacetoxy-2-alkenes (1,4-addition).[1902]

OS **II**, 307; **III**, 217; **IV**, 317; **V**, 647; **VI**, 196, 342, 348; **IX**, 251, 383.

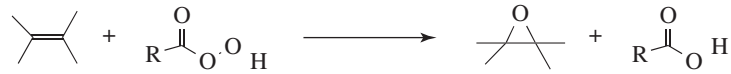
15-45 Dihydroxylation of Aromatic Rings



One π bond of an aromatic ring can be selectively oxidized to give a cyclohexadiene 1,2-diol[1903] by reaction with enzymes associated with *Pseudomonas putida*.[1904] *para*-Substituted arenes were dihydroxylated using *Escherichia coli* JM109 (pDTG601), an organism expressing toluene dioxygenase.[1905] A variety of substituted aromatic compounds can be oxidized, including bromobenzene, chlorobenzene,[1906] and toluene.[1907]. In these latter cases, introduction of the hydroxyl groups generates a chiral molecule that can be used as a template for asymmetric syntheses.[1908]

OS **X**, 217.

15-46 Epoxidation (Addition of Oxygen, Oxygen)[1909]



Alkenes are converted to epoxides (oxiranes) by reaction with many peroxyacids.[1910] The reaction, called the *Prilezhaev reaction*, has wide utility.[1911] The limiting factor concerning choice of the peroxyacid is usually whether or not it is commercially available because an in-lab preparation is potentially rather dangerous. The peroxyacid used most often is probably *m*-chloroperoxybenzoic acid (mcpba). However, peroxyacetic acid and peroxybenzoic

[1902] See Bäckvall, J.E.; Awasthi, A.K.; Renko, Z.D. *J. Am. Chem. Soc.* ***1987***, *109*, 4750 and references cited therein; Bäckvall, J.E. *New. J. Chem.* ***1990***, *14*, 447. For another method, see Uemura, S.; Fukuzawa, S.; Patil, S.R.; Okano, M. *J. Chem. Soc., Perkin Trans. 1* ***1985***, 499.

[1903] Lewis, S.E. *Chem. Commun.* ***2014***, *50*, 2821.

[1904] Gibson, D.T.; Koch, J.R.; Kallio, R.E. *Biochemistry* ***1968***, *7*, 2653; Brown, S.M. in Hudlicky, T. *Organic Synthesis: Theory and Practice*, JAI Press, Greenwich, CT, ***1993***, Vol. 2, p. 113; Carless, H.A.J. *Tetrahedron: Asymmetry* ***1992***, *3*, 795.

[1905] Trant, J.F.; Froese, J.; Hudlicky, T. *Tetrahedron: Asymmetry* ***2013***, *24*, 184.

[1906] See Hudlicky, T.; Price, J.D. *Synlett.* ***1990***, 159.

[1907] Gibson, D.T.; Hensley, M.; Yoshioka, H.; Mabry, T.J. *Biochemistry,* ***1970***, *9*, 1626.

[1908] Hudlicky, T.; Gonzalez, D.; Gibson, D.T. *Aldrichimica Acta* ***1999***, *32*, 35; Ley, S.V.; Redgrave, A.J. *Synlett* ***1990***, 393. Also see, Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 275–277.

[1909] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 249–266.

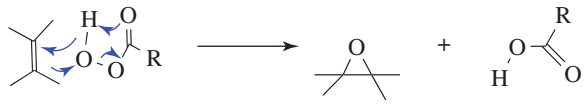
[1910] For a list of reagents, including peroxyacids and others, used for epoxidation, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 915–927.

[1911] See Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, ***1990***, pp. 60–64; Haines, A.H. *Methods for the Oxidation of Organic Compunds*, Academic Press, NY, ***1985***, pp. 98–117, 295–303; Dryuk, V.G. *Russ. Chem. Rev.* ***1985***, *54*, 986; Plesnicar, B. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 211–252; Hiatt, R. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2; Marcel Dekker, NY, ***1971***, pp. 113–140.

acid are available, and trifluoroperoxyacetic acid[1912] and 3,5-dinitroperoxybenzoic acid[1913] are particularly reactive. Magnesium monoperoxyphthalate (MMPP)[1914] is commercially available, and has been shown to be a good substitute for mcpba in a number of reactions.

Alkyl, aryl, hydroxyl, ester, and other groups may be present in the alkene, but not amino groups since they are oxidized by the reagent. The presence of electron-donating groups increases the rate, and the reaction is particularly rapid with tetraalkyl alkenes. Epoxidation has been carried out in ionic liquids using 10% H_2O_2 with $MnSO_4$[1915] or an Fe catalyst.[1916] Epoxidations with peroxyacids have been reported in supercritical CO_2 and using flow conditions (Sec. 7.D).[1917] Epoxidations using silica-supported peroxyacids have been reported.[1918] Hypervalent iodine compounds, such as $PhI(OAc)_2$, in conjunction with a Ru catalyst in aqueous media,[1919] or in an ionic liquid with a Mn catalyst,[1920] converted alkenes to epoxides. Microwave-assisted epoxidations are known using H_2O_2.[1921] Epoxidation of vinyl ethers has been studied.[1922] The conformation of cyclic alkenes can affect the epoxidation reaction.[1923] Transition metal catalysts can facilitate epoxidation of alkenes at low temperatures or with alkenes that may otherwise react sluggishly.[1924]

The one-step mechanism involving a transition state such as **50**[1925] was proposed by Bartlett.[1926]



50

Evidence for this concerted mechanism is as follows:[1927]

1. The reaction is second order. If ionization were the rate-determining step, it would be first order in peroxyacid.
2. The reaction readily takes place in nonpolar solvents, where formation of ions is inhibited.[1928]

[1912] Emmons, W.D.; Pagano, A.S. *J. Am. Chem. Soc.* ***1955***, *77*, 89.
[1913] Rastetter, W.H.; Richard, T.J.; Lewis, M.D. *J. Org. Chem.* ***1978***, *43*, 3163.
[1914] Foti, C.J.; Fields, J.D.; Kropp, P.J. *Org. Lett.* ***1999***, *1*, 903.
[1915] Tong, K.-H.; Wong, K.-Y.; Chan, T.H. *Org. Lett.* ***2003***, *5*, 3423.
[1916] Srinivas, K.A.; Kumar, A.; Chauhan, S.M.S. *Chem. Commun.* ***2002***, 2456.
[1917] Mello, R.; Alcalde-Aragonés, A.; Olmos, A.; González-Núñez, M.E.; Asensio, G. *J. Org. Chem.* ***2012***, *77*, 4706.
[1918] Mello, R.; Aragonés, A.A.; Núñez, M.E.G.; Asensio, G. *J. Org. Chem.* ***2012***, *77*, 6409.
[1919] Tse, M.K.; Bhor, S.; Klawonn, M.; Döbler, C.; Beller, M. *Tetrahedron Lett.* ***2003***, *44*, 7479.
[1920] Li, Z.; Xia, C.-G. *Tetrahedron Lett.* ***2003***, *44*, 2069.
[1921] Bogdal, D.; Lukasiewicz, M.; Pielichowski, J.; Bednarz, S. *Synth. Commun.* ***2005***, *35*, 2973.
[1922] Orendt, A.M.; Roberts, S.W.; Rainier, J.D. *J. Org. Chem.* ***2006***, *71*, 5565.
[1923] Neuenschwander, U.; Hermans, I. *J. Org. Chem.* ***2011***, *76*, 10236.
[1924] See Murphy, A.; Pace, A.; Stack, T.D.P. *Org. Lett.* ***2004***, *6*, 3119.
[1925] See Finn, M.G.; Sharpless, K.B. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Wiley, NY, ***1985***, pp. 247–308; Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *J. Org. Chem.* ***2002***, *67*, 8519.
[1926] Bartlett, P.D. *Rec. Chem. Prog.* ***1957***, *18*, 111. For other proposed mechanisms see Kwart, H.; Hoffman, D.M. *J. Org. Chem.* ***1966***, *31*, 419; Hanzlik, R.P.; Shearer, G.O. *J. Am. Chem. Soc.* ***1975***, *97*, 5231.
[1927] Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *J. Org. Chem.* ***2004***, *69*, 7479. See also, Vedejs, E.; Dent III, W.H.; Kendall, J.T.; Oliver, P.A. *J. Am. Chem. Soc.* ***1996***, *118*, 3556.
[1928] See Gisdakis, P.; Rösch, N. *Eur. J. Org. Chem.* ***2001***, 719.

3. Measurements of the effect on the reaction rate of changes in the substrate structure show that there is no carbocation character in the transition state.[1929]
4. The addition is stereospecific (i.e., a *trans* alkene gives a *trans* epoxide and a *cis* alkene gives a *cis* epoxide) even in cases where electron-donating substituents would stabilize a hypothetical carbocation intermediate.[1930] However, where there is an OH group in the allylic or homoallylic position, the stereospecificity diminishes or disappears, with both *cis* and *trans* isomers giving predominantly and exclusively the product where the incoming oxygen is *syn* to the OH group. This probably indicates a transition state in which there is hydrogen bonding between the OH group and the peroxyacid.[1931]

Although *cis-trans* isomerization of epoxides is not formally associated with this section, it is a potential issue in the conversion of an alkene to an epoxide.

In general, in the absence of transition metal catalysts, peroxides (HOOH[1932] and ROOH) are poor reagents for epoxidation of simple alkenes since OH and OR are poor leaving groups in the concerted mechanism shown above.[1933] Epoxidation occurs with Fe,[1934] Re,[1935] Mn,[1936] Co,[1937] Ti,[1938] W/V,[1939] or V catalysts.[1940] Transition metal catalysts[1941] have been used with alkyl hydroperoxides.[1942] Epoxides can also be prepared by treating alkenes with oxygen or with an alkyl peroxide[1943] catalyzed by a complex of transition metals such as V, Mo, Ti, La,[1944] Y,[1945] or Co.[1946] In the presence of some other

[1929] Schneider, H.; Becker, N.; Philippi, K. *Chem. Ber.* ***1981***, *114*, 1562; Batog, A.E.; Savenko, T.V.; Batrak, T.A.; Kucher, R.V. *J. Org. Chem. USSR* ***1981***, *17*, 1860.

[1930] See Freccero, M.; Gandolfi, R.; Sarzi-Amade, M.; Rastelli, A. *J. Org. Chem.* ***2000***, *65*, 8948.

[1931] See Houk, K.N.; Liu, J.; DeMello, N.C.; Condroski, K.R. *J. Am. Chem. Soc.* ***1997***, *119*, 10147.

[1932] Arends, I.W.C.E. *Angew. Chem. Int. Ed.* ***2006***, *45*, 6250; Wang, C.; Yamamoto, H. *Chem. Asian J.* ***2015***, *10*, 2056. For the role of water, see Goldsmith, B.R.; Hwang, T.; Seritan, S.; Peters, B.; Scott, S.L. *J. Am. Chem. Soc.* ***2015***, *137*, 9604.

[1933] See Deubel, D.V.; Frenking, G.; Gisdakis, P.; Herrmann, W.A.; Rösch, N.; Sundermeyer, J. *Acc. Chem. Res.* ***2004***, *37*, 645.

[1934] Le Maux, P.; Srour, H.F.; Simonneaux, G. *Tetrahedron* ***2012***, *68*, 5824; Mikhalyova, E.A.;Makhlynets, O.V.; Palluccio, T.D.; Filatov, A.S.; Rybak-Akimova, E.V. *Chem. Commun.* ***2012***, *48*, 687.

[1935] Yamazaki, S. *J. Org. Chem.* ***2012***, *77*, 9884; De, S.R.; Kumar, G.; Jat, J.L.; Birudaraju, S.; Lu, B.; Manne, R.; Pulim, N.; Adebesin, A.M.; Falck, J.R. *J. Org. Chem.* ***2014***, *79*, 10323.

[1936] Dai, W.; Shang, S.; Chen, B.; Li, G.; Wang, L.; Ren, L.; Gao, S. *J. Org. Chem.* ***2014***, *79*, 6688; Shen, D.; Qiu, B.; Xu, D.; Miao, C.; Xia, C.; Sun, W. *Org. Lett.* ***2016***, *18*, 372; Moretti, R.A.; Du Bois, J.; Stack, T.D.P. *Org. Lett.* ***2016***, *18*, 2528; Krishnan, K.K.; Thomas, A.M.; Sindhu, K.S.; Anilkumar, G. *Tetrahedron* ***2016***, *72*, 1.

[1937] Hyun, M.Y.; Kim, S.H.; Song, Y.J.; Lee, H.G.; Jo, Y.D.; Kim, J.H.; Hwang, I.H.; Noh, J.Y.; Kang, J.; Kim C. *J. Org. Chem.* ***2012***, *77*, 7307.

[1938] See Talsi, E.P.; Samsonenko, D.G.; Bryliakov, K.P. *Chem. Eur. J.* ***2014***, *20*, 14329; Kim, J.; Chun, J.; Ryoo, R. *Chem. Commun.* ***2015***, *51*, 13102.

[1939] Kamata, K.; Sugahara, K.; Yonehara, K.; Ishimoto, R.; Mizuno, N. *Chem. Eur. J.* ***2011***, *17*, 7549.

[1940] Zeng, W.; Ballard, T.E.; Melander, C. *Tetrahedron Lett.* ***2006***, *47*, 5923. See Malkov, A.V.; Czemerys, L.; Malyshev, D.A. *J. Org. Chem.* ***2009***, *74*, 3350.

[1941] **La**: Nemoto, T.; Kakei, H.; Gnanadesikan, V.; Tosaki, S.-y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* ***2002***, *124*, 14544. **Mn**: Lane, B.S.; Vogt, M.; De Rose, V.T.; Burgess, K. *J. Am. Chem. Soc.* ***2002***, *124*, 11946. **Ti**: Lattanzi, A.; Iannece, P.; Screttri, A. *Tetrahedron Lett.* ***2002***, *43*, 5629. **Pd**: Yu, J.-Q.; Corey, E.J. *Org. Lett.* ***2002***, *4*, 2727. **Ru**: Adam, W.; Alsters, P.L.; Neumann, R.; Saha-Möller, C.; Sloboda-Rozner, D.; Zhang, R. *Synlett* ***2002***, 2011. **V**: Sharpless, K.B.; Verhoeven, T.R. *Aldrichimica Acta* ***1979***, *12*, 63; Torres, G.; Torres, W.; Prieto, J.A. *Tetrahedron* ***2004***, *60*, 10245.

[1942] Hiatt, R. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***, p. 124.

[1943] For example, see Laszlo, P.; Levart, M.; Singh, G.P. *Tetrahedron Lett.* ***1991***, *32*, 3167.

[1944] Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* ***2001***, *123*, 9474.

[1945] Kakei, H.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* ***2005***, *127*, 8962.

[1946] See Jørgensen, K.A. *Chem. Rev.* ***1989***, *89*, 431.

reagents,[1947] peroxides give good yields of the epoxide; such reagents include DCC,[1948] metalloporphyrins,[1949] and arsines in fluorous solvents.[1950] The Ti-catalyzed epoxidation of primary allylic alcohols using *gem*-dihydroperoxides proceeded with good enantioselectivity.[1951] The reaction of alkenes with 2,6-dichloropyridine-*N*-oxide and a Ru catalyst in the presence of HCl gave the epoxide.[1952] The Ru-catalyzed reaction of O_2 with conjugated alkenes gave the epoxide.[1953]

Several homogeneous and heterogeneous asymmetric epoxidation protocols have been developed.[1954] Enzymatic epoxidation[1955] and epoxidation with catalytic antibodies[1956] have been reported. Biomimetic epoxidation in aqueous media was catalyzed by cyclic dipeptides.[1957] The use of chiral additives leads to enantioselective epoxidation,[1958] and organocatalysts have been used as well.[1959] *Cinchona*-derived phase-transfer catalysts, initially used by Wynberg, are now common.[1960] Chiral hydroperoxides have been used for enantioselective epoxidation.[1961] Enantioselectivities can be significantly improved by changes of the catalyst structure as well as the type of oxidant.[1962] A biomimetic Fe catalyst has been used for the epoxidation of alkenes using molecular oxygen.[1963] The Fe-catalyzed asymmetric epoxidation of trisubstituted conjugated esters is known.[1964]

Other epoxidation methods are available. Dioxiranes,[1965] such as dimethyldioxirane (**51**, R = Me),[1966] either isolated or generated *in situ*,[1967] are important epoxidation reagents.

[1947] See Adam, W.; Curci, R.; Edwards, J.O. *Acc. Chem. Res.* ***1989***, *22*, 205; Miao, C.; Wang, B.; Wang, Y.; Xia, C.; Lee, Y.-M.; Nam, W.; Sun, W. *J. Am. Chem. Soc.* ***2016***, *138*, 936.

[1948] See Majetich, G.; Hicks, R.; Sun, G.-r.; McGill, P. *J. Org. Chem.* ***1998***, *63*, 2564.

[1949] Chan, W.-K.; Liu, P.; Yu, W.-Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* ***2004***, *6*, 1597.

[1950] van Vliet, M.C.A.; Arends, I.W.C.E.; Sheldon, R.A. *Tetrahedron Lett.* ***1999***, *40*, 5239.

[1951] Bunge, A.; Hamann, H.-J.; Dietz, D.; Liebscher, J. *Tetrahedron* ***2013***, *69*, 2446. See Matsumoto, K.; Feng, C.; Handa, S.; Oguma, T.; Katsuki, T. *Tetrahedron* ***2011***, *67*, 6474.

[1952] Ujwaldev, S.M.; Sindhu, K.S.; Thankachan, A.P.; Anilkumar, G. *Tetrahedron* ***2016***, *72*, 6175.

[1953] Koya, S.; Nishioka, Y.; Mizoguchi, H.; Uchida, T.; Katsuki, T. *Angew. Chem. Int. Ed.* ***2012***, *51*, 8243.

[1954] Xia, Q.-H.; Ge, H.-Q.; Ye, C.-P.; Liu, Z.-M.; Su, K.-X. *Chem. Rev.* ***2005***, *105*, 1603.

[1955] Kubo, T.; Peters, M.W.; Meinhold, P.; Arnold, F.H. *Chem. Eur. J.* ***2006***, *12*, 1216. For a method of electrochemical regeneration of monooxygenase, see Hollmann, F.; Hofstetter, K.; Habicher, T.; Hauer, B.; Schmid, A. *J. Am. Chem. Soc.* ***2005***, *127*, 6540.

[1956] Chen, Y.; Reymond, J.-L. *Synthesis* ***2001***, 934.

[1957] Bérubé, C.; Voyer, N. *Synth. Commun.* ***2016***, *46*, 395.

[1958] Wang, X.; Reisinger, C.M.; List, B. *J. Am. Chem. Soc.* ***2008***, *130*, 6070; Lu, X.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L. *J. Am. Chem. Soc.* ***2008***, *130*, 8134.

[1959] See Page, P.C.B.; Chan, Y.; Liddle, J.; Elsegood, M.R.J. *Tetrahedron* ***2014***, *70*, 7283.

[1960] See Pluim, H.; Wynberg, H. *J. Org. Chem.* ***1980***, *45*, 2498.

[1961] Košnik, W.; Bocian, W.; Kozerski, L.; Tvaroška, I.; Chmielewski, M. *Chem. Eur. J.* ***2008***, *14*, 6087.

[1962] Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* ***1999***, *55*, 6375; Corey, E.J.; Zhang, F.-Y. *Org. Lett.* ***1999***, *1*, 1287; Lygo, B.; Wainwright, P.G. *Tetrahedron* ***1999***, *55*, 6289. See Adam, W.; Rao, P.B.; Degen, H.-G.; Levai, A.; Patonay, T.; Saha-Moller, C.R. *J. Org. Chem.* ***2002***, *67*, 259.

[1963] Schröder, K.; Join, B.; Amali, A.J.; Junge, K.; Ribas, X.; Costas, M.; Beller, M. *Angew. Chem. Int. Ed.* ***2011***, *50*, 1425.

[1964] Luo, L.; Yamamoto, H. *Eur. J. Org. Chem.* ***2014***, 7803.

[1965] Murray, R.W. *Chem. Rev.* ***1989***, *89*, 1187; Adam, W.; Curci, R.; Edwards, J.O. *Acc. Chem. Res.* ***1989***, *22*, 205; Curci, R.; Dinoi, A.; Rubino, M.E. *Pure Appl. Chem.* ***1995***, *67*, 811; Denmark, S.E.; Wu, Z. *Synlett* ***1999***, 847; Annese, C.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Gandolfi, R.; Curci, R. *J. Am. Chem. Soc.* ***2008***, *130*, 1197.

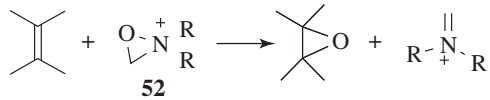
[1966] Frohn, M.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* ***1998***, *63*, 6425. See Angelis, Y.; Zhang, X.; Organopoulos, M. *Tetrahedron Lett.* ***1996***, *37*, 5991 for a discussion of the mechanism of this oxidation.

[1967] See Denmark, S.E.; Wu, Z. *J. Org. Chem.* ***1998***, *63*, 2810 and references cited therein; Masuyama, A.; Yamaguchi, T.; Abe, M.; Nojima, M. *Tetrahedron Lett.* ***2005***, *46*, 213.

51

With dimethyldioxirane, C—H insertion reactions can occur preferentially.[1968] The reaction with alkenes is rapid, mild, and safe, and a variety of methods have been developed using an oxidant as a co-reagent.[1969] Substituent effects in such reactions have been studied[1970] and also substrate variations.[1971]

The most commonly used co-reagent is probably potassium peroxomonosulfate ($KHSO_5$). Oxone ($2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$) is a common source of $KHSO_5$. Oxone reacts with ketones[1972] and sodium bicarbonate to convert an alkene to an epoxide. Oxone, with hydrogen peroxide or a similar oxidant, can be used with chiral ketones[1973] or chiral aldehydes to convert alkenes to chiral, nonracemic epoxides.[1974] This reaction probably converts alkenes to epoxides with good enantioselectivity by *in situ* generation of a dioxirane.[1975] This transformation with chiral carbohydrates is sometimes called *Shi epoxidation*.[1976] Chiral dioxiranes have reportedly given nonracemic epoxides.[1977]



52

Oxone oxidizes iminium salts to an oxaziridinium intermediate **52**, which can transfer oxygen to an alkene to form an epoxide and regenerate the iminium salt.[1978] Epoxidation does not occur in good yields with these reagents in most other solvents, and it is suggested that the active agent that generates dioxirane is peroxyimidic acid MeC(=NH)OOH.[1979] This variation has been applied to asymmetric[1980] epoxidations using chiral iminium salt precursors.[1981] Other asymmetric epoxidation reactions of alkenes use chiral ketones and

[1968] Adam, W.; Prechtl, F.; Richter, M.J.; Smerz, A.K. *Tetrahedron Lett.* ***1993***, *34*, 8427.
[1969] See Zou, L.; Paton, R.S.; Eschenmoser, A.; Newhouse, T.R.; Baran, P.S.; Houk, K.N. *J. Org. Chem.* ***2013***, *78*, 4037.
[1970] Düfert, A.; Werz, D.B. *J. Org. Chem.* ***2008***, *73*, 5514.
[1971] Nieto, N.; Munslow, I.J.; Fernández-Pérez, H.; Vidal-Ferran, A. *Synlett* ***2008***, 2856.
[1972] Limnios, D.; Kokotos, C.G. *J. Org. Chem.* ***2014***, *79*, 4270.
[1973] Shi, Y. *Acc. Chem. Res.* ***2004***, *37*, 488; Yang, D. *Acc. Chem. Res.* ***2004***, *37*, 497; Vega-Pérez, J.M.; Periñán, I.; Vega-Holm, M.; Palo-Nieto, C.; Iglesias-Guerra, F. *Tetrahedron* ***2011***, *67*, 7057; Vega-Pérez, J.M.; Vega-Holm, M.; Periñán, I.; Palo-Nieto, C.; Iglesias-Guerra, F. *Tetrahedron* ***2011***, *67*, 364.
[1974] See Denmark, S.E.; Matsuhashi, H. *J. Org. Chem.* ***2002***, *67*, 3479; Armstrong, A.; Ahmed, G.; Dominguez-Fernandez, B.; Hayter, B.R.; Wailes, J.S. *J. Org. Chem.* ***2002***, *67*, 8610; Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* ***2002***, *124*, 8792; Bez, G.; Zhao, C.-G. *Tetrahedron Lett.* ***2003***, *44*, 7403; Chan, W.-K.; Yu, W.-y.; Che, C.-M.; Wong, M.-K. *J. Org. Chem.* ***2003***, *68*, 6576.
[1975] Shu, L.; Shi, Y. *Tetrahedron Lett.* ***1999***, *40*, 8721. DFT modeling of the enantiomeric excess is discussed in Schneebeli, S.T.; Hall, M.L.; Breslow, R.; Friesner, R. *J. Am. Chem. Soc.* ***2009***, *131*, 3965.
[1976] Shi, Y. *Acc. Chem. Res.* ***2004***, *37*, 488; Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci. USA* ***2004***, *101*, 5794.
[1977] Burke, C.P.; Shi, Y. *Angew. Chem. Int. Ed.* ***2006***, *45*, 4475.
[1978] See Bohé, L.; Kammoun, M. *Tetrahedron Lett.* ***2004***, *45*, 747.
[1979] Arias, L.A.; Adkins, S.; Nagel, C.J.; Bach, R.D. *J. Org. Chem.* ***1983***, *48*, 888.
[1980] See Washington, I.; Houk, K.N. *J. Am. Chem. Soc.* ***2000***, *122*, 2948.
[1981] See Jacobson, E.N. in Ojima, I. *Catalytic Asymmetric Synthesis*, VCH, NY, ***1993***, pp. 159–203; Farah, M.M.; Page, P.C.B.; Buckley, B.R.; Blacker, A.J.; Elsegood, M.R.J. *Tetrahedron* ***2013***, *69*, 758.

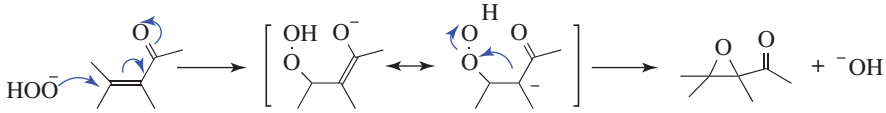
iminium salts with an organocatalyst.[1982] Direct epoxidation of alkenes has been done using oxaziridinium salts.[1983]

It would be useful if triple bonds could be similarly epoxidized to give oxirenes, but they are not stable compounds.[1984]

Oxirene

Two oxirenes have been trapped in solid argon matrices at very low temperatures, but they decayed upon warming to 35 K.[1985] Oxirenes probably form in the reaction,[1986] but react quickly before they can be isolated. Note that oxirenes are expected to be antiaromatic (Sec. 2.B and 2.K.ii).

Conjugated dienes can be epoxidized (1,2-addition), although the reaction is slower than for corresponding alkenes, but α,β-unsaturated ketones do not generally give epoxides when treated with peroxyacids.[1987] α,β-Unsaturated compounds can be epoxidized by alkyl hydroperoxides and a base,[1988] or with H_2O_2 and a base,[1989] or heteropoly acids.[1990] The epoxidation of α,β-unsaturated ketones with hydrogen peroxide under basic conditions, which involves attack by HO_2^-,[1991] is known as the *Waits-Scheffer epoxidation* and was discovered in 1921.[1992] This reaction has been extended to α,β-unsaturated ketones, aldehydes, and sulfones.[1993]



The reaction has been carried out with LiOH and polymer-bound quaternary ammonium salts.[1994] A Yb/BINOL complex with *t*-BuOOH led to epoxidation of conjugated ketones with high asymmetric induction,[1995] as did a mixture of NaOCl and a *Cinchona*

[1982] Wong, O.A.; Shi, Y. *Chem. Rev.* ***2008***, *108*, 3958; Page, P.C.B.; Buckley, B.R.; Farah, M.M.; Blacker, A.J. *Eur. J. Org. Chem.* ***2009***, 3413.
[1983] Biscoe, M.R.; Breslow, R. *J. Am. Chem. Soc.* ***2005***, *127*, 10812.
[1984] See Lewars, E.G. *Chem. Rev.* ***1983***, *83*, 519.
[1985] Torres, M.; Bourdelande, J.L.; Clement, A.; Strausz, O.P. *J. Am. Chem. Soc.* ***1983***, *105*, 1698. See also, Laganis, E.D.; Janik, D.S.; Curphey, T.J.; Lemal, D.M. *J. Am. Chem. Soc.* ***1983***, *105*, 7457.
[1986] Ibne-Rasa, K.M.; Pater, R.H.; Ciabattoni, J.; Edwards, J.O. *J. Am. Chem. Soc.* ***1973***, *95*, 7894; Ogata, Y.; Sawaki, Y.; Inoue, H. *J. Org. Chem.* ***1973***, *38*, 1044.
[1987] See, however, Hart, H.; Verma, M.; Wang, I. *J. Org. Chem.* ***1973***, *38*, 3418. For diiron catalysis, see Marchi-Delapierre, C.; Jorge-Robin, A.; Thibon, A.; Ménage, S. *Chem. Commun.* ***2007***, 1166.
[1988] See Arai, S.; Tsuge, H.; Oku, M.; Miura, M.; Shioiri, T. *Tetrahedron* ***2002***, *58*, 1623; Honma, T.; Nakajo, M.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* ***2002***, *43*, 6229.
[1989] See Marigo, M.; Franzén, J.; Poulsen, T.B.; Zhuang, W.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2005***, *127*, 6964.
[1990] Oguchi, T.; Sakata, Y.; Takeuchi, N.; Kaneda, K.; Ishii, Y.; Ogawa, M. *Chem. Lett.* ***1989***, 2053.
[1991] Apeloig, Y.; Karni, M.; Rappoport, Z. *J. Am. Chem. Soc.* ***1983***, *105*, 2784. See Patai, S.; Rappoport, Z. in Patai, S. *The Chemistry of Alkenes*, pt. 1, Wiley, NY, ***1964***, pp. 512–517.
[1992] Weitz, E.; Scheffer, A. *Ber. Dtsch. Chem. Ges.* ***1921***, *54*, 2327. See Enders, D.; Zhu, J.; Raabe, G. *Angew. Chem. Int. Ed.* ***1996***, *35*, 1725.
[1993] See Zwanenburg, B.; ter Wiel, J. *Tetrahedron Lett.* ***1970***, 935.
[1994] Anand, R.V.; Singh, V.K. *Synlett* ***2000***, 807.
[1995] Watanabe, S.; Arai, T.; Sasai, H.; Bougauchi, M.; Shibasaki, M. *J. Org. Chem.* ***1998***, *63*, 8090.

alkaloid.[1996] The asymmetric epoxidation of conjugated carbonyl compounds used a *Cinchona* primary amine catalyst with H_2O_2.[1997] The asymmetric bio-epoxidation of enones has been reported,[1998] and the asymmetric epoxidation of alkenes has been achieved using flow conditions (Sec. 7.D).[1999] β,β-Disubstituted enones have been epoxidized with good enantioselectivity using an Fe catalyst.[2000]

Another important asymmetric epoxidation of a conjugated system is the reaction of alkenes with poly(leucine),[2001] DBU, and urea/H_2O_2, giving an epoxy carbonyl compound with good enantioselectivity.[2002] The hydroperoxide anion epoxidation of conjugated carbonyl compounds with a polyamino acid such as poly-L-alanine or poly-L-leucine is known as the *Juliá-Colonna epoxidation*.[2003] Epoxidation of conjugated ketones to give nonracemic epoxy ketones was done with aq. NaOCl and a *Cinchona* alkaloid derivative as catalyst.[2004] β-Peptides have been used as catalysts in this reaction.[2005]

When a carbonyl group is elsewhere in the molecule but not conjugated with the double bond, the *Baeyer-Villiger reaction* (**18-19**) may compete. Allenes[2006] are converted by peroxyacids to allene oxides[2007] or spiro dioxides, both of which species can in certain cases be isolated[2008] but more often are unstable under the reaction conditions and react further to give other products.[2009]

Allylic alcohols can be converted to epoxy alcohols with *tert*-butylhydroperoxide on molecular sieves,[2010] or with peroxyacids.[2011] Asymmetric epoxidation using a Ti catalyst has been reported.[2012] The addition of an appropriate chiral ligand to the metal-catalyzed hydroperoxide epoxidation of allylic alcohols leads to high enantioselectivity. This important modification is known as the *Sharpless asymmetric epoxidation*,[2013] where *allylic alcohols are converted to optically active epoxides* with excellent enantioselectivity by treatment with *t*-BuOOH, titanium tetraisopropoxide, and optically active diethyl

[1996] Lygo, B.; Wainwright, P.G. *Tetrahedron Lett.* ***1998***, *39*, 1599.
[1997] Lifchits, O.; Mahlau, M.; Reisinger, C.M.; Lee, A.; Farès, C.; Polyak, I.; Gopakumar, G.; Thiel, W.; List, B. *J. Am. Chem. Soc.* ***2013***, *135*, 6677.
[1998] Liu, Y.-C.; Wu, Z.-L. *Chem. Commun.* ***2016***, *52*, 1158.
[1999] Dai, W.; Mi, Y.; Lv, Y.; Shang, S.; Li, G.; Chen, G.; Gao, S. *Synthesis* ***2016***, *48*, 2653.
[2000] Nishikawa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* ***2011***, *133*, 8432.
[2001] For a mechanistic discussion of polypeptide-catalyzed epoxidation, see Mathew, S.P.; Gunathilagan, S.; Roberts, S.M.; Blackmond, D.G. *Org. Lett.* ***2005***, *7*, 4847.
[2002] Bentley, P.A.; Bickley, J.F.; Roberts, S.M.; Steiner, A. *Tetrahedron Lett.* ***2001***, *42*, 3741; Cussó, O.; Garcia-Bosch, I.; Ribas, X.; Lloret-Fillol, J.; Costas, M. *J. Am. Chem. Soc.* ***2013***, *135*, 14871.
[2003] For reviews, see Lin, P. *Tetrahedron: Asymmetry* ***1998***, *9*, 1457; Ebrahim, S.; Wills, M. *Tetrahedron: Asymmetry* ***1997***, *8*, 3163. Also see Demizu, Y.; Yamagata, N.; Nagoya, S.; Sato, Y.; Doi, M.; Tanaka, M.; Nagasawa, K.; Okuda, H.; Kurihara, M. *Tetrahedron* ***2011***, *67*, 6155.
[2004] Lygo, B.; Wainwright, P.G. *Tetrahedron* ***1999***, *55*, 6289.
[2005] Coffey, P.E.; Drauz, K.-H.; Roberts, S.M.; Skidmore, J.; Smith, J.A. *Chem. Commun.* ***2001***, 2330.
[2006] See Jacobs, T.L. in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, pp. 417–510, 483–491.
[2007] For a review of allene oxides, see Chan, T.H.; Ong, B.S. *Tetrahedron* ***1980***, *36*, 2269.
[2008] Crandall, J.K.; Batal, D.J. *J. Org. Chem.* ***1988***, *53*, 1338.
[2009] See Crandall, J.K.; Rambo, E. *J. Org. Chem.* ***1990***, *55*, 5929.
[2010] Antonioletti, R.; Bonadies, F.; Locati, L.; Scettri, A. *Tetrahedron Lett.* ***1992***, *33*, 3205.
[2011] Fringuelli, F.; Germani, R.; Pizzo, F.; Santinelli, F.; Savelli, G. *J. Org. Chem.* ***1992***, *57*, 1198.
[2012] Wang, C.; Yamamoto, H. *J. Am. Chem. Soc.* ***2014***, *136*, 1222.
[2013] See Pfenninger, A. *Synthesis* ***1986***, 89; Rossiter, B.E. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, pp. 193–246. For histories of its discovery, see Sharpless, K.B. *Chem. Br.* ***1986***, 38. Also see, Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 261–264; Heravi, M.M.; Lashaki, T.B.; Poorahmad, N. *Tetrahedron: Asymmetry* ***2015***, *26*, 405.

tartrate.[2014] Since the allylic alcohol moiety is necessary for binding to the catalyst, asymmetric induction with nonallylic alcohols is poor to nonexistent. The $Ti(O\textit{i}\text{-}Pr)_4$ and diethyl tartrate can be present in catalytic amounts (15–10 mol %) if molecular sieves are present.[2015] The use of a tartrate-PEG reagent (PEG_{350} or PEG_{750}) allows generation of both enantiomers.[2016] Both (+)- and (−)-diethyl tartrate are readily available, so either enantiomer of the product can be prepared.

Epoxidation has been successful for a wide range of primary allylic alcohols, including substrates where the double bond is mono-, di-, tri-, and tetrasubstituted,[2017] and is highly useful in natural product synthesis. The mechanism of the Sharpless epoxidation is believed to involve reaction of the substrate with a complex[2018] formed from titanium alkoxide and diethyl tartrate that also contains the substrate and the *t*-BuOOH.[2019]

Homoallylic alcohols have been converted to the epoxide, however, using a V catalyst in the presence of a chiral bis(hydroxyamide).[2020] Simple alkenes can be epoxidized enantioselectively with sodium hypochlorite (NaOCl, commercial bleach) and an optically active manganese complex catalyst.[2021] Apart from the commonly used NaOCl, urea/H_2O_2 has been used.[2022]

The use of a manganese/salen complex[2023] with various oxidizing agents, in what is called the *Jacobsen-Katsuki reaction*,[2024] converts simple alkenes to the corresponding epoxide with high enantioselectivity.[2025] In addition to Mn, Cr/salen complexes,[2026] Ti/salen complexes,[2027] and Ru/salen complexes[2028] have been used for epoxidation.[2029] Note that salen ligands are based on salen, which is 2,2′-ethylenebis(nitrilomethylidene) diphenol. The mechanism of this reaction has been examined.[2030] Radical intermediates

[2014] Sharpless, K.B.; Woodard, S.S.; Finn, M.G. *Pure Appl. Chem.* ***1983***, *55*, 1823 and references cited therein.

[2015] Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1987***, *109*, 5765. See Massa, A.; D'Ambrosi, A.; Proto, A.; Screttri, A. *Tetrahedron Lett.* ***2001***, *42*, 1995. For another improvement, see Wang, Z.; Zhou, W. *Tetrahedron* ***1987***, *43*, 2935.

[2016] Reed, N.N.; Dickerson, T.J.; Boldt, G.E.; Janda, K.D. *J. Org. Chem.* ***2005***, *70*, 1728.

[2017] See the table in Finn, M.G.; Sharpless, K.B. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, pp. 249–250. See also, Schweiter, M.J.; Sharpless, K.B. *Tetrahedron Lett.* ***1985***, *26*, 2543.

[2018] Williams, I.D.; Pedersen, S.F.; Sharpless, K.B.; Lippard, S.J. *J. Am. Chem. Soc.* ***1984***, *106*, 6430.

[2019] See Finn, M.G.; Sharpless, K.B. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, p. 247. Also see Takano, S.; Iwebuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* ***1991***, *113*, 2786; Cui, M.; Adam, W.; Shen, J.H.; Luo, X.M.; Tan, X.J.; Chen, K.X.; Ji, R.Y.; Jiang, H.L. *J. Org. Chem.* ***2002***, *67*, 1427.

[2020] Noji, M.; Kobayashi, T.; Uechi, Y.; Kikuchi, A.; Kondo, H.; Sugiyama, S.; Ishii, K. *J. Org. Chem.* ***2015***, *80*, 3203.

[2021] Jacobsen, E.N.; Zhang, W.; Muci, A.R.; Ecker, J.R.; Deng, L. *J. Am. Chem. Soc.* ***1991***, *113*, 7063. See also, Halterman, R.L.; Jan, S. *J. Org. Chem.* ***1991***, *56*, 5253.

[2022] Kureshy, R.I.; Khan, N.H.; Abdi, S.H.R.; Patel, S.T.; Jasra, R.V. *Tetrahedron: Asymmetry* ***2001***, *12*, 433.

[2023] Wu, M.; Wang, B.; Wang, S.; Xia, C.; Sun, W. *Org. Lett.* ***2009***, *11*, 3622. See Adam, W.; Mock-Knoblauch, C.; Saha-Moller, C.R.; Herderich, M. *J. Am. Chem. Soc.* ***2000***, *122*, 9685.

[2024] Brandes, B.D.; Jacobsen, E.N. *Tetrahedron Lett.* ***1995***, *36*, 5123; Nishikori, H.; Ohta, C.; Katsuki, T. *Synlett* ***2000***, 1557. See Fristrup, P.; Dideriksen, B.B.; Tanner, D.; Norrby, P.-O. *J. Am. Chem. Soc.* ***2005***, *127*, 13672. See Kürti, L.; Blewett, M.M.; Corey, E.J. *Org. Lett.* ***2009***, *11*, 4592.

[2025] See Nishida, T.; Miyafuji, A.; Ito, Y.N.; Katsuki, T. *Tetrahedron Lett.* ***2000***, *41*, 7053.

[2026] Daly, A.M.; Renehan, M.F.; Gilheany, D.G. *Org. Lett.* ***2001***, *3*, 663; O'Mahony, C.P.; McGarrigle, E.M.; Renehan, M.F.; Ryan, K.M.; Kerrigan, N.J.; Bousquet, C.; Gilheany, D.G. *Org. Lett.* ***2001***, *3*, 3435. See the references cited therein.

[2027] Matsumoto, K.; Oguma, T.; Katsuki, T. *Angew. Chem. Int. Ed.* ***2009***, *48*, 7432.

[2028] Nakata, K.; Takeda, T.; Mihara, J.; Hamada, T.; Irie, R.; Katsuki, T. *Chem. Eur. J.* ***2001***, *7*, 3776.

[2029] McGarrigle, E.M.; Gilheany, D.G. *Chem. Rev.* ***2005***, *105*, 1563.

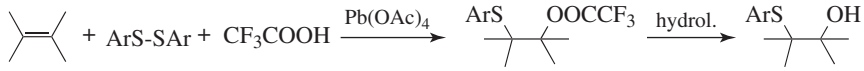
[2030] See Linker, T. *Angew. Chem. Int. Ed.* ***1997***, *36*, 2060; Adam, W.; Roschmann, K.J.; Saha-Möller, C.R. *Eur. J. Org. Chem.* ***2000***, 3519. Also see Cavallo, L.; Jacobsen, H. *J. Org. Chem.* ***2003***, *68*, 6202.

have been suggested for this reaction.[2031] Both Mn porphyrin complexes[2032] and Co complexes[2033] have been used for asymmetric epoxidation.

Thiiranes can be prepared directly from alkenes using specialized reagents.[2034] Thiourea with a Sn catalyst gives the thiirane, for example.[2035] Interestingly, internal alkynes were converted to 1,2-dichorothiiranes by reaction with S_2Cl_2 (sulfur monochloride).[2036] It is noted that epoxides are converted to thiiranes with ammonium thiocyanate and a Ce complex.[2037] A *trans*-thiiration reaction occurs with a Mo catalyst, in which an alkene reacts with styrene thiirane to give the new thiirane.[2038]

OS **I**, 494; **IV**, 552, 860; **V**, 191, 414, 467, 1007; **VI**, 39, 320, 679, 862; **VII**, 121, 126, 461; **VIII**, 546; **IX**, 288; **X**, 29; **80**, 9.

15-47 Hydroxysulfenylation (Addition of Oxygen, Sulfur)



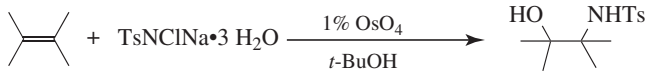
Both a hydroxy group and an aryl thio group are added to a double bond by treatment with an aryl disulfide and lead tetraacetate in the presence of trifluoroacetic acid.[2039] Manganese and copper acetates have been used instead of $Pb(OAc)_4$.[2040] Addition of the groups OH and RSO has been achieved by treatment of alkenes with O_2 and a thiol RSH.[2041] Addition of RS groups to give *vic*-dithiols was observed by treatment of the alkene with a disulfide (RSSR) and BF_3 etherate.[2042] This reaction has been carried out intramolecularly.[2043] In a similar manner, the reaction of alkenes with ceric ammonium nitrate and diphenyl diselenide in methanol leads to vicinally substituted phenylselenyl methyl ethers.[2044] Dimethyl diselenide adds to alkenes to form vicinal bis-methylselenyl compounds in the presence of tin tetrachloride.[2045]

The reaction of styrene derivatives and aryl thiols with a *t*-BuOOH catalyst and exposure to air gave the corresponding vicinal aryl thio alcohol.[2046] Aryl thiols reacted with terminal

[2031] Cavallo, L.; Jacobsen, H. *Angew. Chem. Int. Ed.* ***2000***, *39*, 589.
[2032] Konishi, K.; Oda, K.; Nishida, K.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* ***1992***, *114*, 1313.
[2033] Takai, T.; Hata, E.; Yorozu, K.; Mukaiyama, T. *Chem. Lett.* ***1992***, 2077.
[2034] Adam, W.; Bargon, R.M. *Eur. J. Org. Chem.* ***2001***, 1959; See Sugihara, Y.; Onda, K.; Sato, M.; Suzu, T. *Tetrahedron Lett.* ***2010***, *51*, 4110.
[2035] Tangestaninejad, S.; Mirkhani, V. *Synth. Commun.* ***1999***, *29*, 2079.
[2036] Nakayama, J.; Takahashi, K.; Watanabe, T.; Sugihara, Y.; Ishii, A. *Tetrahedron Lett.* ***2000***, 41, 8349.
[2037] Iranpoor, N.; Tamami, B.; Shekarriz, M. *Synth. Commun.* ***1999***, *29*, 3313.
[2038] Adam, W.; Bargon, R.M.; Schenk, W.A. *J. Am. Chem. Soc.* ***2003***, *125*, 3871.
[2039] Trost, B.M.; Ochiai, M.; McDougal, P.G. *J. Am. Chem. Soc.* ***1978***, *100*, 7103; see Zefirov, N.S.; Zyk, N.V.; Kutateladze, A.G.; Kolbasenko, S.I.; Lapin, Yu.A. *J. Org. Chem. USSR* ***1986***, *22*, 190.
[2040] See Samii, Z.K.M.A.E.; Ashmawy, M.I.A.; Mellor, J.M. *Tetrahedron Lett.* ***1986***, *27*, 5289.
[2041] Chung, M.; D'Souza, V.T.; Szmant, H.H. *J. Org. Chem.* ***1987***, *52*, 1741 and other papers in this series.
[2042] Inoue, H.; Murata, S. *Heterocycles* ***1997***, *45*, 847.
[2043] Tuladhar, S.M.; Fallis, A.G. *Tetrahedron Lett.* ***1987***, *28*, 523. See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 905–908.
[2044] Bosman, C.; D'Annibale, A.; Resta, S.; Trogolo, C. *Tetrahedron Lett.* ***1994***, *35*, 6525. See Ogawa, A.; Tanaka, H.; Yokoyama, H.; Obayashi, R.; Yokoyama, K.; Sonoda, N. *J. Org. Chem.* ***1992***, *57*, 111.
[2045] Hermans, B.; Colard, N.; Hevesi, L. *Tetrahedron Lett.* ***1992***, *33*, 4629.
[2046] Zhou, S.-F.; Pan, X.; Zhou, Z.-H.; Shoberu, A.; Zou, J.-P. *J. Org. Chem.* ***2015***, *80*, 3682.

alkynes and a catalytic amount of water and *t*-BuOOH to give the phenyl thioenol that tautomerized to the α-phenyl thioaldehyde.[2047] Alkenes reacted with sodium arylsulfonates, a Ni catalyst, and aqueous acetic acid to give the β-hydroxy sulfone.[2048] The reaction of enones and aryl thiols in the presence of O_2, 2 equivalents of $PhCO_2H$, and a Cu catalyst gave β-aryl thio-α-hydroxy ketones.[2049] Styrene derivatives reacted with aryl thiols in the presence of I_2 in DMSO to give the β-hydroxy sulfide.[2050] The selenosulfonation of alkynes by reaction with tosylhydrazine, Ph_2Se_2, and 2 equivalents of $K_2S_2O_8$, catalyzed by copper, gave (*E*)-β-selenovinyl sulfones.[2051]

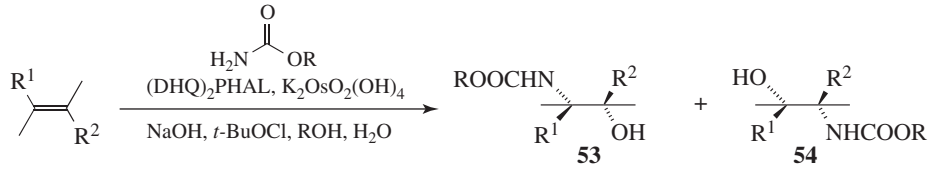
15-48 Oxyamination (Addition of Oxygen, Nitrogen)



N-Tosylated β-hydroxy alkylamines (which can be easily hydrolyzed to β-hydroxyamines[2052]) can be prepared[2053] by treatment of alkenes with the trihydrate of Chloramine-T (*N*-chloro-*p*-toluenesulfonamide, sodium salt)[2054] and a catalytic amount of OsO_4.[2055] In some cases, yields can be improved by the use of phase-transfer catalysis.[2056] The reaction has been carried out enantioselectively.[2057] Alkenes can be converted to amido alcohols enantioselectively by modification of this basic scheme. The *Sharpless asymmetric aminohydroxylation* employs a catalyst consisting of *Cinchona* alkaloid-derived ligands and an osmium species in combination with a stoichiometric nitrogen source that also functions as the oxidant.[2058] Bromamine-T has been used as the amine source.[2059] *N*-Chlorosulfonyl isocyanate has been used to prepare 1,2-amino alcohols.[2060] The Cu-catalyzed hydroxyamination of alkenes was reported using Boc-hydroxylamine.[2061] Carboxylic acids, alcohols, or amides that have a distal alkene unit reacted with $(PhSO_2)_2NPh$ in the presence of a Cu ligand to give the cyclic ether with an amidomethyl unit.[2062]

[2047] Zhou, S.-F.; Pan, X.-Q.; Zhou, Z.-H.; Shoberu, A.; Zhang, P.-Z.; Zou, J.-P. *J. Org. Chem.* ***2015***, *80*, 5348.
[2048] Taniguchi, N. *J. Org. Chem.* ***2015***, *80*, 7797.
[2049] Xi, H.; Deng, B.; Zong, Z.; Lu, S.; Li, Z. *Org. Lett.* ***2015***, *17*, 1180.
[2050] Tehri, P.; Aegurula, B.; Peddinti, R.K. *Tetrahedron Lett.* ***2017***, *58*, 2062.
[2051] Liu, Y.; Zheng, G.; Zhang, Q.; Li, Y.; Zhang, Q. *J. Org. Chem.* ***2017***, *82*, 2269.
[2052] See Bäckvall, J.E.; Oshima, K.; Palermo, R.E.; Sharpless, K.B. *J. Org. Chem.* ***1979***, *44*, 1953.
[2053] Sharpless, K.B.; Chong, A.O.; Oshima, K. *J. Org. Chem.* ***1976***, *41*, 177. See Rudolph, J.; Sennhenn, P.C.; Vlaar, C.P.; Sharpless, K.B. *Angew. Chem. Int. Ed.* ***1996***, *35*, 2810.
[2054] See Bremner, D.H. in Pizey, J.S. *Synthetic Reagents*, Vol. 6, Wiley, NY, ***1985***, pp. 9–59; Campbell, M.M.; Johnson, G. *Chem. Rev.* ***1978***, *78*, 65.
[2055] See Fokin, V.V.; Sharpless, K.B. *Angew. Chem. Int. Ed.* ***2001***, *40*, 3455.
[2056] Herranz, E.; Sharpless, K.B. *J. Org. Chem.* ***1978***, *43*, 2544.
[2057] Hassine, B.B.; Gorsane, M.; Pecher, J.; Martin, R.H. *Bull. Soc. Chim. Belg.* ***1985***, *94*, 759.
[2058] For a review, see Bodkin, J.A.; McLeod, M.D. *J. Chem. Soc., Perkin Trans. 1* ***2002***, 2733.
[2059] Borah, A.J.; Phukan, P. *Tetrahedron Lett.* ***2014***, *55*, 713.
[2060] Kim, J.D.; Kim, I.S.; Hua, J.C.; Zee, O.P.; Jung, Y.H. *Tetrahedron Lett.* ***2005***, *46*, 1079.
[2061] Kalita, B.; Nicholas, K.M. *Tetrahedron Lett.* ***2005***, *46*, 1451.
[2062] Xie, J.; Wang, Y.-W.; Qi, L.-W; Zhang, B. *Org. Lett.* ***2017***, *19*, 1148.

The reaction of a carbamate with $(DHQ)_2PHAL$ (**49**) and the osmium compound, with NaOH and *tert*-butyl hypochlorite, leads to a diastereomeric mixture of amido alcohols **53** and **54**, each formed with high enantioselectivity.[2063]



The aminohydroxylation of trisubstituted and 1,1-disubstituted alkenes with benzoyloxycarbamate and a OsO_4 catalyst gave the more-substituted alcohol isomer.[2064] An organocatalytic reaction has been reported.[2065] An enantioselective aminohydroxylation of acrylamides has been reported.[2066] The Cu-catalyzed reaction of protected β-aryl enamines with PhI=NNs and an alcohol gave the *syn* β-alkoxydiamine.[2067] The Mn reaction is also known.[2068]

In general, the nitrogen adds to the less sterically hindered carbon of the alkene to give the major product. *N*-Bromo amides, in the presence of a catalytic amount of $(DHQ)_2PHAL$ and LiOH, converts conjugated esters to β-amido-α-hydroxy esters with good enantioselectivity.[2069] Another oxyamination reaction involves treatment of a Pd complex of the alkene with a secondary or primary amine, followed by lead tetraacetate or another oxidant.[2070]

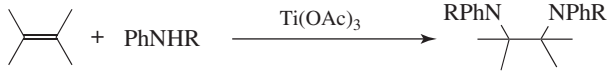
An organolanthanide-catalyzed alkene hydroamination has been reported.[2071] With this approach, amino alkenes (not enamines) can be cyclized to form cyclic amines,[2072] and amino alkynes lead to cyclic imines.[2073] The use of synthesized C-1[2074] and C-2 symmetric[2075] chiral organolanthanide complexes give the amino alcohol with good enantioselectivity. β-Amino alcohols can be prepared by treatment of an alkene with a reagent prepared from HgO and HBF_4 along with aniline to give an aminomercurial compound PhHN—C—C—$HgBF_4$ (aminomercuration; see **15-7**), which is hydrolyzed to PhHN—C—C—OH.[2076] The use of an alcohol instead of water gives the corresponding amino ether. β-Azido alcohols are prepared by the reaction of an alkene with $Me_3SiOOSiMe_3$, Me_3SiN_3, and 20% $(Cl_2SnO)_n$, followed by treatment with aqueous acetic acid.[2077]

[2063] Li, G.; Chang, H.-T.; Sharpless, K.B. *Angew. Chem. Int. Ed.* ***1996***, *35*, 451.
[2064] Ma, Z.; Naylor, B.C.; Loertscher, B.M.; Hafen, D.D.; Li, J.M.; Castle, S.L. *J. Org. Chem.* ***2012***, *77*, 1208. See Masruri, Willis, A.C.; McLeod, M.D. *J. Org. Chem.* ***2012***, *77*, 8480.
[2065] Cruz, D.C.; Sánchez-Murcia, P.A.; Jørgensen, K.A. *Chem. Commun.* ***2012***, *48*, 6112.
[2066] Streuff, J.; Osterath, B.; Nieger, M.; Muñiz, K. *Tetrahedron: Asymmetry* ***2005***, *16*, 3492.
[2067] Nakanishi, M.; Minard, C.; Retailleau, P.; Cariou, K.; Dodd, R.H. *Org. Lett.* ***2011***, *13*, 5792.
[2068] Zhang, G.-Y.; Li, C.K.; Li, D.-P.; Zeng, R.-S.; Shoberu, A.; Zou, J.-P. *Tetrahedron* ***2016***, *72*, 2972.
[2069] Demko, Z.P.; Bartsch, M.; Sharpless, K.B. *Org. Lett.* ***2000***, *2*, 2221.
[2070] Bäckvall, J.E.; Björkman, E.E. *Acta Chem. Scand. Ser. B* ***1984***, *38*, 91.
[2071] Ryu, J.-S.; Li, G.Y.; Marks, T.J. *J. Am. Chem. Soc.* ***2003***, *125*, 12584. For a review, see Hong, S.; Marks, T.J. *Acc. Chem. Res.* ***2004***, *37*, 673.
[2072] Gagné, M.R.; Stern, C.L.; Marks, T.J. *J. Am. Chem. Soc.* ***1992***, *114*, 275.
[2073] Li, Y.; Marks, T.J. *J. Am. Chem. Soc.* ***1998***, *120*, 1757.
[2074] See Douglass, M.R.; Ogasawara, M.; Hong, S.; Metz, M.V.; Marks, T.J. *Organometallics* ***2002***, *21*, 283.
[2075] Hong, S.; Tian, S.; Metz, M.V.; Marks, T.J. *J. Am. Chem. Soc.* ***2003***, *125*, 14768.
[2076] Barluenga, J.; Alonso-Cires, L.; Asensio, G. *Synthesis* ***1981***, 376.
[2077] Sakurada, I.; Yamasaki, S.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* ***2000***, *41*, 2415.

The amidoselenation and the amidotelluration reactions of alkenes used oxygen as an oxidant.[2078] The acetoxyphosphorylation of styrene was mediated by manganese.[2079] The Cu/Fe-mediated oxyphosphorylation of terminal alkynes gave the corresponding β-ketophosphonate.[2080]

OS **VII**, 223, 375.

15-49 Diamination (Addition of Nitrogen, Nitrogen)



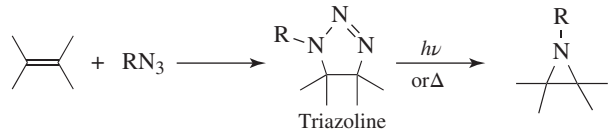
Two amine and/or two amide units can be added to a C=C unit (diamination).[2081] Primary (R = H) and secondary aromatic amines react with alkenes in the presence of thallium(III) acetate to give *vic*-diamines in good yields.[2082] The reaction is not successful for primary aliphatic amines. In another procedure, alkenes can be diaminated by treatment with the Os compounds R_3NOsO (R = *t*-Bu) and R_2NOsO_2,[2083] analogous to the Os compound mentioned at **15-52**.[2084] The Pd-promoted method of **15-49** has also been extended to diamination.[2085] The Pd-catalyzed addition of saccharin and $H(NTs)_2$ with an alkene, in the presence of a hypervalent iodine oxidant, leads to a precursor that can be converted to a 1,2-diamine.[2086] Styrene derivatives reacted with $ArI(NTs)_2$ reagents to give the vicinal diamide derivative.[2087] The diamination of styrenes used a chiral hypervalent iodine(III) reagent as an oxidant and bis(mesylimide) as a nitrogen source.[2088] To achieve the diamination of buta-1,3-dienes, they were reacted with amines and a hypervalent iodine reagent to give the diamination product and, depending on the substrate, this reaction proceeds either with 1,2- or 1,4-regioselectivity.[2089]

Two azido groups can be added to double bonds by treatment with sodium azide and iodosobenzene in acetic acid:[2090]

$$C{=}C + NaN_3 + PhIO \rightarrow N_3{-}C{-}C{-}N_3$$

[2078] Sun, K.; Wang, X.; Zhang, C; Zhang, S.; Chen, Y.; Jiao, H.; Du, W. *Chem. Asian J.* ***2017***, *12*, 713.
[2079] Zhou, S.-F.; Li, D.-P.; Liu, K.; Zou, J.-P.; Asekun, O.T. *J. Org. Chem.* ***2015***, *80*, 1212.
[2080] Yi, N.; Wang, R.; Zou, H.; He, W.; Fu, W.; He, W. *J. Org. Chem.* ***2015***, *80*, 5023.
[2081] Jong, S.D.; Nosal, D.G.; Wardrop, D.J. *Tetrahedron* ***2012***, *68*, 4067. See Muñiz, K. *Pure Appl. Chem.* ***2013***, *85*, 755.
[2082] Gómez Aranda, V.; Barluenga, J.; Aznar, F. *Synthesis* ***1974***, 504.
[2083] Chong, A.O.; Oshima, K.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1977***, *99*, 3420. See also, Sharpless, K.B.; Singer, S.P. *J. Org. Chem.* ***1976***, *41*, 2504.
[2084] For a X-ray structure of the osmium intermediate, see Muñiz, K.; Iesato, A.; Nieger, M. *Chem. Eur. J.* ***2003***, *9*, 5581.
[2085] Bäckvall, J. *Tetrahedron Lett.* ***1978***, 163.
[2086] Iglesias, Á.; Pérez, E.G.; Muñiz, K. *Angew. Chem. Int. Ed.* ***2010***, *49*, 8109.
[2087] See Romero, R.M.; Souto, J.A.; Muñiz, K. *J. Org. Chem.* ***2016***, *81*, 6118. Also see Weng, S.S.; Hsieh, K.Y.; Zeng, Z.-J.; Zhang, J.-W. *Tetrahedron Lett.* ***2017***, *58*, 670.
[2088] Röben, C.; Souto, J.A.; González, Y.; Lishchynskyi, A.; Muñiz, K. *Angew. Chem. Int. Ed.* ***2011***, *50*, 9478.
[2089] Lishchynskyi, A.; Muñiz, K. *Chem. Eur. J.* ***2012***, *18*, 2212.
[2090] Moriarty, R.M.; Khosrowshahi, J.S. *Tetrahedron Lett.* ***1986***, *27*, 2809. See Fristad, W.E.; Brandvold, T.A.; Peterson, J.R.; Thompson, S.R. *J. Org. Chem.* ***1985***, *50*, 3647.

15-50 Formation of Aziridines (Addition of Nitrogen, Nitrogen)



Aziridines can be prepared directly from double bond compounds by photolysis or thermolysis of a mixture of the substrate and an azide.[2091] The reaction has been carried out with R = aryl, cyano, EtOOC, and RSO_2, as well as other groups. The reaction can take place by at least two pathways.

In one pathway, a 1,3-dipolar addition (**15-54**) takes place to give a triazoline (which can be isolated), followed by thermal extrusion of nitrogen (**17-32**). Evidence for the nitrene pathway is most compelling for R = acyl groups. In the other pathway, the azide is converted to a nitrene, which adds to the double bond in a manner analogous to that of carbene addition (**15-60**). Sulfonyloxy amines, such as $ArSO_2ONHCO_2Et$, form an aziridine when treated with CaO in the presence of a conjugated carbonyl compound,[2092] and nitrene precursors that have an attached chiral ester have been prepared.[2093] In the presence of Cu,[2094] Co,[2095] or Rh complexes,[2096] ethyl diazoacetate adds to imines to give aziridines. Diazirenes (Sec. 5.D.ii) with *n*-butyllithium converted conjugated amides to α,β-aziridino amides.[2097] The oxidation of hydrazine derivatives in the presence of alkenes gave the *N*-aminoaziridine derivative.[2098] Alkenes reacted with aryl azides in the presence of an Fe catalyst to give the aziridine.[2099] The reaction of alkenes with $TMSN_3$ and a Mn catalyst in the presence of air, followed by PPh_3, gave the corresponding azido alcohol.[2100] The conjugate addition of *N*-chloro-*N*-sodiocarbamates with conjugated carbonyl compounds that have a chiral auxiliary gave the *N*-acyl aziridine in the presence of a chiral ammonium salt.[2101]

Alkyl azides add to conjugated alkenes in the presence of an acid.[2102] Tosylamines react with alkenes in the presence of a Rh catalyst[2103] or with iodine/$PhI(OAc)_2$.[2104] Trichloroethylsulfamate esters react with $PhI(OAc)_2$ and a Rh catalyst to give the

[2091] See Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, ***1969***, pp. 68–79; Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***. See Singh, G.S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* ***2007***, *107*, 2080; Degennaro, L.; Trinchera, P.; Luisi, R. *Chem. Rev.* ***2014***, *114*, 7881. For a review of oxaziridines, see Williamson, K.S.; Michaelis, D.J.; Yoon, T.P. *Chem. Rev.* ***2014***, *114*, 8016.

[2092] Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P.A. *Synthesis* ***2001***, 1975. For an enantioselective version, see Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P.A. *J. Org. Chem.* ***2002***, *67*, 4972.

[2093] Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P.A. *Tetrahedron Lett.* ***2003***, *44*, 3031.

[2094] Sanders, C.J.; Gillespie, K.M.; Scott, P. *Tetrahedron: Asymmetry* ***2001***, *12*, 1055; Ma, J.-A.; Wang, L.-X.; Zhang, W.; Zhou, W.; Zhou, Q.-L. *Tetrahedron: Asymmetry* ***2001***, *12*, 2801.

[2095] Ikeno, T.; Nishizuka, A.; Sato, M.; Yamada, T. *Synlett* ***2001***, 406.

[2096] See Moran, M.; Bernardinelli, G.; Müller, P. *Helv. Chim. Acta* ***1995***, *78*, 2048.

[2097] Ishihara, H.; Ito, Y.N.; Katsuki, T. *Chem. Lett.* ***2001***, 984.

[2098] Kuznetsov, M.A.; Kuznetsova, L.M.; Pankova, A.S. *Tetrahedron Lett.* ***2016***, *57*, 3575.

[2099] Cramer, S.A.; Jenkins, D.M. *J. Am. Chem. Soc.* ***2011***, *133*, 19342.

[2100] Sun, X.; Li, X.; Song, S.; Zhu, Y.; Liang, Y.-F.; Jiao, N. *J. Am. Chem. Soc.* ***2015***, *137*, 6059.

[2101] Murakami, Y.; Takeda, Y.; Minakata, S. *J. Org. Chem.* ***2011***, *76*, 6277.

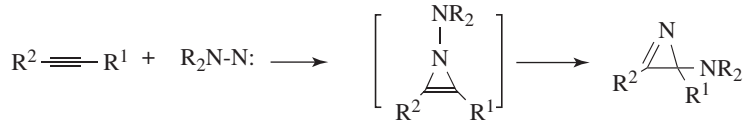
[2102] Mahoney, J.M.; Smith, C.R.; Johnston, J.N. *J. Am. Chem. Soc.* ***2005***, *127*, 1354.

[2103] Catino, A.J.; Nichols, J.M.; Forslund, R.E.; Doyle, M.P. *Org. Lett.* ***2005***, *7*, 2787.

[2104] Fan, R.; Pu, D.; Gan, J.; Wang, B. *Tetrahedron Lett.* ***2008***, *49*, 4925.

corresponding *N*-sulfonyl aziridine.[2105] Enantioselective aziridination of enones has been investigated.[2106] The formation of sulfonyl nitrene from *N*,*N*-dibromo-*p*-toluenesulfonamide ($TsNBr_2$) when treated with K_2CO_3 gave aziridines.[2107]

As discussed in Sec. 5.E, singlet nitrenes add stereospecifically while triplet nitrenes do not. Aminonitrenes (R_2NN:) have been shown to add to alkenes[2108] to give *N*-substituted aziridines and to triple bonds to give 1-azirines, which arise from rearrangement of the initially formed 2-azirines.[2109]



2-Azirine 1-Azirine

An electrocatalytic method for the preparation of aziridines has been reported by the reaction of alkenes with *N*-aminophthalimide, a catalytic amount of Bu_4NI, and $LiClO_4$ in ethanol.[2110]

1*H*-Azirines are unstable and tend to rearrange to the more stable 2*H*-azirine. 2*H*-Azirines are analogous to strained imines and can be reduced to give chiral aziridines.[2111] 2*H*-Azirines are commonly prepared by thermolysis of vinyl azides via formation of a nitrene.[2112] However, 1*H*-azirines are thought be short-lived intermediates, and the isoquinoline-catalyzed synthesis of 1*H*-azirines from phenacyl bromides and *N*,*N*′-dialkylcarbodiimides did not give the antiaromatic 1*H*-azirines, but rather *N*-acyl-*N*,*N*′-dialkylureas.[2113]

Chloramine-T and NBS also give the *N*-tosyl aziridine,[2114] while Bromamine-T ($TsNBr^- Na^+$)[2115] and TsNIK[2116] have also been used in a similar manner. Other sulfonamide reagents can be used.[2117] The reaction of alkenes and PhI=NTs,[2118] as well as other

[2105] See Espino, C.G.; Fiori, K.W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* ***2004***, *126*, 15378; Keaney, G.F.; Wood, J.L. *Tetrahedron Lett.* ***2005***, *46*, 4031; Guthikonda, K.; Wehn, P.M.; Caliando, B.J.; Du Bois, J. *Tetrahedron* ***2006***, *62*, 11331.

[2106] Armstrong, A.; Pullin, R.D.C.; Jenner, C.R.; Foo, K.; White, A.J.P.; Scutt, J.N. *Tetrahedron: Asymmetry* ***2014***, *25*, 74.

[2107] Saikia, I.; Kashyap, B.; Phukan, P. *Chem. Commun.* ***2011***, *47*, 2967.

[2108] Siu, T.; Yudin, A.K. *J. Am. Chem. Soc.* ***2002***, *124*, 530.

[2109] Anderson, D.J.; Gilchrist, T.L.; Rees, C.W. *Chem. Commun.* ***1969***, 147.

[2110] Chen, J.; Yan, W.-Q.; Lam, C.M.; Zeng, C.-C.; Hu, L.-M.; Little, R.D. *Org. Lett.* ***2015***, *17*, 986. See Yoshimura, A.; Middleton, K.R.; Zhu, C.; Nemykin, V.N.; Zhdankin, V.V. *Angew. Chem. Int. Ed.* ***2012***, *51*, 8059, 8183.

[2111] Roth, P.; Andersson, P.G.; Somfai, P. *Chem. Commun.* ***2002***, 1752.

[2112] Palacios, F.; Ochoa de Retana, A.M.; Martinez de Marigorta, E.; de los Santos, J.M. *Eur. J. Org. Chem.* ***2001***, 2401.

[2113] Banert, K.; Hagedorn, M.; Peisker, H. *Synlett* ***2012***, *23*, 2943.

[2114] Thakur, V.V.; Sudalai, A. *Tetrahedron Lett.* ***2003***, *44*, 989. See Wu, H.; Xu, L.-W.; Xia, C.-G.; Ge, J.; Yang, L. *Synth. Commun.* ***2005***, *35*, 1413; Karabal, P.U.; Chouthaiwale, P.V.; Shaikh, T.M.; Suryavanshi, G.; Sudalai, A. *Tetrahedron Lett.* ***2010***, *51*, 6460.

[2115] See Hayer, M.F.; Hossain, M.M. *J. Org. Chem.* ***1998***, *63*, 6839; Antunes, A.M.M.; Bonifácio, V.D.B.; Nascimento, S.C.C.; Lobo, A.M.; Branco, P.S.; Prabhakar, S. *Tetrahedron* ***2007***, *63*, 7009.

[2116] Jain, S.L.; Sain, B. *Tetrahedron Lett.* ***2003***, *44*, 575.

[2117] See Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* ***2002***, *124*, 13672. See also, Dichenna, P.H.; Robert-Peillard, F.; Dauban, P.; Dodd, R.H. *Org. Lett.* ***2004***, *6*, 4503.

[2118] See Vedernikov, A.N.; Caulton, K.G. *Org. Lett.* ***2003***, *5*, 2591; Cui, Y.; He, C. *J. Am. Chem. Soc.* ***2003***, *125*, 16202. See Nishimura, M.; Minakata, S.; Takahashi, T.; Oderaotoshi, Y.; Komatsu, M. *J. Org. Chem.* ***2002***, *67*, 2101.

nitrene precursors, with a Cu or Co catalyst, gave the aziridine with good enantioselectivity.[2119] Chloramine-T has been used in ionic liquids with a Cu[2120] or Pd[2121] catalyst and methyl trioxorhenium ($MeReO_3$) can be used in these reactions.[2122] Arylsulfonamides react with alkenes via the nitrene using an Au catalyst[2123] or a Cu catalyst.[2124] Diazoalkanes react with imines to give aziridines.[2125]

Aziridines were formed by the reaction of amino alcohols and $ClSO_3H$ followed by reaction with aqueous NaOH.[2126] Alkenes reacted with $ArI{=}NSO_2R$ using flow conditions (Sec. 7.D) to generate aziridines *in situ*, which then reacted with nucleophiles to give the sulfonamide derivative.[2127] Cyclic alkenes reacted with $Cl_3CCH_2OCON_3$ with an Ir catalyst and exposure to visible light to give the *N*-Troc aziridine.[2128] The Cu-catalyzed intramolecular hydroamination of hydroxylamine esters gave alkyl-substituted chiral aziridines.[2129] A Rh-catalyzed aziridination of alkenes used hydroxylamine-*O*-sulfonic acids as the nitrogen source.[2130]

The cation radical-induced cycloaddition of aryl imines and ethyl diazoacetate gave the aziridine.[2131] Organocatalysts have been used for the enantioselective aziridination of the C=C unit in conjugated aldehydes.[2132] The hydrozirconation of Boc-protected chiral allylic amines via reaction with $Cp_2Zr(H)Cl$ and then iodine, followed by reaction with NaHMDS, gave enantiomerically enriched *cis*-2,3-disubstituted azetidines.[2133] Nitrenes can also add to aromatic rings to give ring expansion products analogous to those mentioned in **15-58**.[2134]

OS **VI**, 56.

15-51 Aminosulfenylation (Addition of Nitrogen, Sulfur)

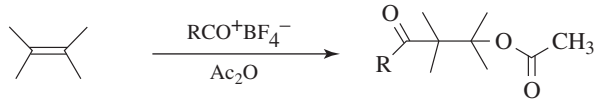
An amino group and an aryl thio group can be added to a double bond by treatment with a sulfenanilide (PhSNHAr) in the presence of BF_3-etherate.[2135] The addition is *anti*, and the mechanism probably involves a thiiranium ion. In another aminosulfenylation procedure,

[2119] Jung, N.; Bräse, S.; *Angew. Chem. Int. Ed.* ***2012***, *51*, 5538. See Gillespie, K.M.; Sanders, C.J.; O'Shaughnessy, P.; Westmoreland, I.; Thickitt, C.P.; Cott, P. *J. Org. Chem.* ***2002***, *67*, 3450.
[2120] Kantam, M.L.; Neeraja, V.; Kavita, B.; Haritha, Y. *Synlett* ***2004***, 525.
[2121] Antunes, A.M.M.; Marto, S.J.L.; Branco, P.S.; Prabhakar, S.; Lobo, A.M. *Chem. Commun.* ***2001***, 405.
[2122] Jean, H.-J.; Nguyen, S.B.T. *Chem. Commun.* ***2001***, 235.
[2123] Li, Z.; Ding, X.; He, C. *J. Org. Chem.* ***2006***, *71*, 5876.
[2124] Jain, S.L.; Sharma, V.B.; Sain, B. *Synth. Commun.* ***2005***, *35*, 9.
[2125] Casarrubios, L.; Pérez, J.A.; Brookhart, M.; Templeton, J.L. *J. Org. Chem.* ***1996***, *61*, 8358.
[2126] Buckley, B.R.; Patel, A.P.; Wijayantha, K.G.U. *J. Org. Chem.* ***2013***, *78*, 1289.
[2127] Hsueh, N.; Clarkson, G.J.; Shipman, M. *Org. Lett.* ***2016***, *18*, 4908.
[2128] Scholz, S.O.; Farney, E.P.; Kim, S.; Bates, D.M.; Yoon, T.P. *Angew. Chem. Int. Ed.* ***2016***, *55*, 2239. See Matsuzawa, K.; Nagasawa, Y.; Yamaguchi, E.; Tada, N.; Itoh, A. *Synthesis 2016*, *48*, 2845.
[2129] Wang, H.; Yang, J.C.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2017***, *139*, 8428.
[2130] Ma, Z.; Zhou, Z.; Kürti, L. *Angew. Chem. Int. Ed.* ***2017***, *56*, 9886.
[2131] Huo, C.; Sun, C.; Hu, D.; Jia, X.; Xu, X.; Liu, Z. *Tetrahedron Lett.* ***2011***, *52*, 7008.
[2132] Vesely, J.; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Córdova, A. *Angew. Chem. Int. Ed.* ***2007***, *46*, 778.
[2133] Pradhan, T.K.; Krishnan, K.S.; Vasse, J.-L.; Szymoniak, J. *Org. Lett.* ***2011***, *13*, 1793.
[2134] See Lwowski, W.; Johnson, R.L. *Tetrahedron Lett.* ***1967***, 891.
[2135] Benati, L.; Montavecchi, P.C.; Spagnolo, P. *Tetrahedron Lett.* ***1984***, *25*, 2039. See also, Brownbridge, P. *Tetrahedron Lett.* ***1984***, *25*, 3759.

the substrate is treated with dimethyl(methylthio)sulfonium fluoroborate (MeS^+SMe_2 BF_4^-) and ammonia or an amine,[2136] the latter acting as a nucleophile. This reaction was extended to other nucleophiles:[2137] N_3^-,[2138] NO_2^-, CN^-, ^-OH, and ^-OAc to give MeS—C—C—A, where A = N_3, NO_2, CN, OH, and OAc, respectively. An RS (R = alkyl or aryl) and an NHCOMe group have been added in an electrochemical procedure.[2139]

The Lewis basic selenophosphoramide catalyst and a Brønsted acid co-catalyst gave enantioselective, intramolecular sulfenoamination of anion derivatives with alkene substituents that led to indolines, tetrahydroquinolines, and tetrahydrobenzazepines with good enantioselectivity.[2140] The vicinal sulfonamination of alkynes gave 3-sulfonylindoles by the reaction of 2-alkynyl arylazides with sulfinic acids in the presence of *tert*-butyl hydroperoxide.[2141]

15-52 Acyloxylation, Acylthiolation, and Acylamidation (Addition of Oxygen–Carbon, Sulfur–Carbon, or Nitrogen–Carbon)



An acyl group and an acyloxy group can be added to a double bond by treatment with an acyl fluoroborate and acetic anhydride.[2142] As expected, the addition follows Markovnikov's rule, with the electrophile Ac^+ going to the carbon with more hydrogen atoms.

Mediated by Ar_2I^+ BF_4^- and an Ir catalyst with visible light, styrene derivatives reacted with alcohols to give the diaryl alcohol and reacted with nitriles to give the diaryl amide.[2143] The Cu-catalyzed 1,2-alkyl esterification of 1,3-dienes with diacyl peroxides gave branched allylic esters.[2144] Aryldiazonium salts reacted with styrene derivatives with KOAc in aqueous acetonitrile to give the diaryl alcohol.[2145] The reaction of alkenes with phthalimides and O_2 gave the *trans*-amido alcohol derivative[2146] whereas oxidation with $PhI(OAc)_2$ gave the *cis*-enamine.[2147]

In an analogous reaction, an acyl group and an amido group can be added to give a β-amido ketone, if a nitrile is used in place of the anhydride. Similarly, halo acetoxylation is known.[2148] Allenes reacted with anilines, CO, and methanol using $Cu(OCOEt)_2$ and a Pd catalyst to give the α-arylamino acrylate derivative.[2149] The intramolecular carboamination reaction of tosylamides with a distal alkene with Selectfluor and AgOTf with a Pd

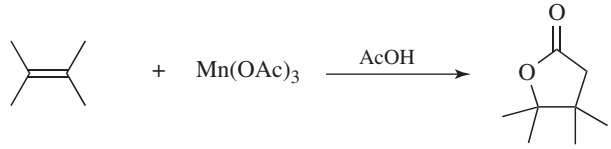
[2136] Trost, B.M.; Shibata, T. *J. Am. Chem. Soc.* ***1982***, *104*, 3225; Caserio, M.C.; Kim, J.K. *J. Am. Chem. Soc.* ***1982***, *104*, 3231.
[2137] See Trost, B.M.; Shibata, T.; Martin, S.J. *J. Am. Chem. Soc.* ***1982***, *104*, 3228.
[2138] Sreekumar, R.; Padmakumar, R.; Rugmini, P. *Chem. Commun.* ***1997***, 1133.
[2139] Bewick, A.; Coe, D.E.; Mellor, J.M.; Owton, M.W. *J. Chem. Soc., Perkin Trans. 1* ***1985***, 1033.
[2140] Denmark, S.E.; Chi, H.M. *J. Org. Chem.* ***2017***, *82*, 3826.
[2141] Chen, F.; Meng, Q.; Han, S.-Q.; Han, B. *Org. Lett.* ***2016***, *18*, 3330.
[2142] Shastin, A.V.; Balenkova, E.S. *J. Org. Chem. USSR* ***1984***, *20*, 870.
[2143] Fumagalli, G.; Boyd, S.; Greaney, M.F. *Org. Lett.* ***2013***, *15*, 4398.
[2144] Li, Y.; Han, Y.; Xiong, H.; Zhu, N.; Qian, B.; Ye, C.; Kantchev, E.A.B.; Bao, H. *Org. Lett.* ***2016***, *18*, 392.
[2145] Kindt, S.; Wicht, K.; Heinrich, M.R. *Angew. Chem. Int. Ed.* ***2016***, *55*, 8744.
[2146] See Wang, Z.; Kanai, M.; Kuninobu, Y. *Org. Lett.* ***2017***, *19*, 2398.
[2147] Martínez, C.; Wu, Y.; Weinstein, A.B.; Stahl, S.S.; Liu, G.; Muñiz, K. *J. Org. Chem.* ***2013***, *78*, 6309.
[2148] Hashem, Md.A.; Jung, A.; Ries, M.; Kirschning, A. *Synlett* ***1998***, 195.
[2149] Liu, J.; Han, Z.; Wang, X.; Wang, Z.; Ding, K. *J. Am. Chem. Soc.* ***2015***, *137*, 15346.

catalyst gave the 3-OCF_3-substituted piperidine.[2150] The Cu-catalyzed intramolecular reaction of *N*-allyl amidines using $PhI(OAc)_2$ as an oxygen source gave 4-acetoxymethyl-4,5-dihydroimidazoles.[2151] The Pd-catalyzed reaction of an halomethylamide that has a distal alkene unit gave intramolecular aminoalkylation of unactivated alkenes which led to the pyrrolidinone derivative.[2152]

Both γ-lactams and pyrrolidines were prepared by the irradiation of alkenes and activated unsaturated amides or protected unsaturated amines using a mesityl acridinium single-electron photooxidant and a thiophenol co-catalyst.[2153]

This reaction has also been carried out on triple bonds, via addition.[2154]

15-53 The Conversion of Alkenes or Alkynes to Lactones (Addition of Oxygen, Carbon)



This reaction is clearly related to forming esters and lactones[2155] by reaction of carboxylic acids with alkenes (**15-6**), but the Mn reagent leads to differences. Alkenes react with manganese(III) acetate to give γ-lactones.[2156] The mechanism is probably free radical, involving addition of $\bullet CH_2COOH$ to the double bond. Ultrasound improves the efficiency of the reaction.[2157] In a related reaction, cyclohexene reacted with $MeO_2CCH_2CO_2K$ and $Mn(OAc)_3$ to give an α-carbomethoxy bicyclic lactone.[2158] The use of dimethyl malonate and ultrasound in this reaction gave the same type of product.[2159] Lactone formation has also been accomplished by treatment of alkenes with α-bromo carboxylic acids in the presence of benzoyl peroxide as catalyst,[2160] and with alkylidene $Cr(CO)_5$ complexes.[2161] Cyclic dienes react with β-keto esters, in the presence of a Ga[2162] catalyst and water, to give an α-acyl bicyclic lactone.

The enantioselective cyclization of carboxylic acids with a distal alkene unit gave the corresponding lactone via radical formation by treatment with 2 equivalents of 2,6-di-*t*-butylpyridine, Cu catalyst, and, in a reaction with various electrophiles (including aryldiazonium salts), gave the aryl derivative.[2163] Xanthates were used in 5-*exo-trig*

[2150] Chen, C.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* ***2015***, *137*, 1564.
[2151] Sanjaya, S.; Chiba, S. *Org. Lett.* ***2012***, *14*, 5342.
[2152] Ye, L.; Lo, K.-Y.; Gu, Q.; Yang, D. *Org. Lett.* ***2017***, *19*, 308.
[2153] Gesmundo, N.J.; Grandjean, J.-M.M.; Nicewicz, D.A. *Org. Lett.* ***2015***, *17*, 1316.
[2154] Gridnev, I.D.; Balenkova, E.S. *J. Org. Chem. USSR* ***1988***, *24*, 1447.
[2155] See Mao, B.; Fañanás-Mastral, M.; Feringa, B.L. *Chem. Rev.* ***2017***, *117*, 10502.
[2156] Shundo, R.; Nishiguchi, I.; Matsubara, Y.; Hirashima, T. *Tetrahedron* ***1991***, *47*, 831. See also, Corey, E.J.; Gross, A.W. *Tetrahedron Lett.* ***1985***, *26*, 4291.
[2157] D'Annibale, A.; Trogolo, C. *Tetrahedron Lett.* ***1994***, *35*, 2083.
[2158] Lamarque, L.; Méou, A.; Brun, P. *Tetrahedron* ***1998***, *54*, 6497.
[2159] Allegretti, M.; D'Annibale, A.; Trogolo, C. *Tetrahedron* ***1993***, *49*, 10705.
[2160] Nakano, T.; Kayama, M.; Nagai, Y. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 1049. See also, Kraus, G.A.; Landgrebe, K. *Tetrahedron Lett.* ***1984***, *25*, 3939.
[2161] Wang, S.L.B.; Su, J.; Wulff, W.D. *J. Am. Chem. Soc.* ***1992***, *114*, 10665.
[2162] Nguyen, R.V.; Li, C.-J. *J. Am. Chem. Soc.* ***2005***, *127*, 17184.
[2163] Zhu, R.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2015***, *137*, 8069.

radical cyclizations to give lactones.[2164] The cyclization of 4-bromo-3-yn-1-ols to give γ-butyrolactones used a Au catalyst in wet toluene.[2165] The Au-catalyzed cycloisomerization/oxidation of homopropargyl alcohols using mcpba as the oxidant gave γ-lactones.[2166] The Ir-catalyzed reaction under visible light photoredox conditions gave the γ-lactone by reaction of arylalkenes and α-bromo esters in aqueous acetonitrile and $LiBF_4$.[2167] The reaction of lithium enediolates, generated by reaction of aliphatic carboxylic acids with butyllithium or LDA, followed by reaction with vinylsulfoxonium and α,β-unsaturated sulfoxonium salts gave primarily the *trans*-α,β-disubstituted γ-lactones.[2168] γ-Lactones and γ-lactams were prepared by intramolecular Pd-catalyzed reactions.[2169]

Larger ring conjugated lactones were prepared by the reaction of 2-alkoxytetra hydropyrans with 1-trimethylislyl alkynes with $BF_3{\bullet}OEt_2$.[2170] Homoallylic carboxylic acids such as (*E*)-4-phenylbut-3-enoic acid reacted with *N*-trifluoromethylthiosaccharin as the SCF_3 reagent and a selenide as the catalyst in the presence of triflic acid and gave the β-trifluoromethylthiolated lactone.[2171]

Alkenyl acids cyclize to the corresponding lactone upon treatment with sodium hypochlorite and a Lewis acid.[2172] Alkynyl acids cyclize upon treatment with PIFA [phenyliodine(III)-bis(trifluoroacetate)] to give ω-acyl lactones.[2173] A variation of this reaction also employs a diselenide.[2174] Treatment of alkynyl acids with a Au catalyst[2175] leads to an alkylidene lactone. An intramolecular variation involving amides is known, and generates a lactam.[2176]

OS **VII**, 400.

15.C.iv. Cycloaddition Reactions

15-54 1,3-Dipolar Addition (Addition of Oxygen, Nitrogen, Carbon)[2177]

There is a large group of reactions ([3 + 2] cycloadditions) in which five-membered heterocyclic compounds are prepared by addition of 1,3-dipolar compounds to alkenes or

[2164] Davy, J.A.; Mason, J.W.; Moreau, B.; Wulff, J.E. *J. Org. Chem.* ***2012***, *77*, 6332.
[2165] Reddy, M.S.; Kumar, Y.K.; Thirupathi, N. *Org. Lett.* ***2012***, *14*, 824.
[2166] Shu, C.; Liu, M.-Q.; Sun, Y.-Z.; Ye, L.-W. *Org. Lett.* ***2012***, *14*, 4958.
[2167] Wei, X.-J.; Yang, D.T.; Wang, L.; Song, T.; Wu, L.-Z.; Liu, Q. *Org. Lett.* ***2013***, *15*, 6054.
[2168] Peraino, N.J.; Wheeler, K.A.; Kerrigan, N.J. *Org. Lett.* ***2015***, *17*, 1735.
[2169] Kammerer, C.; Prestat, G.; Madec, D.; Poli, G. *Acc. Chem. Res.* ***2014***, *47*, 3439.
[2170] Zhao, W.; Li, Z.; Sun, J. *J. Am. Chem. Soc.* ***2013***, *135*, 4680.
[2171] Liu, X.; An, R.; Zhang, X.; Luo, J.; Zhao, X. *Angew. Chem. Int. Ed.* ***2016***, *55*, 5846.
[2172] López-López, J.A.; Guerra, F.M.; Moreno-Dorado, F.J.; Jorge, Z.D.; Massanet, G.M. *Tetrahedron Lett.* ***2007***, *48*, 1749.
[2173] Tellitu, I.; Serna, S.; Herrero, M.T.; Moreno, I.; Domínguez, E.; SanMartin, R. *J. Org. Chem.* ***2007***, *72*, 1526.
[2174] Browne, D.M.; Niyomura, O.; Wirth, T. *Org. Lett.* ***2007***, *9*, 3169.
[2175] Harkat, H.; Weibel, J.-M.; Pale, P. *Tetrahedron Lett.* ***2006***, *47*, 6273.
[2176] Davies, D.T.; Kapur, N.; Parsons, A.F. *Tetrahedron Lett.* ***1998***, *39*, 4397.
[2177] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 820–832.

alkynes.[2178] This reaction is quite useful in the synthesis of alkaloids,[2179] including asymmetric syntheses.[2180] These dipolar compounds have a sequence of three atoms *a*—*b*—*c*, of which *a* has a sextet of electrons in the outer shell and *c* an octet with at least one unshared pair (see Table 15.3).[2181] The reaction can then be formulated as shown to generate a five-membered ring. Note that the initial reaction of potassium permanganate (**15-44**) occurs by [3 + 2] cycloaddition to give a manganate ester (**47**).[2182]

1,3-Dipoles of the type shown in Table 15.3 have an atom with six electrons in the outer shell, which is usually unstable, and they will delocalize the charge to alleviate this electronic arrangement (i.e., they are *resonance stabilized*). 1,3-Dipolar compounds can be divided into two main types:

1. Those in which the dipolar canonical form has a double bond and the other canonical form has a triple bond on that atom:

$$^{-}a{-}b{=}c^{+} \leftrightarrow {}^{-}a{-}b{\equiv}c^{+}$$

   If the discussion is limited to the first row of the periodic table, *b* can only be nitrogen, *c* can be carbon or nitrogen, and *a* can be carbon, oxygen, or nitrogen; hence there are six types. Among these are azides ($a = b = c = N$) and diazoalkanes.
2. Those in which the dipolar canonical form has single bonds and the other form has a double bond:

$$^{-}a{-}^{+}b{-}c \leftrightarrow {}^{-}a{-}^{+}b{=}c$$

   Here *b* can be nitrogen or oxygen, and *a* and *c* can be nitrogen, oxygen, or carbon, but there are only 12 types, since, for example, N—N—C is only another form of C—N—N. Examples are shown in Table 15.3.

[2178] Singh, M.S.; Chowdhury, S.; Koley, S. *Tetrahedron* ***2016***, *72*, 1603. See Fernández, I.; Cossío, F.P.; Bickelhaupt, F.M. *J. Org. Chem.* ***2011***, *76*, 2310; Domingo, L.R.; Ríos-Gutiérrez, M.; Pérez, P. *Tetrahedron* ***2017***, *73*, 1718.

[2179] See Broggini, G.; Zecchi, G. *Synthesis* ***1999***, 905; Zhang, W. *Chem. Lett.* ***2013***, *42*, 676.

[2180] Karlsson, S.; Högberg, H.-E. *Org. Prep. Proceed. Int.* ***2001***, *33*, 103.

[2181] See Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Elmsford, NY, ***1990***; Huisgen, R. *Helv. Chim. Acta* ***1967***, *50*, 2421; *Angew. Chem. Int. Ed.* ***1963***, *2*, 565, 633; Torssell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH, NY, ***1988***; Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, ***1984***; Stanovnik, B. *Tetrahedron* ***1991***, *47*, 2925 (diazoalkanes); Kanemasa, S.; Tsuge, O. *Heterocycles* ***1990***, *30*, 719 (nitrile oxides); Paton, R.M. *Chem. Soc. Rev.* ***1989***, *18*, 33 (nitrile sulfides); Terao, Y.; Aono, M.; Achiwa, K. *Heterocycles* ***1988***, *27*, 981; Coldham, I.; Hufton, R. *Chem. Rev.* ***2005***, *105*, 2765 (azomethine ylids); Vedejs, E. *Adv. Cycloaddit.* ***1988***, *1*, 33 (azomethine ylids); DeShong, P.; Lander Jr., S.W.; Leginus, J.M.; Dicken, C.M. *Adv. Cycloaddit.* ***1988***, *1*, 87 (nitrones); Balasubramanian, N. *Org. Prep. Proced. Int.* ***1985***, *17*, 23 (nitrones); Confalone, P.N.; Huie, E.M. *Org. React.* ***1988***, *36*, 1 (nitrones); Padwa, A. in Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, ***1984***, pp. 313–374 (nitrile ylids); Bianchi, G.; Gandolfi, R.; Grünanger, P. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wiley, NY, ***1983***, pp. 752–784 (nitrile oxides); Stuckwisch, C.G. *Synthesis* ***1973***, 469 (azomethine ylids, azomethine imines). For reviews of intramolecular 1,3-dipolar additions see Padwa, A. in Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, ***1984***, Vol. 2, pp. 277–406; Padwa, A.; Schoffstall, A.M. *Adv. Cycloaddit.* ***1990***, *2*, 1; Tsuge, O.; Hatta, T.; Hisano, T. in Patai, S. *The Chemistry of Double-Bonded Functional Groups, Supplement A*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 345–475; Padwa, A. *Angew. Chem. Int. Ed.* ***1976***, *15*, 123. For a review of azomethine ylids, see Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* ***1989***, *45*, 231. For reviews of 1,3-dipolar cycloreversions, see Bianchi, G.; De Micheli, C.; Gandolfi, R. *Angew. Chem. Int. Ed.* ***1979***, *18*, 721. For the use of this reaction to synthesize natural products, see papers in *Tetrahedron* ***1985***, *41*, 3447.

[2182] Houk, K.N.; Strassner, T. *J. Org. Chem.* ***1999***, *64*, 800.

Of the 18 systems, some of which are unstable and must be generated *in situ*,[2183] the reaction has been accomplished for at least 15, but not in all cases with a carbon–carbon double bond (the reaction also can be carried out with other double bonds[2184]). Not all alkenes undergo 1,3-dipolar addition equally well. The reaction is most successful for those that are good dienophiles in the *Diels-Alder reaction* (**15-56**).

The addition is stereospecific and *syn*, largely controlled by frontier molecular orbital (FMO) considerations,[2185] and the mechanism is probably a one-step concerted process.[2186] Reactivity has been shown to correlate with the energy required to distort 1,3-dipoles and dipolarophiles to the transition state.[2187] In-plane aromaticity has been invoked for these dipolar cycloadditions.[2188] As expected for this type of mechanism, the rates do not vary much with changes in solvent,[2189] although rate acceleration has been observed in ionic liquids.[2190]

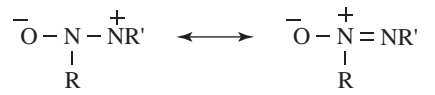
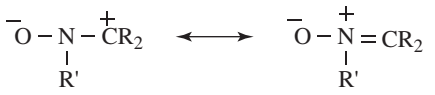
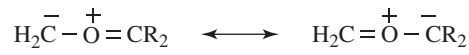
TABLE 15.3 Some common 1,3-dipolar partners

Compound	Reactions
	Type 1
Azide	$R-\overset{-}{N}-N=\overset{+}{N} \longleftrightarrow R-\overset{-}{N}-\overset{+}{N}\equiv N$
Diazoalkane	$R_2\overset{-}{C}-N=\overset{+}{N} \longleftrightarrow R_2\overset{-}{C}-\overset{+}{N}\equiv N$
Nitrous oxide	$\overset{-}{O}-N=\overset{+}{N} \longleftrightarrow \overset{-}{O}-\overset{+}{N}\equiv N$
Nitrile imine	$R-\overset{-}{N}-N=\overset{+}{C}R' \longleftrightarrow R-\overset{-}{N}-\overset{+}{N}\equiv CR'$
Nitrile ylid	$R_2\overset{-}{C}-N=\overset{+}{C}R' \longleftrightarrow R_2\overset{-}{C}-\overset{+}{N}\equiv CR'$
Nitrile oxide	$\overset{-}{O}-N=\overset{+}{C}R \longleftrightarrow \overset{-}{O}-\overset{+}{N}\equiv CR$
	Type 2
Azomethine imine	$R_2\overset{-}{C}-N(R^2)-\overset{+}{N}R' \longleftrightarrow R_2\overset{-}{C}-\overset{+}{N}(R^2)=NR'$

(*continued*)

[2183] For a review of some aspects of this, see Grigg, R. *Chem. Soc. Rev.* ***1987***, *16*, 89.
[2184] See Bianchi, G.; De Micheli, C.; Gandolfi, R. in Patai, S. *The Chemistry of Double-Bonded Functional Groups, Supplement A*, pt. 1, Wiley, NY, ***1977***, pp. 369–532. Also see Dunn, A.D.; Rudorf, W. *Carbon Disulfide in Organic Chemistry*, Wiley, NY, ***1989***, pp. 97–119.
[2185] Caramella, P.; Gandour, R.W.; Hall, J.A.; Deville, C.G.; Houk, K.N. *J. Am. Chem. Soc.* ***1977***, *99*, 385 and references cited therein.
[2186] Di Valentin, C.; Freccero, M.; Gandolfi, R.; Rastelli, A. *J. Org. Chem.* ***2000***, *65*, 6112. See Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F.P. *J. Am. Chem. Soc.* ***2000***, *122*, 6078. See Ess, D.H.; Houk, K.N. *J. Am. Chem. Soc.* ***2007***, *129*, 10646.
[2187] Engels, B.; Christl, M. *Angew. Chem. Int. Ed.* ***2009***, *48*, 7968.
[2188] Cossío, F.P.; Marao, I.; Jiao, H.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1999***, *121*, 6737.
[2189] For a review of the role of solvents in this reaction, see Kadaba, P.K. *Synthesis* ***1973***, 71.
[2190] Dubreuil, J.F.; Bazureau, J.P. *Tetrahedron Lett.* ***2000***, *41*, 7351.

TABLE 15.3 (*Continued*)

Compound	Reactions
Azoxy compound	
Azomethine ylid	
Nitrone	
Carbonyl oxide	
Ozone	
Carbonyl ylid	

See the following for more details: azides,[2191] diazoalkanes,[2192] nitrile imines,[2193] nitrile ylids,[2194] nitrile oxides,[2195] azomethine imines,[2196] azomethine ylids,[2197] nitrones,[2198] carbonyl oxides,[2199] and carbonyl ylids.[2200]

[2191] Wang, Y.-C.; Xie, Y.-Y.; Qu, H.-E.; Wang, H.-S.; Pan, Y.-M.; Huang, F.-P. *J. Org. Chem.* ***2014***, *79*, 4463. For a reaction with sodum azide, see Mani, P.; Singh, A.K.; Awasthi, S.K. *Tetrahedron Lett.* ***2014***, *55*, 1879; Prajapti, S.K.; Nagarsenkar, A.; Babu, B.N. *Tetrahedron Lett.* ***2014***, *55*, 3507; Patouret, R.; Kamenecka, T.M. *Tetrahedron Lett.* ***2016***, *57*, 1597; Hyatt, I.F.D.; Kloss, F.; Köhn, U.; Jahn, B.O.; Hager, M.D.; Görls, H.; Schubert, U.S. *Chem. Asian J.* ***2011***, *6*, 2816.

[2192] Mani, N.S.; Fitzgerald, A.E. *J. Org. Chem.* ***2014***, *79*, 8889; Gold, B.; Aronoff, M.R.; Raines, R.T. *J. Org. Chem.* ***2016***, *81*, 5998.

[2193] Sibi, M.P.; Stanley, L.M.; Jasperse, C.P. *J. Am. Chem. Soc.* ***2005***, *127*, 8276. See Bégué, D.; Wentrup, C. *J. Org. Chem.* ***2014***, *79*, 1418.

[2194] Bégué, D.; Addicott, C.; Burgard, R.; Bednarek, P.; Guille, E.; Baraille, I.; Wentrup, C. *J. Org. Chem.* ***2014***, *79*, 2148; Domingo, L.R.; Ríos-Gutiérrez, M.; Pérez, P. *Tetrahedron* ***2016***, *72*, 1524.

[2195] Haberhauer, G.; Gleiter, R.; Woitschetzki, S. *J. Org. Chem.* ***2015***, *80*, 12321; Singhal, A.; Parumala, S.K.R.; Sharma, A.; Peddinti, R.K. *Tetrahedron Lett.* ***2016***, *57*, 719; Heaney, F. *Eur. J. Org. Chem.* ***2012***, 3043; Boruah, M.; Konwar, D. *Synth. Commun.* ***2012***, *42*, 3261; Tabolin, A.A.; Ioffe, S.I. *Isr. J. Chem.* ***2016***, *56*, 385. For the reaction of nitrile oxides using flow conditions (Sec. 7.D), see Brasholz, M.; Saubern, S.; Savage, G.P. *Aust. J. Chem.* ***2011***, *64*, 1397.

[2196] Xu, H.; Ma, S.; Xu, Y.; Bian, L.; Ding, T.; Fang, X.; Zhang, W.; Ren, Y. *J. Org. Chem.* ***2015***, *80*, 1789; Winterton, S.E.; Ready, J.M. *Org. Lett.* ***2016***, *18*, 2608.

[2197] Pascual-Escudero, A.; de Cózar, A.; Cossío, F.P.; Adrio, J.; Carretero, J.C. *Angew. Chem. Int. Ed.* ***2016***, *55*, 15334; Li, J.; Zhao, H.; Zhang, Y. *Synlett* ***2015***, *26*, 2745; Otero-Fraga, J.; Montesinos-Magraner, M.; Mendoza, A. *Synthesis* ***2017***, *49*, 802; Navarro, V.J.; Delso, I.; Tejero, T.; Merino, P. *Chem. Eur. J.* ***2016***, *22*, 11527; Narayan, R.; Potowski, M.; Jia, Z.-J.; Antonchick, A.P.; Waldmann, H. *Acc. Chem. Res.* ***2014***, *47*, 1296.

[2198] See Darù, A.; Roca-López, D.; Tejero, T.; Merino, P. *J. Org. Chem.* ***2016***, *81*, 673; Sirotkina, E.V.; Efremova, M.M.; Novikov, A.S.; Zarubaev, V.V.; Orshanskaya, I.R.; Starova, G.L.; Kostikov, R.R.; Molchanov, A.P. *Tetrahedron* ***2017***, *73*, 3025; Nguyen, T.B.; Martel, A.; Gaulon-Nourry, C.; Dhal, R.; Dujardin, G. *Org. Prep. Proceed. Int.* ***2012***, *44*, 1; Yang, J. *Synlett* ***2012***, *23*, 2293; Jiong, Y. *Synlett* ***2012***, *23*, 2293.

[2199] Iesce, M.R.; Cermola, F.; Giordano, F.; Scarpati, R.; Graziano, M.L. *J. Chem. Soc., Perkin Trans. 1* ***1994***, 3295; MuCullough, K.J.; Sugimoto, T.; Tanaka, S.; Kusabayashi, S.; Nojima, M. *J. Chem. Soc., Perkin Trans. 1* ***1994***, 643.

[2200] See Domingo, L.R.; Sáez, J.A. *J. Org. Chem.* ***2011***, *76*, 373.

There are no simple rules covering orientation in 1,3-dipolar additions. The regioselectivity has been explained by molecular orbital treatments,[2201] where overlap of the largest orbital coefficients of the atoms forming the new bonds leads to the major regioisomer. In a theoretical study of the 1,3-dipolar cycloadditions (diazomethane and ethene; fulminic acid [H—C≡N—O] and ethyne),[2202] calculations based on valence bond descriptions suggest that many concerted 1,3-dipolar cycloaddition reactions follow an electronic heterolytic mechanism where the movement of well-identifiable orbital pairs is retained along the entire reaction path from reactants to product.[2203] When the 1,3-dipolar compound is a thiocarbonyl ylid ($R_2C{=}S^+{-}CH_2{}^-$), the addition has been shown to be nonstereospecific with certain substrates but stereospecific with others, indicating a nonsynchronous mechanism in these cases. In fact, a diionic intermediate (see mechanism *c* in **15-59**, category 4) has been trapped in one such case.[2204]

Many of the cycloadducts formed from the dipoles in Table 15.3 are unstable, leading to other products. The reaction of alkyl azides with alkenes generates triazolines (**15-50**), which extrude nitrogen (N≡N) upon heating or photolysis to give an aziridine.[2205] With a transition metal catalyst, alkyl azides add to alkynes to give triazoles.[2206] Retro [3 + 2] cycloaddition reactions are also known.[2207] Cycloaddition of azides to allenes leads to pyrrolidines.[2208] The 1,3-dipolar reagent can in some cases be generated by the *in situ* opening of a suitable three-membered ring system. For example, aziridines open to give a zwitterion that can add to activated double bonds to give pyrrolidines.[2209] Conjugated dienes generally give exclusive 1,2-addition, although 1,4-addition (a [3 + 4] cycloaddition) has been reported.[2210]

A lot of research continues in this area. It is noted that diazomethane has been generated using flow conditions (Sec. 7.D).[2211] The reaction of azides and nitriles gave tetrazoles, and has been done using flow conditions.[2212] The chemistry of nitrilium ions has been reviewed.[2213] Diazoketones reacted with ynamides using both batch and flow photochemical conditions.[2214] It is noted that diazoketones have been prepared using flow conditions (Sec. 7.D).[2215]

[2201] See Houk, K.N.; Yamaguchi, K. in Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*, Vol. 2, Wiley, NY, ***1984***, pp. 407–450. See also, Burdisso, M.; Gandolfi, R.; Quartieri, S.; Rastelli, A. *Tetrahedron* ***1987***, *43*, 159.

[2202] Karadakov, P.B.; Cooper, D.L.; Gerratt, J. *Theor. Chem. Acc.* ***1998***, *100*, 222.

[2203] Blavins, J.J.; Karadakov, P.B.; Cooper, D.L. *J. Org. Chem.* ***2001***, *66*, 4285.

[2204] Huisgen, R.; Mloston, G. *Tetrahedron Lett.* ***1989***, *30*, 7041.

[2205] For a discussion of reactivity and regioselectivity with strained alkenes and alkynes, see Schoenebeck, F.; Ess, D.H.; Jones, G.O.; Houk, K.N. *J. Am. Chem. Soc.* ***2009***, *131*, 8121.

[2206] Kamata, K.; Nakagawa, Y.; Yamaguchi, K.; Mizuno, N. *J. Am. Chem. Soc.* ***2008***, *130*, 15304.

[2207] da Silva, G.; Bozzelli, J.W. *J. Org. Chem.* ***2008***, *73*, 1343.

[2208] Feldman, K.S.; Iyer, M.R. *J. Am. Chem. Soc.* ***2005***, *127*, 4590.

[2209] Lown, J.W. in Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*, Vol. 1, Wiley, NY, ***1984***, pp. 683–732.

[2210] Baran, J.; Mayr, H. *J. Am. Chem. Soc.* ***1987***, *109*, 6519.

[2211] Mastronardi, F.; Gutmann, B.; Kappe, C.O. *Org. Lett.* ***2013***, *15*, 5590; Maurya, R.A.; Park, C.-P.; Lee, J.H.; Kim, D.-P. *Angew. Chem. Int. Ed.* ***2011***, *50*, 5952.

[2212] Palde, P.B.; Jamison, T.F. *Angew. Chem. Int. Ed.* ***2011***, *50*, 3525.

[2213] van Dijk, T.; Slootweg, J.C.; Lammertsma, K. *Org. Biomol. Chem.* ***2017***, *15*, 10134.

[2214] Willumstad, T.P.; Haze, O.; Mak, X.-Y.; Lam, T.Y.; Wang, Y.-P.; Danheiser, R.L. *J. Org. Chem.* ***2013***, *78*, 11450.

[2215] Martin, L.J.; Marzinzik, A.L.; Ley, S.V.; Baxendale, I.R. *Org. Lett.* ***2011***, *13*, 320.

Nitrile oxide cycloadditions have also been done in supercritical carbon dioxide.[2216] Oximes are precursors to nitrile oxides.[2217] Ionic liquids have been developed for cycloaddition reactions of azides.[2218] Brønsted acid-catalyzed reactions of hydrazones gave hydrazonium/phosphoramide anion complexes and [3 + 2] cycloadditions with alkenes gave pyrazolidines.[2219] The first 1,3-dipolar cycloaddition of 1,2-cyclohexadiene, generated *in situ*, and trapped with nitrones gave isoxazolidine products.[2220] Oxallyl cations have been used in [3 + 2] cycloaddition reactions,[2221] and the reaction with alkynes leads to cyclopentanone derivatives (**15-55**) Trimethylenemethane reacted with imines using a Pd catalyst to give pyrrolidines.[2222] The Rh-catalyzed [3 + 2] cycloaddition of vinyldiazoacetates with nitrones gave 2,5-dihydroisoxazoles.[2223] The reaction of isocyanides and alkynes gave pyrroles using a Ag catalyst,[2224] and oxazoles were formed by reaction with carboxylic acids and a Zn catalyst.[2225]

When diazoalkanes (including diazo acetates such as ethyl diazoacetate, N_2CHCO_2Et) react with an alkene and a Cr catalyst, the initially formed product is a five-membered ring, a pyrazoline.[2226] *Pyrazolines are generally unstable and extrusion of nitrogen leads to a cyclopropane*.[2227] Nitrones react with conjugated carbonyl compounds, with a transition metal catalyst such as a Ti complex, to give an 1,2-oxazoline.[2228] [3 + 2] cycloaddition reactions occur intramolecularly to generate bicyclic and polycyclic compounds.[2229] The intramolecular cycloaddition of azomethine imines give bicyclic pyrazolidines, for example.[2230]

There are many cases where the [3 + 2] cycloaddition leads to cycloadducts with high enantioselectivity.[2231] Cycloaddition of diazo esters with a Co catalyst having a chiral

[2216] Lee, C.K.Y.; Holmes, A.B.; Al-Duri, B.; Leeke, G.A.; Santos, R.C.D.; Seville, J.P.K. *Chem. Commun.* ***2004***, 2622.

[2217] Xie, F.; Yu, S.; Qi, Z.; Li, X. *Angew. Chem. Int. Ed.* ***2016***, *55*, 15351; Yoshimura, A.; Middleton, K.R.; Todora, A.D.; Kastern, B.J.; Koski, S.R.; Maskaev, A.V.; Zhdankin, V.V. *Org. Lett.* ***2013***, *15*, 4010.

[2218] Thompson, R.L.; Damodaran, K.; Luebke, D.; Nulwala, H. *Synlett* ***2013***, *24*, 1093; Koguchi, S.; Nakamura, K. *Synlett* ***2013***, *24*, 2305.

[2219] Hong, X.; Küçük, H.B.; Maji, M.S.; Yang, Y.-F.; Rueping, M.; Houk, K.N. *J. Am. Chem. Soc.* ***2014***, *136*, 13769.

[2220] Barber, J.S.; Styduhar, E.D.; Pham, H.V.; McMahon, T.C.; Houk, K.N.; Garg, N.K. *J. Am. Chem. Soc.* ***2016***, *138*, 2512.

[2221] Li, H.; Wu, J. *Synthesis* ***2015***, *47*, 22.

[2222] Trost, B.M.; Silverman, S.M. *J. Am. Chem. Soc.* ***2012***, *134*, 4941; Trost, B.M.; Lam, T.M.; Herbage, M.A. *J. Am. Chem. Soc.* ***2013***, *135*, 2459.

[2223] Qin, C.; Davies, H.L. *J. Am. Chem. Soc.* ***2013***, *135*, 14516.

[2224] Gao, M.; He, C.; Chen, H.; Bai, R.; Cheng, B.; Lei, A. *Angew. Chem. Int. Ed.* ***2013***, *52*, 6958. For a magnetically recoverable catalyst, see Tiwari, D.K.; Phanindrudu, M.; Aravilli, V.K.; Sridhar, B.; Likhar, P.R.; Tiwari, D.K. *Chem. Commun.* ***2016***, *52*, 4675.

[2225] Odabachian, Y.; Tong, S.; Wang, Q.; Wang, M.-X.; Zhu, J. *Angew. Chem. Int. Ed.* ***2013***, *52*, 10878.

[2226] For an enantioselective reaction, see Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* ***2006***, *128*, 2174.

[2227] Jan, D.; Simal, F.; Demonceau, A.; Noels, A.F.; Rufanov, K.A.; Ustynyuk, N.A.; Gourevitch, D.N. *Tetrahedron Lett.* ***1999***, *40*, 5695.

[2228] Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* ***2005***, *127*, 11926.

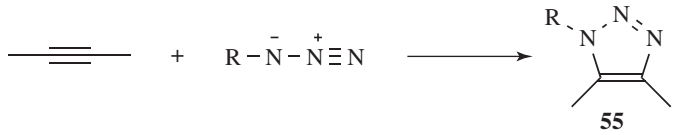
[2229] See Padwa, A. *Angew. Chem. Int. Ed.* ***1976***, *15*, 123; Oppolzer, W. *Angew. Chem. Int. Ed.* ***1977***, *16*, 10 (see pp. 18–22).

[2230] Dolle, R.E.; Barden, M.C.; Brennan, P.E.; Ahmed, G.; Tran, V.; Ho, D.M. *Tetrahedron Lett.* ***1999***, *40*, 2907.

[2231] Stanley, L.M.; Sibi, M.P. *Chem. Rev.* ***2008***, *108*, 2887. See Bădoiu, A.; Brinkmann,Y.; Viton, F.; Kündig, E.P. *Pure Appl. Chem.* ***2008***, *80*, 1013.

ligand leads to cyclopropane derivatives with good enantioselectivity.[2232] Cycloaddition of nitrones and pyrazolinones with a Cu catalyst and a chiral ligand leads to pyrrolidine derivatives with good enantioselectivity.[2233] In the presence of a Ni catalyst and a chiral ligand, nitrones react with activated cyclopropanes to give tetrahydro-1,2-oxazines, with high enantioselectivity.[2234]

Carbon–carbon triple bonds can also undergo 1,3-dipolar addition.[2235] For example, azides react with alkynes to give triazoles, **55**. This reaction has been called the *Huisgen cycloaddition*,[2236] and this reaction has been identified by Sharpless as one of the important reactions for "click" chemistry.[2237] It has been shown that cyclohexyne can also be used.[2238]



55

Enantioselective Ni-catalyzed cycloaddition reactions have been reviewed.[2239] The Ru-catalyzed azide alkyne cycloaddition has been reviewed.[2240] Cyclooctyne derivatives that have a distal azide moiety as well as a distal oxime moiety reacted intramolecularly via the alkyne unit and the azide to give the 1,2,3-triazole in methanol and via the alkene and the nitrile oxide derived from the oxime when treated with [bis(acetoxy)iodo]benzene to give the isoxazole.[2241] Aziridines also add to C≡C triple bonds as well as to other unsaturated linkages, including C═O, C═N, and C≡N.[2242] In some of these reactions it is a C—N bond of the aziridine that opens rather than the C—C bond.

OS **V**, 957, 1124; **VI**, 592, 670; **VIII**, 231. Also see, OS **IV**, 380.

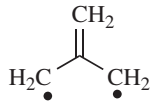
A. Carbon on Both Sides[2243]

15-55 All-Carbon [3 + 2] Cycloadditions[2244]

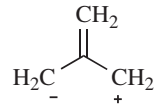
Several methods have been reported for the formation of cyclopentanes by [3 + 2] cycloadditions.[2245] Heating conjugated ketones with trialkylphosphines generates an intermediate

[2232] Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* ***2000***, *41*, 3647.
[2233] Sibi, M.P.; Ma, Z.; Jasperse, C.P. *J. Am. Chem. Soc.* ***2004***, *126*, 718.
[2234] Sibi, M.P.; Ma, Z.; Jasperse, C.P. *J. Am. Chem. Soc.* ***2005***, *127*, 5764.
[2235] See Bastide, J.; Hamelin, J.; Texier, F.; Quang, Y.V. *Bull. Soc. Chim. Fr.* ***1973***, 2555, 2871; Fuks, R.; Viehe, H.G. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, p. 460–477.
[2236] Huisgen, R. *Proc. Chem. Soc. London* ***1961***, 357.
[2237] Kolb, H.C.; Sharpless, K.B. *Drug Discov. Today* ***2003***, *8*, 1128. See Lal, S.; Díez-González, S. *J. Org. Chem.* ***2011***, *76*, 2367; Singh, M.S.; Chowdhury, S.; Koley, S. *Tetrahedron* ***2016***, *72*, 5257.
[2238] Medina, J.M.; McMahon, T.C.; Jiménez-Osés, G.; Houk, K.N.; Garg, N.K. *J. Am. Chem. Soc.* ***2014***, *136*, 14706.
[2239] Pellissier, H. *Tetrahedron* ***2015***, *71*, 8855.
[2240] Johansson, J.R.; Beke-Somfai, T.; Stålsmeden, A.S.; Kann, N. *Chem. Rev.* ***2016***, *116*, 14726.
[2241] Sanders, B.C.; Friscourt, F.; Ledin, P.A.; Mbua, N.E.; Arumugam, S.; Guo, J.; Boltje, T.J.;. Popik, V.V.; Boons, G.J. *J. Am. Chem. Soc.* ***2011***, *133*, 949.
[2242] See Lown, J.W. *Rec. Chem. Prog.* ***1971***, *32*, 51; Gladysheva, F.N.; Sineokov, A.P.; Etlis, V.S. *Russ. Chem. Rev.* ***1970***, *39*, 118.
[2243] For a system of classification of cycloaddition reactions, see Huisgen, R. *Angew. Chem. Int. Ed.* ***1968***, *7*, 321. See Posner, G.H. *Chem. Rev.* ***1986***, *86*, 831.
[2244] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 820–832.
[2245] See Trost, B.M.; Seoane, P.; Mignani, S.; Acemoglu, M. *J. Am. Chem. Soc.* ***1989***, *111*, 7487.

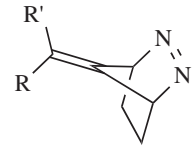
that adds to conjugated alkynes.[2246] One method involves reagents that produce intermediates **56** or **57**.[2247] Note that **57** also reacts with *N*-tosyl aziridines, with 20% *n*-butyllithium and 10% of $Pd(OAc)_2$, to give a vinylidene piperidine derivative.[2248] Similar or identical intermediates generated from bicyclic azo compounds **58** (see **17-32**) or methylenecyclopropane **59**[2249] also add to activated double bonds. With suitable substrates, the addition can be enantioselective.[2250]



56



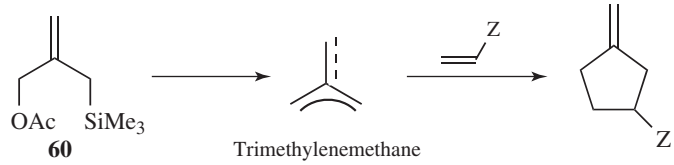
57



58

59

A synthetically useful example[2251] uses 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate (**60**) (which is commercially available) and a Pd or other transition metal catalyst to generate **56** or **57**, which adds to double bonds to give cyclopentanes with an exocyclic double bond. The reaction occurs with **60** to generate trimethylenemethane *in situ*, which reacts with alkenes to give methylenecyclopentane derivatives.[2252]



60 Trimethylenemethane

A similar reaction occurs with imines to give methylene pyrrolidines.[2253] The Pd-catalyzed reaction with carbon dioxide leads to butenolides.[2254] The Pd-catalyzed reaction of trimethylenemethane with aldehydes gave methylenetetrahydrofurans.[2255] Tetramethyleneethane equivalents have been used for cycloaddition reactions.[2256]

The Rh(I)-catalyzed intramolecular [3 + 2] cycloaddition reactions of 1-ene- and 1-yne-vinylcyclopropanes gave bicyclic products.[2257] The [3 + 2] reaction of aryl cyclopropyl ketones with alkenes, using a photocatalytic system comprising $Ru(bpy)_3^{2+}$, $La(OTf)_3$, and TMEDA, gave cyclopentane rings via an intermediate radical anion.[2258] Cyclopropyl

[2246] Wang, J.-C.; Ng, S.-S.; Krische, M.J. *J. Am. Chem. Soc.* ***2003***, *125*, 3682.
[2247] See Trost, B.M. *Pure Appl. Chem.* ***1988***, *60*, 1615; *Angew. Chem. Int. Ed.* ***1986***, *25*, 1.
[2248] Hedley, S.J.; Moran, W.J.; Price, D.A.; Harrity, J.P.A. *J. Org. Chem.* ***2003***, *68*, 4286.
[2249] See Yamago, S.; Nakamura, E. *J. Am. Chem. Soc.* ***1989***, *111*, 7285.
[2250] See Chaigne, F.; Gotteland, J.; Malacria, M. *Tetrahedron Lett.* ***1989***, *30*, 1803.
[2251] See Trost, B.M.; Lynch, J.; Renaut, P.; Steinman, D.H. *J. Am. Chem. Soc.* ***1986***, *108*, 284.
[2252] Trost, B.M.; MacPherson, D.T. *J. Am. Chem. Soc.* ***1987***, *109*, 3483; Trost, B.M.; Cramer, N.; Silverman, S.M. *J. Am. Chem. Soc.* ***2007***, *129*, 12396.
[2253] Trost, B.M.; Silverman, S.M.; Stambuli, J.P. *J. Am. Chem. Soc.* ***2007***, *129*, 12398.
[2254] Greco, G.E.; Gleason, B.L.; Lowery, T.A.; Kier, M.J.; Hollander, L.B.; Gibbs, S.A.; Worthy, A.D. *Org. Lett.* ***2007***, *9*, 3817.
[2255] See Trost, B.M.; Debien, L. *J. Am. Chem. Soc.* ***2015***, *137*, 11606; Lee, H.-Y. *Acc. Chem. Res.* ***2015***, *48*, 2308.
[2256] Wender, P.A.; Jeffreys, M.S.; Raub, A.G. *J. Am. Chem. Soc.* ***2015***, *137*, 9088.
[2257] Jiao, L.; Lin, M.; Yu, Z.-X. *J. Am. Chem. Soc.* ***2011***, *133*, 447; Trost, B.M.; Morris, P.J.; Sprague, S.J. *J. Am. Chem. Soc.* ***2012***, *134*, 17823.
[2258] Lu, Z.; Shen, M.; Yoon, T.P. *J. Am. Chem. Soc.* ***2011***, *133*, 1162.

ketones also reacted with alkynes using a Ni/Al co-catalyst system.[2259] The cycloaddition of allenes to acrylates gave cyclopentenes using a dipeptide-derived phosphine catalyst.[2260]

The phosphine-catalyzed intramolecular [3 + 2] annulation of allenes with alkenes gave cyclopentene derivatives.[2261] The $Sc(OTf)_3$-catalyzed [3 + 2] annulation reaction between cyclopropenones and donor–acceptor cyclopropanes gave 4-oxaspiro[2.4]hept-1-ene derivatives.[2262]

An antibody-catalyzed [3 + 2] cycloaddition has been reported.[2263] Metal-assisted dipolar additions are also known.[2264] In a different metal-mediated reaction, alkenyl *Fischer carbene complexes* reaction with alkynes, in the presence of a Ni catalyst, to give cyclopentenones.[2265] Fischer carbene complexes take the form $R_2C{=}M(CO)_x$,[2266] and the metals include those of low oxidation state, and Fe, Mo, Cr, or W. Ligands include π electron acceptors and π donor substituents on methylene groups, such as alkoxy and amino groups.

In a different type of procedure, [3 + 2] cycloadditions are performed with allylic anions. Such reactions are called 1,3-anionic cycloadditions.[2267] For example, α-methylstyrene adds to stilbene on treatment with the strong base LDA to give 1,3,5-triphenylcyclopentane.[2268] In these cases the reagent is an allylic anion, but similar [3 + 2] cycloadditions involving allylic cations have also been reported.[2269]

OS **VIII**,173, 347.

15-56 The Diels-Alder Reaction[2270]

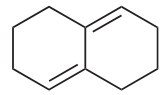
In the prototype *Diels-Alder reaction* the double bond of an alkene adds 1,4 to a conjugated diene (a [4 + 2] cycloaddition),[2271] so the product is always a cyclohexene. The cycloaddition is not limited to alkenes or to dienes (see **15-57**). The substrate that reacts with the diene is called a *dienophile*. The reaction is of very broad scope[2272] and reactivity of

[2259] Tamaki, T.; Ohashi, M.; Ogoshi, S. *Angew. Chem. Int. Ed.* ***2011***, *50*, 1206.
[2260] Han, X.; Wang, Y.; Zhong, F.; Lu, Y. *J. Am. Chem. Soc.* ***2011***, *133*, 1726.
[2261] Lee, S.Y.; Fujiwara, Y.; Nishiguchi, A.; Kalek, M.; Fu, G.F. *J. Am. Chem. Soc.* ***2015***, *137*, 4587.
[2262] Rivero, A.R.; Fernández, I.; de Arellano, C.R.; Sierra, M.A. *J. Org. Chem.* ***2015***, *80*, 1207.
[2263] Toker, J.D.; Wentworth Jr., P.; Hu, Y.; Houk, K.N.; Janda, K.D. *J. Am. Chem. Soc.* ***2000***, *122*, 3244.
[2264] Kanemasa, S. *Synlett* ***2002***, 1371.
[2265] Barluenga, J.; Barrio, P.; Riesgo, L.; López, L.A.; Tomás, M. *J. Am. Chem. Soc.* ***2007***, *129*, 14422.
[2266] See Fischer, H. *Chem. Ber.* ***1980***, *113*, 193.
[2267] Kauffmann, T. *Top. Curr. Chem.* ***1980***, *92*, 109 (pp. 111–116); *Angew. Chem. Int. Ed.* ***1974***, *13*, 627; Gembus, V.; Postikova, S.; Levacher, V.; Brière, J.-F. *J. Org. Chem.* ***2011***, *76*, 4194. See Sasaki, M.; Kondo, Y.; Nishio, T.; Takeda, K. *Org. Lett.* ***2016***, *18*, 3858.
[2268] Eidenschink, R.; Kauffmann, T. *Angew. Chem. Int. Ed.* ***1972***, *11*, 292. See, however, Beak, P.; Burg, D.A. *J. Org. Chem.* ***1989***, *54*, 1647.
[2269] See Noyori, R.; Hayakawa, Y. *Tetrahedron* ***1985***, *41*, 5879.
[2270] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 743–783.
[2271] Wasserman, A. *Diels-Alder Reactions*, Elsevier, NY, ***1965***; Roush, W.R. *Adv. Cycloaddit.* ***1990***, *2*, 91; Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Elmsford, NY, ***1990***; Brieger, G.; Bennett, J.N. *Chem. Rev.* ***1980***, *80*, 63; Oppolzer, W. *Angew. Chem. Int. Ed.* ***1977***, *16*, 10; Sauer, J. *Angew. Chem. Int. Ed.* ***1966***, *5*, 211; ***1967***, *6*, 16; Taber, D.F. *Intramolecular Diels-Alder and Alder Ene Reactions*, Springer, NY, ***1984***; Deslongchamps, P. *Aldrichimica Acta* ***1991***, *24*, 43; Craig, D. *Chem. Soc. Rev.* ***1987***, *16*, 187. For a list of references to various aspects of the Diels-Alder reaction, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 523–544.
[2272] See Konovalov, A.I. *Russ. Chem. Rev.* ***1983***, *52*, 1064.

dienes and dienophiles can be predicted based on analysis of the HOMOs[2273] and LUMOs of these species (using frontier molecular orbital theory, FMO).[2274] Ethylene and simple alkenes make poor dienophiles, unless high temperatures and/or pressures are used.[2275] Most dienophiles are of the form —C═C—Z or Z—C═C—Z′, where Z and Z′ are electron-withdrawing groups.[2276] The industrial applications of the Diels-Alder reaction have been reviewed.[2277]

Electron-withdrawing groups may be incorporated to facilitate the Diels-Alder reaction of simple alkenes and then removed after cycloaddition. An example is phenyl vinyl sulfone $PhSO_2CH{=}CH_2$,[2278] as the $PhSO_2$ group can be easily removed with Na/Hg after the ring-closure reaction. Similarly, phenyl vinyl sulfoxide $PhSOCH{=}CH_2$ can be used as a synthon for acetylene.[2279] In this case PhSOH is lost from the sulfoxide product (**17-10**). Dehydrogenation of pericyclic reactions leads to dehydropericyclic processes, and formation of strained or reactive intermediates.[2280]

Electron-donating substituents in the diene accelerate the reaction; electron-withdrawing groups retard it.[2281] For the dienophile it is just the reverse: electron-donating groups decrease the rate, and electron-withdrawing groups increase it. The *s-cis* (cisoid) conformation is required for the cycloaddition,[2282] and acyclic dienes are conformationally mobile so the *s-cis* conformation will be available.[2283] Cyclic dienes, in which the *s-cis* conformation is built in, usually react faster than the corresponding open-chain compounds, which have to achieve the *s-cis* conformation by rotation.[2284] Dienes may not be frozen into a *s-trans* (transoid) conformation (see **64**). Nearly all conjugated dienes undergo the reaction with suitable dienophiles.[2285] Quinones are important dienophiles[2286] and arynes have been used as dienophiles.[2287]



64

[2273] See Nelson, D.J.; Li, R.; Brammer, C. *J. Org. Chem.* ***2001***, *66*, 2422.

[2274] Spino, C.; Rezaei, H.; Dory, Y.L. *J. Org. Chem.* ***2004***, *69*, 757. For tables of HOMOs and LUMOs for dienes and dienophiles, see Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 743–765.

[2275] See Levandowski, B.J.; Houk, K.N. *J. Org. Chem.* ***2015***, *80*, 3530.

[2276] See Domingo, L.R. *Eur. J. Org. Chem.* ***2004***, 4788; McClure, C.K.; Herzog, K.J.; Bruch, M.D. *Tetrahedron Lett.* ***1996***, *37*, 2153.

[2277] Funel, J.-A.; Abele, S. *Angew. Chem. Int. Ed.* ***2013***, *52*, 3822.

[2278] See Kinney, W.A.; Crouse, G.D.; Paquette, L.A. *J. Org. Chem.* ***1983***, *48*, 4986.

[2279] See De Lucchi, O.; Pasquato, L. *Tetrahedron* ***1988***, *44*, 6755.

[2280] Skraba-Joiner, S.L.; Johnson, R.P.; Agarwal, J. *J. Org. Chem.* ***2015***, *80*, 11779.

[2281] See Domingo, L.R.; Aurell, M.J.; Pérez, P.; Contreras, R. *Tetrahedron* ***2002***, *58*, 4417.

[2282] For ground state conformations, see Bur, S.K.; Lynch, S.M.; Padwa, A. *Org. Lett.* ***2002***, *4*, 473.

[2283] For a discussion of conformational thermodynamic and kinetic parameters of methyl buta-1,3-dienes, see Squillacote, M.E.; Liang, F. *J. Org. Chem.* ***2005***, *70*, 6564.

[2284] Sauer, J.; Wiest, H. *Angew. Chem. Int. Ed.* ***1962***, *1*, 269. See, however, Scharf, H.; Plum, H.; Fleischhauer, J.; Schleker, W. *Chem. Ber.* ***1979***, *112*, 862.

[2285] For a monograph on dienes, with tables showing >800 types, see Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*, Wiley, NY, ***1990***. See Danishefsky, S. *Chemtracts: Org. Chem.* ***1989***, *2*, 273; Petrzilka, M.; Grayson, J.I. *Synthesis* ***1981***, 753; Smith, M.B. *Org. Prep. Proced. Int.* ***1990***, *22*, 315; Robiette, R.; Cheboub-Benchaba, K.; Peeters, D.; Marchand-Brynaert, J. *J. Org. Chem.* ***2003***, *68*, 9809; Huang, Y.; Iwama, T.; Rawal, V.H. *J. Am. Chem. Soc.* ***2002***, *122*, 5950.

[2286] The use of quinones in synthesis has been reviewed, see Nawrat, C.C.; Moody, C.J. *Angew. Chem. Int. Ed.* ***2014***, *53*, 2056.

[2287] See Bhojgude, S.S.; Bhunia, A.; Biju, A.T. *Acc. Chem. Res.* ***2016***, *49*, 1658.

While Diels-Alder reactions generally require no catalyst, they do require heating. Brønsted acids have been used to accelerate the rate of the Diels-Alder reaction.[2288] Diels-Alder reactions have been done in ionic liquids (Sec. 9.D.iii).[2289] Solvent-free Diels-Alder reactions are known.[2290] Lewis acids are effective catalysts,[2291] particularly for those reactions in which Z (an electron-withdrawing group) in the dienophile is a C=O or C=N group.[2292] Chemoselectivity is related to the choice of Lewis acid or Brønsted-Lowry acid catalyst.[2293] A Lewis acid catalyst usually increases both the regioselectivity of the reaction (in the sense given above) and the extent of *endo* addition,[2294] and, in the case of enantioselective reactions, the extent of enantioselectivity. It has been shown that a rigid bicyclo[2.2.2]octene-based diene lowers the Diels-Alder activation energy by 5.4 kcal mol^{-1} (22.6 kJ mol^{-1}) compared with the acyclic analog in a so-called proximity-induced Diels-Alder reaction.[2295]

A great many catalysts have been developed for aqueous Diels-Alder reactions[2296] including catalysts that can be used for ionic Diels-Alder reactions.[2297] Transition metal-based catalysts have been developed, including those based on Cu[2298] or Fe.[2299] Lanthanum triflate [$La(OTf)_3$] has been reported as a reusable catalyst[2300] and Me_3SiNTf_2 has been used as a green Lewis acid catalyst.[2301] Trimethylaluminum/triflimide complexes have been used to catalyze the Diels-Alder reaction of highly hindered systems.[2302] Certain antibodies have been developed that catalyze Diels-Alder reactions.[2303] Natural Diels-Alderase enzymes have been reported but whether the reactions proceed via the concerted, synchronous pericyclic transition state required is an open question.[2304] Several organocatalysts have been developed, including amino catalysts,[2305] *N*-heterocyclic carbenes,[2306] and organocatalysts that are suitable for ionic liquid/water phases.[2307] An

[2288] Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc,* ***1996***, *118*, 3049.

[2289] For a study of the influence of Lewis acids in ionic liquids, see Silvero, G.; Arévalo, M.J.; Bravo, J.L.; Ávalos, M.; Jiménez, J.L.; López, I. *Tetrahedron* ***2005***, *61*, 7105. See López, I.; Silvero, G.; Arévalo, M.J.; Babiano, R.; Palacios, J.C.; Bravo, J.L. *Tetrahedron* ***2007***, *63*, 2901.

[2290] Sun, D.; Sato, F.; Yamada, Y.; Sato, S. *Bull. Chem. Soc. Jpn.* ***2013***, *86*, 276.

[2291] Avalos, M.; Babiano, R.; Bravo, J.L.; Cintas, P.; Jiménez, J.L.; Palacios, J.C.; Silva, M.A. *J. Org. Chem.* ***2000***, *65*, 6613; Zheng, M.; Zhang, M.-H.; Shao, J.-G.; Zhong, Q. *Org. Prep. Proceed. Int.* ***1996***, *28*, 117; Ishihara, J.; Nakadachi, S.; Watanabe, Y.; Hatakeyama, S. *J. Org. Chem.* ***2015***, *80*, 2037.

[2292] For a discussion of the effect of Lewis acids, see Celebi-Olcum, N.; Ess, D.H.; Aviyente, V.; Houk, K.N. *J. Org. Chem.* ***2008***, *73*, *7472*.

[2293] See Shen, J.; Tan. C.-H. *Org. Biomol. Chem.* ***2008***, *6*, 3229.

[2294] See Alston, P.V.; Ottenbrite, R.M. *J. Org. Chem.* ***1975***, *40*, 1111.

[2295] Krenske, E.H.; Perry, E.W.; Jerome, S.V.; Maimone, T.J.; Baran, P.S.; Houk, K.N. *Org. Lett.* ***2012***, *14*, 3016.

[2296] See Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Eur. J. Org. Chem.* ***2001***, 439.

[2297] Chavan, S.P.; Sharma, P.; Krishna, G.R.; Thakkar, M. *Tetrahedron Lett.* ***2003***, *44*, 3001.

[2298] Reymond, S.; Cossy, J. *Chem. Rev.* ***2008***, *108*, 5359.

[2299] Fujiwara, K.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* ***2012***, *134*, 5512.

[2300] Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* ***1992***, *33*, 6815.

[2301] Mathieu, B.; Ghosez, L. *Tetrahedron* ***2002***, *58*, 8219.

[2302] Jung, M.E.; Guzaev, M. *Org. Lett.* ***2012***, *14*, 5169.

[2303] Zhang, X.; Deng, Q.; Yoo, S.H.; Houk, K.N. *J. Org. Chem.* ***2002***, *67*, 9043.

[2304] Klas, K.; Tsukamoto, S.; Sherman, D.H.; Williams, R.M. *J. Org. Chem.* ***2015***, *80*, 11672. For a review of natural [4+2] cyclases, see Jeon, B.-s.; Wang, S.-A.; Ruszczycky, M.W.; Liu, H.-w. *Chem. Rev.* ***2017***, *117*, 5367.

[2305] Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2011***, *133*, 5053; Li, J.-L.; Liu, T.-Y.; Chen, Y.-C. *Acc. Chem. Res.* ***2012***, *45*, 1491.

[2306] Candish, L.; Levens, A.; Lupton, D.W. *J. Am. Chem. Soc.* ***2014***, *136*, 14397; Chen, D.-F.; Rovis, T. *Synthesis* ***2017***, *49*, 293.

[2307] De Nino, A.; Bortolini, O.; Maiuolo, L.; Garofalo, A.; Russo, B.; Sindona, G. *Tetrahedron Lett.* ***2011***, *52*, 1415.

enantioselective, organocatalyzed Diels-Alder reaction has been reported using flow conditions (Sec. 7.D).[2308]

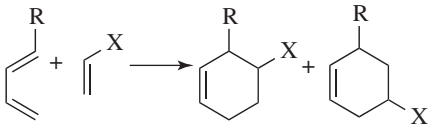
Cationic Diels-Alder catalysts have been developed, such as oxazaborolidine catalysts.[2309] Zirconocene-catalyzed cationic Diels-Alder reactions are known.[2310] Some Diels-Alder reactions can also be catalyzed by the addition of a stable cation radical.[2311] Radical cation Diels-Alder reactions have been reported using visible light photocatalysis.[2312] Photochemically induced Diels-Alder reactions are also known.[2313]

Apart from addition of Lewis acids, a number of other methods have been reported for the acceleration of Diels-Alder reactions,[2314] including the use of microwave irradiation,[2315] ultrasound,[2316] and the use of an ultracentrifuge[2317] (one of several ways to achieve reaction at high pressures).[2318] Solid state Diels-Alder reactions are known,[2319] reactions on solid supports have also been reported,[2320] and zeolites have been used in conjunction with catalytic agents.[2321] One of the most common methods is to use water as a solvent or a co-solvent (a hydrophobic effect).[2322] There are cases of hydrogen-bonding acceleration.[2323] The influence of hydrophobicity of reactants on the reaction has been examined,[2324] as has micellular effects.[2325] It is noted that Diels-Alder reactions have been done in supercritical CO_2[2326] and in supercritical water.[2327] Diels-Alder reactions can be done in ionic liquids,[2328] including asymmetric Diels-Alder reactions.[2329] It has been pointed out that the rate of Diels-Alder reactions is faster in water than in ionic liquids.[2330] Solvent effects are clearly important in cycloaddition reactions.[2331] Another alternative reaction medium is the

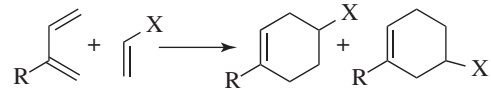
[2308] Porta, R.; Benaglia, M.; Chiroli, V.; Coccia, F.; Puglisi, A. *Isr. J. Chem.* ***2014***, *54*, 381.
[2309] See Sprott, K.T.; Corey, E.J. *Org. Lett.* ***2003***, *5*, 2465; Corey, E.J.; Shibata, T.; Lee, T.W. *J. Am. Chem. Soc.* ***2002***, *124*, 3808.
[2310] Wipf, P.; Xu, W. *Tetrahedron* ***1995***, *51*, 4551.
[2311] For a review, see Bauld, N.L. *Tetrahedron* ***1989***, *45*, 5307. See Gao, D.; Bauld, N.L. *J. Org. Chem.* ***2000***, *65*, 6276. See Saettel, N.J.; Oxgaard, J.; Wiest, O. *Eur. J. Org. Chem.* ***2001***, 1429.
[2312] Lin, S.; Ischay, M.A.; Fry, C.G.; Yoon, T.P. *J. Am. Chem. Soc.* ***2011***, *133*, 19350.
[2313] See Wessig, P.; Matthes, A.; Pick, C. *Org. Biomol. Chem.* ***2011***, *9*, 7599.
[2314] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 765–773.
[2315] For a review, see de la Hoz, A.; Díaz-Ortis, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* ***2000***, 3659; Kaval, N.; Dehaen, W.; Kappe, C.O.; van der Eycken, E. *Org. Biomol. Chem.* ***2004***, *2*, 154.
[2316] Raj, C.P.; Dhas, N.A.; Cherkinski, M.; Gedanken, A.; Braverman, S. *Tetrahedron Lett.* ***1998***, *39*, 5413.
[2317] Dolata, D.P.; Bergman, R. *Tetrahedron Lett.* ***1987***, *28*, 707.
[2318] For reviews, see Isaacs, N.S.; George, A.V. *Chem. Br.* ***1987***, 47–54; Asano, T.; le Noble, W.J. *Chem. Rev.* ***1978***, *78*, 407. See also, Firestone, R.A.; Smith, G.M. *Chem. Ber.* ***1989***, *122*, 1089.
[2319] Kim, J.H.; Hubig, S.M.; Lindeman, S.V.; Kochi, J.K. *J. Am. Chem. Soc.* ***2001***, *123*, 87.
[2320] Yli-Kauhaluoma, J. *Tetrahedron* ***2001***, *57*, 7053.
[2321] Eklund, L.; Axelsson, A.-K.; Nordahl, Å.; Carlson, R. *Acta Chem. Scand.* ***1993***, *47*, 581.
[2322] Breslow, R. *Acc. Chem. Res.* ***1991***, *24*, 159; Breslow, R.; Rizzo, C.J. *J. Am. Chem. Soc.* ***1991***, *113*, 4340; Engberts, J.B.F.N. *Pure Appl. Chem.* ***1995***, *67*, 823; Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* ***1993***, *93*, 741; Otto, S.; Blokzijl, W.; Otto, S.; Egberts, J.B.F.N. *Pure. Appl. Chem.* ***2000***, *72*, 1365; Deshpande, S.S.; Kumar, A. *Tetrahedron* ***2005***, *61*, 8025; Hayashi, Y.; Takeda, M.; Shoji, M.; Morita, M. *Chem. Lett.* ***2007***, *36*, 68.
[2323] Pearson, R.J.; Kassianidis, E.; Philip, D. *Tetrahedron Lett.* ***2004***, *45*, 4777.
[2324] Meijer, A.; Otto, S.; Engberts, J.B.F.N. *J. Org. Chem.* ***1998***, *63*, 8989.
[2325] Jaeger, D.A.; Wang, J. *Tetrahedron Lett.* ***1992***, *33*, 6415.
[2326] Oakes, R.S.; Heppenstall, T.J.; Shezad, N.; Clifford, A.A.; Rayner, C.M. *Chem. Commun.* ***1999***, 1459. For an asymmetric cycloaddition, see Fukuzawa, S.-i.; Metoki, K.; Esumi, S.-i. *Tetrahedron* ***2003***, *59*, 10445.
[2327] Harano, Y.; Sato, H.; Hirata, F. *J. Am. Chem. Soc.* ***2000***, *122*, 2289.
[2328] Bini, R.; Chiappe, C.; Mestre, V.L.; Pomelli, C.S.; Welton, T. *Org. Biomol. Chem.* ***2008***, *6*, 2522.
[2329] Meracz, I.; Oh, T. *Tetrahedron Lett.* ***2003***, *44*, 6465.
[2330] Tiwari, S.; Kumar, A. *Angew. Chem. Int. Ed.* ***2006***, *45*, 4824.
[2331] Tuvi-Arad, I.; Avnir, D. *J. Org. Chem.* ***2011***, *76*, 4973.

use of 5 M $LiClO_4$ in Et_2O as solvent.[2332] An alternative to lithium perchlorate in ether is lithium triflate in acetonitrile.[2333] The addition of HPO_4^- to an aqueous ethanol solution has also been shown to give a small rate enhancement.[2334]

When an unsymmetrical diene adds to an unsymmetrical dienophile, regioisomeric products (not counting stereoisomers) are possible. Rearrangements have been encountered in some cases.[2335] In simple cases, 1-substituted dienes give cyclohexenes with a 1,2- and a 1,3-substitution pattern. 2-Substituted dienes lead to 1,4- and 1,3-disubstituted products. Although mixtures are often obtained, one usually predominates, the one labeled "major," but selectivity depends on the nature of the substituents on both diene and alkene.



Major



Major

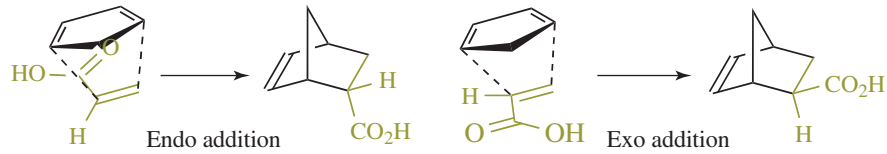
This regioselectivity, in which the "*ortho*" or "*para*" product is favored over the "*meta*," has been explained by molecular orbital considerations.[2336] Competing reactions are polymerization of the diene or dienophile, or both, and [1,2] cycloaddition (**15-59**).

The stereochemistry of the Diels-Alder reaction can be considered from several aspects:[2337]

1. With respect to the dienophile, the addition is stereospecifically *syn*, with very few exceptions.[2338] This means that groups that are *cis* in the alkene will be *cis* in the cyclohexene ring, and groups that are *trans* in the alkene will be *trans* in the cyclohexene ring.
2. With respect to 1,4-disubstituted dienes, fewer cases have been investigated, but here too the reaction is stereospecific and *syn*. Thus, *trans*,*trans*-1,4-diphenylbuta-1,3-diene gives *cis*-1,4-diphenylcyclohexene derivatives. This selectivity is predicted by disrotatory motion of the substituent in the transition state[2339] of the reaction (see **18-27**).
3. The diene must be in the *s-cis* conformation. If it is frozen into the *s-trans* conformation, as in **64** (see above), the reaction does not take place. The diene either must be frozen into the *s-cis* conformation or must be able to achieve it during the reaction.
4. There are two possible ways in which addition can occur to a cyclic diene, if the dienophile is not symmetrical – say a monosubstituted alkene. The substituent on

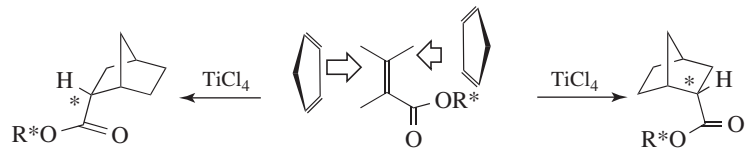
[2332] Grieco, P.A.; Handy, S.T.; Beck, J.P. *Tetrahedron Lett.* ***1994***, *35*, 2663. See Handy, S.T.; Grieco, P.A.; Mineur, C.; Ghosez, L. *Synlett* ***1995***, 565.
[2333] Augé, J.; Gil, R.; Kalsey, S.; Lubin-Germain, N. *Synlett* ***2000***, 877.
[2334] Pai, C.K.; Smith, M.B. *J. Org. Chem.* ***1995***, *60*, 3731.
[2335] Murali, R.; Scheeren, H.W. *Tetrahedron Lett.* ***1999***, *40*, 3029.
[2336] Alston, P.V.; Gordon, M.D.; Ottenbrite, R.M.; Cohen, T. *J. Org. Chem.* ***1983***, *48*, 5051; Kahn, S.D.; Pau, C.F.; Overman, L.E.; Hehre, W.J. *J. Am. Chem. Soc.* ***1986***, *108*, 7381.
[2337] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 759–765; Bakalova, S.M.; Santos, A.G. *J. Org. Chem.* ***2004***, *69*, 8475.
[2338] For an exception, see Meier, H.; Eckes, H.; Niedermann, H.; Kolshorn, H. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1046.
[2339] Robiette, R.; Marchand-Brynaert, J.; Peeters, D. *J. Org. Chem.* ***2002***, *67*, 6823.

the dienophile (usually an electron-withdrawing substituent) may approach under the ring (*endo addition*), or away from the ring (*exo addition*), as shown.



Most of the time, the addition is predominantly *endo*; that is, the more bulky side of the alkene is under the ring, and this is probably true for open-chain dienes also.[2340] However, exceptions are known, and in many cases mixtures of *exo* and *endo* addition products are found.[2341] Secondary orbital interactions[2342] have been invoked, but this approach has been called into question.[2343] There has been a direct evaluation of such interactions, however.[2344] It has been argued that facial selectivity is not due to torsional angle decompression.[2345] The *endo*/*exo* ratio can be influenced by the nature of the solvent.[2346]

5. As seen previously, the Diels-Alder reaction can be both stereoselective and regioselective.[2347] In some cases, the Diels-Alder reaction can be made enantioselective,[2348] as described above. Solvent effects are important in such reactions.[2349] The role of reactant polarity on the course of the reaction has been examined.[2350] Most enantioselective Diels-Alder reactions have used a chiral dienophile (e.g., **65**) and an achiral diene,[2351] along with a Lewis acid catalyst.



66 **65** **67**

R = (+) or (–)-Phenylmenthyl

[2340] See Baldwin, J.E.; Reddy, V.P. *J. Org. Chem.* ***1989***, *54*, 5264. For a theoretical study for *endo* selectivity, see Imade, M.; Hirao, H.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* ***1999***, *64*, 6697.

[2341] See Mülle, P.; Bernardinelli, G.; Rodriguez, D.; Pfyffer, J.; Schaller, J. *Chimia* ***1987***, *41*, 244.

[2342] Hoffmann, R.; Woodward, R.B. *J. Am. Chem. Soc.* ***1965***, *87*, 4388, 4389.

[2343] García, J.I.; Mayoral, J.A.; Salvatella, L. *Acc. Chem. Res.* ***2000***, *33*, 658; García, J.I.; Mayoral, J.A.; Salvatella, L. *Eur. J. Org. Chem.* ***2005***, 85.

[2344] Arrieta, A.; Cossío, F.P.; Lecea, B. *J. Org. Chem.* ***2001***, *66*, 6178.

[2345] Hickey, E.R.; Paquette, L.A. *Tetrahedron Lett.* ***1994***, *35*, 2309, 2313.

[2346] Cainelli, G.; Galletti, P.; Giacomini, D.; Quintavalla, A. *Tetrahedron Lett.* ***2003***, *44*, 93.

[2347] Mörschel, P.; Janikowski, J.; Hilt, G.; Frenking, G. *J. Am. Chem. Soc.* ***2008***, *130*, 8952.

[2348] See Corey, E.J.; Sarshar, S.; Lee, D.-H. *J. Am. Chem. Soc.* ***1994***, *116*, 12089; Helmchen, G.; Karge, R.; Weetman, J. *Mod. Synth. Methods* ***1986***, *4*, 261; Oppolzer, W. *Angew. Chem. Int. Ed.* ***1984***, *23*, 876. See also Macaulay, J.B.; Fallis, A.G. *J. Am. Chem. Soc.* ***1990***, *112*, 1136. See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 791–798.

[2349] Ruiz-López, M.F.; Assfeld, X.; García, J.I.; Mayoral, J.A.; Salvatella, L. *J. Am. Chem. Soc.* ***1993***, *115*, 8780.

[2350] Sustmann, R.; Sicking, W. *J. Am. Chem. Soc.* ***1996***, *118*, 12562.

[2351] For the use of chiral dienes, see Tripathy, R.; Carroll, P.J.; Thornton, E.R. *J. Am. Chem. Soc.* ***1991***, *113*, 7630; Rieger, R.; Breitmaier, E. *Synthesis* ***1990***, 697.

In such cases, addition of the diene to the two faces[2352] of **65** takes place at different rates, and **66** and **67** are formed in different amounts.[2353] An achiral compound can be converted to a chiral compound by a chemical reaction with a compound that is diastereoselective, but each diastereomer is enantiopure. After the reaction, the resulting diastereomers can be separated, providing enantiopure compounds, each with a bond between the molecule of interest and the chiral compound (a chiral auxiliary). Common chiral auxiliaries include chiral carboxylic acids, alcohols, or sultams. In the case illustrated, hydrolysis of the product removes the chiral R group, making it a chiral auxiliary in this reaction. Asymmetric Diels-Alder reactions have also been carried out with achiral dienes and achiral dienophiles, but with an optically active catalyst.[2354] In many cases, asymmetric Lewis acids form a chiral complex with the dienophile.[2355] Chiral organocatalysts are increasingly important.[2356]

Triple bond compounds (—C≡C—Z or Z—C≡C—Z′) may be dienophiles,[2357] generating nonconjugated cyclohexadienes (**68**), and this reaction can be catalyzed by transition metal compounds.[2358]

68

Aromatic rings can be generated by cycloaddition of aryl alkynes.[2359] Allenes react as dienophiles,[2360] but without activating groups they are very poor dienophiles.[2361] Ketenes, however, do not undergo Diels-Alder reactions.[2362]

Many interesting compounds can be prepared by the Diels-Alder reaction,[2363] some of which would be hard to make in any other way. Benzynes, although not isolable, act as

[2352] See Xidos, J.D.; Poirier, R.A.; Pye, C.C.; Burnell, D.J. *J. Org. Chem.* ***1998***, *63*, 105.

[2353] Tomioka, K.; Hamada, N.; Suenaga, T.; Koga, K. *J. Chem. Soc., Perkin Trans. 1* ***1990***, 426; Cativiela, C.; López, P.; Mayoral, J.A. *Tetrahedron: Asymmetry* ***1990***, *1*, 61.

[2354] Evans, D.A.; Barnes, D.M.; Johnson, J.S.; Lectka, T.; von Matt, P.; Miller, S.J.; Murry, J.A.; Norcross, R.D.; Shaughnessy, E.A.; Campos, K.R. *J. Am. Chem. Soc.* ***1999***, *121*, 7582; Corey, E.J. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1651; Doyle, M.P.; Phillips, I.M.; Hu, W. *J. Am. Chem. Soc.* ***2001***, *123*, 5366; Owens, T.D.; Hollander, F.J.; Oliver A.G.; Ellman, J.A. *J. Am. Chem. Soc.* ***2001***, *123*, 1539; Fukuzawa, S.; Komuro, Y.; Nakano, N.; Obara, S. *Tetrahedron Lett.* ***2003***, *44*, 3671.

[2355] Hawkins, J.M.; Loren, S.; Nambu, M. *J. Am. Chem Soc.* ***1994***, *116*, 1657. See Sibi, M.P.; Venkatraman, L.; Liu, M.; Jaspersé, C.P. *J. Am. Chem. Soc.* ***2001***, *123*, 8444.

[2356] Liu, D.; Canales, E.; Corey, E.J. *J. Am. Chem. Soc.* ***2007***, *129*, 1498; Singh, R.P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc.* ***2008***, *130*, 2422; Paddon-Row, M.N.; Kwan, L.C.H.; Willis, A.C.; Sherburn, M.S. *Angew. Chem. Int. Ed.* ***2008***, *47*, 7013.

[2357] See Bastide, J.; Henri-Rousseau, O. in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 447–522; Fuks, R.; Viehe, H.G. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 477–508.

[2358] See Paik, S.-J.; Son, S.U.; Chung, Y.K. *Org. Lett.* ***1999***, *1*, 2045.

[2359] This type of Diels-Alder reaction has been called the dehydro-Diels-Alder. See Wessig, P.; Gunnar Müller, G. *Chem. Rev.* ***2008***, *108*, 2051; Dunetz, J.R.; Danheiser, R.L. *J. Am. Chem. Soc.* ***2005***, *127*, 5776; Dai, M.; Sarlah, D.; Yu, M.; Danishefsky, S.J.; Jones, G.O.; Houk, K.N. *J. Am. Chem. Soc.* ***2007***, *129*, 645.

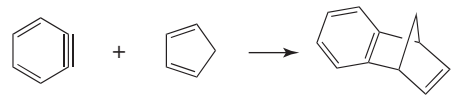
[2360] Pham, H.V.; Houk, K.N. *J. Org. Chem.* ***2014***, *79*, 8968.

[2361] See Hopf, H. in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, pp. 563–577. See Nendel, M.; Tolbert, L.M.; Herring, L.E.; Islam, Md.N.; Houk, K.N. *J. Org. Chem.* ***1999***, *64*, 976.

[2362] Ketenes react with conjugated dienes to give 1,2 addition (see **15-45**).

[2363] See Nicolaou, K.C.; Snyder, S.A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1669.

dienophiles and can be trapped with dienes, as shown for the preparation of **69** from benzyne and cyclopentadiene.[2364]



69

Naphthalene and phenanthrene are poor reaction partners, although naphthalene has given Diels-Alder addition at high pressures.[2365] Anthracene and other compounds with at least three linear benzene rings give Diels-Alder reactions readily.

For both all-carbon and hetero systems, the "diene" can be a conjugated enyne. If the geometry of the molecule is suitable, the diene can even be nonconjugated, as shown with bicyclo[2.2.1]hepta-2,5-diene.[2366]

The reaction shown above is known as the *homo-Diels-Alder reaction*. A similar reaction has been reported with alkynes, using a mixture of a Co complex, ZnI_2, and $Bu_4N^+ BH_4^-$.[2367]

Intramolecular versions of the Diels-Alder reaction are well known,[2368] and they are a powerful method for the synthesis of mono- and polycyclic compounds.[2369] The origin of *cis*/*trans* stereoselectivity has been examined using density functional theory.[2370] Enantioselective organocatalytic intramolecular Diels-Alder reactions are known.[2371]

Internal Diels-Alder reactions can be accomplished by linking the diene and alkene by a tether, usually of carbon atoms. Dienophile twisting and substituent effects influence the rate of cycloaddition.[2372] Replacing the tether with functional groups allow the selectivity inherent to the intramolecular cycloaddition, but the tether can be cleaved to give a functionalized cyclohexene derivative. Such tethered reactions allow enhancement of stereoselectivity,[2373] and sometimes reactivity, relative to an untethered reaction,

[2364] See Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, ***1967***, pp. 200–239; Bryce, M.R.; Vernon, J.M. *Adv. Heterocycl. Chem.* ***1981***, *28*, 183–229. Also see Liu, W.; You, F.; Mocella, C.J.; Harman, W.D. *J. Am. Chem. Soc.* ***2006***, *128*, 1426.

[2365] Plieninger, H.; Wild, D.; Westphal, J. *Tetrahedron* ***1969***, *25*, 5561.

[2366] See Paquette, L.A.; Kesselmayer, M.A.; Künzer, H. *J. Org. Chem.* ***1988***, *53*, 5183.

[2367] Hilt, G.; du Mesnil, F.-X. *Tetrahedron Lett.* ***2000***, *41*, 6757.

[2368] For a review of natural product syntheses using Diels-Alder reactions, see Takao, K.-i.; Munakata, R.; Tadano, K.-i. *Chem. Rev.* ***2005***, *105*, 4779.

[2369] Oppolzer, W. *Angew. Chem. Int. Ed.* ***1977***, *16*, 1; Brieger, G.; Bennett, J.N. *Chem. Rev.* ***1980***, *80*, 63 (see p. 67); Fallis, A.G. *Can. J. Chem.* ***1984***, *62*, 183; Smith, M.B. *Org. Prep. Proceed. Int.* ***1990***, *22*, 315; Parvatkar, P.T.; Kadam, H.K.; Tilve, S.G. *Tetrahedron* ***2014***, *70*, 2857.

[2370] Paddon-Row, M.N.; Moran, D.; Jones, G.A.; Sherburn, M.S. *J. Org. Chem.* ***2005***, *70*, 10841.

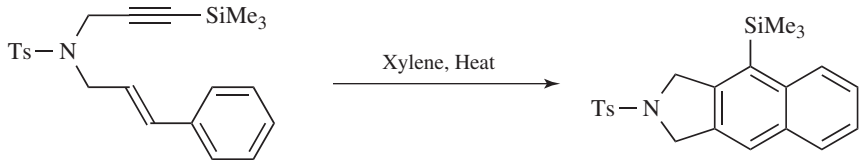
[2371] Duarte, F.J.S.; Santos, A.G. *J. Org. Chem.* ***2012***, *77*, 3252.

[2372] Khuong, K.S.; Beaudry, C.M.; Trauner, D.; Houk, K.N. *J. Am. Chem. Soc.* ***2005***, *127*, 3688.

[2373] See Tantillo, D.J.; Houk, K.N.; Jung, M.E. *J. Org. Chem.* ***2001***, *66*, 1938.

giving an indirect method for enhancing those parameters. Tethers or linkages include C—O—SiR_2—C,[2374] C—O—SiR_2—O—C,[2375] or hydroxamides.[2376] The nature of the tether plays a role in *cis*/*trans* selectivity for the intramolecular reaction.[2377]

Aromatic derivatives can be prepared from more saturated precursors via a two-step process defined as a *dehydrogenative Diels-Alder reaction*.[2378] In initial studies, the dehydrogenative cycloaddition of dieneynes possessing a diene in the form of a styrene moiety, such as **70**, gave the cycloadduct, **71**.[2378] A hexadehydro Diels-Alder cycloisomerization has been reported.[2379]



70 **71**

The Diels-Alder reaction is usually reversible, although the retro reaction typically occurs at significantly higher temperatures than the forward reaction. However, the reaction is reversible[2380] and this fact has been used synthetically. The *retro*-Diels-Alder reaction has also been done in water.[2381] A convenient substitute for butadiene in the Diels-Alder reaction is the compound 3-sulfolene since the latter is a solid, which is easy to handle, while butadiene is gas.[2382] Butadiene is generated *in situ*; 3-sulfolene is heated and a reverse Diels-Alder reaction generates SO_2 and buta-1,3-diene, which reacts with a suitable alkene.

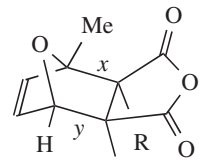
There are, broadly speaking, three possible mechanisms that have been considered for the uncatalyzed Diels-Alder reaction.[2383]

[2374] Stork, G.; Chan, T.Y.; Breault, G.A. *J. Am. Chem. Soc.* ***1992***, *114*, 7578.
[2375] Craig, D.; Reader, J.C. *Tetrahedron Lett.* ***1992***, *33*, 6165.
[2376] Ishikawa, T.; Senzaki, M.; Kadoya, R.; Morimoto, T.; Miyake, N.; Izawa, M.; Saito, S.; Kobayashi, H. *J. Am. Chem. Soc.* ***2001***, *123*, 4607.
[2377] Paddon-Row, M.N.; Longshaw, A.I.; Willis, A.C.; Sherburn, M.S. *Chem. Asian J.* ***2009***, *4*, 126.
[2378] Ozawa, T.; Kurahashi, T.; Matsubara, S. *Org. Lett.* ***2011***, *13*, 5390. See Yu, P.; Yang, Z.; Liang, Y.; Hong, X.; Li, Y.; Houk, K.N. *J. Am. Chem. Soc.* ***2016***, *138*, 8247; Ajaz, A.; Bradley, A.Z.; Burrell, R.C.; Hoi, W.; Li, H.; Daoust, K.J.; Bovee, L.B.; DiRico, K.J.; Johnson, R.P. *J. Org. Chem.* ***2011***, *76*, 9320; Kocsis, L.S.; Benedetti, E.; Brummond, K.M. *Org. Lett.* ***2012***, *14*, 4430. For an example of a dehydrogenative reaction that takes place prior to the Diels-Alder reaction, see Stang, E.M.; White, M.C. *J. Am. Chem. Soc.* ***2011***, *133*, 14892.
[2379] Wang, T.; Niu, D.; Hoye, T.R. *J. Am. Chem. Soc.* ***2016***, *138*, 7832.
[2380] See Ichihara, A. *Synthesis* ***1987***, 207; Lasne, M.; Ripoll, J.L. *Synthesis* ***1985***, 121; Kwart, H.; King, K. *Chem. Rev.* ***1968***, *68*, 415.
[2381] Wijnen, J.W.; Engberts, J.B.F.N. *J. Org. Chem.* ***1997***, *62*, 2039.
[2382] Sample Jr., T.E.; Hatch, L.F. *Org. Synth.* ***VI***, 454. For a review, see Chou, T.; Tso, H. *Org. Prep. Proced. Int.* ***1989***, *21*, 257.
[2383] See Sauer, J.; Sustmann, R. *Angew. Chem. Int. Ed.* ***1980***, *19*, 779; Houk, K.N. *Top. Curr. Chem.* ***1979***, *79*, 1; Babichev, S.S.; Kovtunenko, V.A.; Voitenko, Z.V.; Tyltin, A.K. *Russ. Chem. Rev.* ***1988***, *57*, 397. For a discussion of synchronous vs. nonsynchronous mechanisms, see Beno, B.R.; Houk, K.N.; Singleton, D.A. *J. Am. Chem. Soc.* ***1996***, *118*, 9984; Singleton, D.A.; Schulmeier, B.E.; Hang, C.; Thomas, A.A.; Leung, S.-W.; Merrigan, S.R. *Tetrahedron* ***2001***, *57*, 5149. Also see, Li, Y.; Houk, K.N. *J. Am. Chem. Soc.* ***1993***, *115*, 7478.

1. The bulk of the evidence suggests that most Diels-Alder reactions take place by the one-step cyclic mechanism,[2384] although it is possible that a diradical[2385] or even a diion[2386] mechanism may be taking place in some cases.
2. Electrophilicity/nucleophilicity indices have been analyzed to understand the mechanism of polar Diels-Alder reactions.[2387]
3. Radical cation Diels-Alder reactions have been considered.[2388]

The main evidence in support of the one-step mechanism is as follows:

1. The reaction is stereospecific in both the diene and dienophile. A completely free diradical or diion probably would not be able to retain its configuration.
2. In general, the rates of Diels-Alder reactions depend very little on the nature of the solvent. This observation would rule out a diion intermediate because polar solvents increase the rates of reactions that develop charges in the transition state.
3. It was shown that, in the decomposition of **72**, the isotope effect k_I/k_{II} was equal to 1.00 within experimental error.[2389]



I: R = H, R' = D

II: R = D, R' = H

72

If bond *x* were to break before bond *y*, there should surely be a secondary isotope effect. This result strongly indicates that the bond breaking of *x* and *y* is simultaneous. This is the reverse of a Diels-Alder reaction and, by the principle of microscopic reversibility, the mechanism of the forward reaction should involve simultaneous formation of bonds *x* and *y*. Subsequently, a similar experiment was carried out on the forward reaction[2390] and the result was the same. There is other evidence for this mechanism.[2391] However, the fact that the mechanism is concerted does not necessarily mean that it is synchronous.[2392] In the transition state of a synchronous reaction both new σ bonds would be formed to the same extent. However, a Diels-Alder reaction with nonsymmetrical components might very well be nonsynchronous;[2393] that is, it could have a transition state in which one bond has been

[2384] For a contrary view, see Dewar, M.J.S.; Olivella, S.; Stewart, J.J.P. *J. Am. Chem. Soc.* ***1986***, *108*, 5771. For arguments against this view, see Houk, K.N.; Lin, Y.; Brown, F.K. *J. Am. Chem. Soc.* ***1986***, *108*, 554; Gajewski, J.J.; Peterson, K.B.; Kagel, J.R.; Huang, Y.C.J. *J. Am. Chem. Soc.* ***1989***, *111*, 9078.

[2385] See van Mele, B.; Huybrechts, G. *Int. J. Chem. Kinet.* ***1987***, *19*, 363; ***1989***, *21*, 967.

[2386] See Gassman, P.G.; Gorman, D.B. *J. Am. Chem. Soc.* ***1990***, *112*, 8624.

[2387] Domingo, L.R.; Sáez, J.A. *Org. Biomol. Chem.* ***2009***, *7*, 3576. See also, Soto-Delgado, J.; Domingo, L.R.; Contreras, R. *Org. Biomol. Chem.* ***2010***, *8*, 3678.

[2388] Haberl, U.; Wiest, O.; Steckhan, E. *J. Am. Chem. Soc.* ***1999***, *121*, 6730.

[2389] Seltzer, S. *J. Am. Chem. Soc.* ***1965***, *87*, 1534; Gajewski, J.J. *Isot. Org. Chem.* ***1987***, *7*, 115–176.

[2390] van Sickle, D.E.; Rodin, J.O. *J. Am. Chem. Soc.* ***1964***, *86*, 3091.

[2391] See Rücker, C.; Lang, D.; Sauer, J.; Friege, H.; Sustmann, R. *Chem. Ber.* ***1980***, *113*, 1663; Tolbert, L.M.; Ali, M.B. *J. Am. Chem. Soc.* ***1981***, *103*, 2104.

[2392] For a study of a reaction that is concerted but asynchronous, see Avalos, M.; Babiano, R.; Clemente, F.R.; Cintas, P.; Gordillo, R.; Jiménez, J.L.; Palacios, J.C. *J. Org. Chem.* ***2000***, *65*, 8251.

[2393] Houk, K.N.; Loncharich, R.J.; Blake, J.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***1989***, *111*, 9172; Lehd, M.; Jensen, F. *J. Org. Chem.* ***1990***, *55*, 1034.

formed to a greater degree than the other.[2393,2394] A biradical mechanism has been proposed for some Diels-Alder reactions.[2395]

Normally, a reactive alkene has electron-withdrawing groups and is considered to be an electrophile.[2396] If the alkene contains strongly electron-releasing groups and the diene has strongly electron-withdrawing groups, reactivity can be reversed. Perchlorocyclopentadiene reacts better with cyclopentene than with maleic anhydride, for example, and not at all with tetracyanoethylene, although the latter is normally the most reactive dienophile known. Reactions of this type are said to proceed with *inverse electron demand*.[2397] It is known that alkynyl boronates participate in inverse electron demand cyclization.[2398] The Ag-catalyzed inverse demand reaction of 1,2-diazines and siloxyalkynes has been reported.[2399]

The Diels-Alder reaction generally takes place rapidly and conveniently. In sharp contrast, the apparently similar dimerization of alkenes to cyclobutanes (**15-59**) gives very poor results in most cases, except when photochemically induced. Woodward and Hoffmann have shown that these contrasting results can be explained by the *principle of conservation of orbital symmetry*,[2400] which predicts that certain reactions are allowed and others forbidden. The orbital symmetry rules (also called the *Woodward-Hoffmann rules*)[2401] apply *only to concerted reactions*, for example, and are based on the principle that reactions take place in such a way as to maintain maximum bonding throughout the course of the reaction. In separate work, Fukui[2402] used molecular orbital arguments to explain these reactions. There are several ways of applying the orbital symmetry principle to cycloaddition reactions, three of which are used more frequently than others.[2403] Of these three, two will be discussed: the frontier orbital method and the Möbius-Hückel method. The third, called the correlation diagram method,[2404] is less convenient to apply than the other two.

[2394] See Domingo, L.R.; Aurell, M.J.; Pérez, P.; Contreras, R. *J. Org. Chem.* ***2003***, *68*, 3884.

[2395] de Echagüen, C.O.; Ortuño, R.M. *Tetrahedron Lett.* ***1995***, *36*, 749. See Li, Y.; Padias, A.B.; Hall Jr., H.K. *J. Org. Chem.* ***1993***, *58*, 7049 for a discussion of diradicals in concerted Diels-Alder reactions.

[2396] Sauer, J.; Wiest, H. *Angew. Chem. Int. Ed.* ***1962***, *1*, 269.

[2397] Boger, D.L.; Patel, M. *Prog. Heterocycl. Chem.* ***1989***, *1*, 30. Also see, Wan, Z.-K.; Snyder, J.K. *Tetrahedron Lett.* ***1998***, *39*, 2487. See Jiang, X.; Wang, R. *Chem. Rev.* ***2013***, *113*, 5515. See Levandowski, B.J.; Hamlin, T.A.; Bickelhaupt, F.M.; Houk, K.N. *J. Org. Chem.* ***2017***, *82*, 8668.

[2398] For a mechanistic study, see Gomez-Bengoa, E.; Helm, M.D.; Plant, A.; Harrity, J.P.A. *J. Am. Chem. Soc.* ***2007***, *129*, 2691.

[2399] Türkmen, Y.E.; Montavon, T.J.; Kozmin, S.E.; Rawal, V.E. *J. Am. Chem. Soc.* ***2012***, *134*, 9062.

[2400] Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, ***1999***, pp. 31–56; Gilchrist, T.L.; Storr, R.C. *Organic Reactions and Orbital Symmetry*, 2nd ed., Cambridge University Press, Cambridge, ***1979***; Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, Wiley, NY, ***1976***; Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970*** [the text of this book also appears in *Angew. Chem. Int. Ed.* ***1969***, *8*, 781]; Simonetta, M. *Top. Curr. Chem.* ***1973***, *42*, 1; Houk, K.N. *Surv. Prog. Chem.* ***1973***, *6*, 113; Gill, G.B. *Q. Rev. Chem. Soc.* ***1968***, *22*, 338; Miller, S.I. *Adv. Phys. Org. Chem.* ***1968***, *6*, 185; Miller, S.I. *Bull. Soc. Chim. Fr.* ***1966***, 4031.

[2401] Chattaraj, P.K.; Fuentealba, P.; Gómez, B.; Contreras, R. *J. Am. Chem. Soc.* ***2000***, *122*, 348. See Carpenter, B.K. *J. Org. Chem.* ***2015***, *80*, 11630.

[2402] Fukui, K.; Yonezawa, T.; Nagata, C.; Shingu, H. *J. Chem. Phys.* ***1954***, *22*, 1433; Fukui, K. in *Molecular Orbitals in Chemistry, Physics and Biology*, Löwdin, P.-O.; Pullman, B. (Eds.), Academic Press, NY, ***1964***, p. 513.

[2403] See Epiotis, N.D. *Theory of Organic Reactions*, Springer, NY, ***1978***; Ponec, R. *Collect. Czech. Chem. Commun.* ***1984***, *49*, 455; ***1985***, *50*, 1121; Hua-ming, Z.; De-xiang, W. *Tetrahedron* ***1986***, *42*, 515; Bernardi, F.; Olivucci, M.; Robb, M.A. *Res. Chem. Intermed.* ***1989***, *12*, 217; *Acc. Chem. Res.* ***1990***, *23*, 405.

[2404] See Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***; *Angew. Chem. Int. Ed.* ***1969***, *8*, 781; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 352–366; Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 378–389; Yates, K. *Hückel Molecular Orbital Theory*, Academic Press, NY, ***1978***, pp. 263–276.

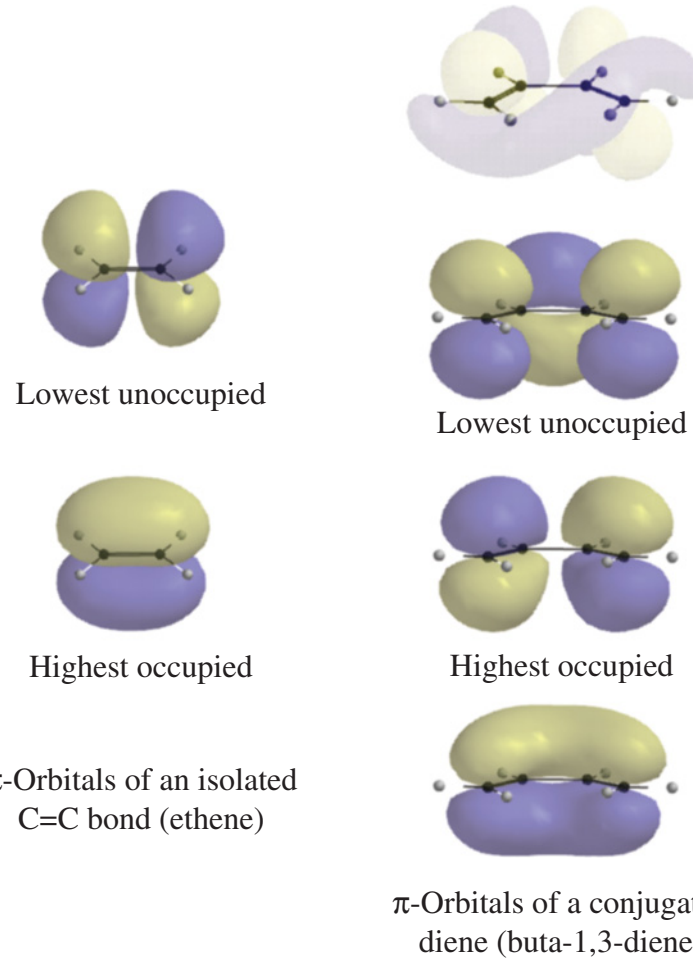


FIGURE 15.1. Schematic drawings of the π orbitals of an isolated C═C bond and a conjugated diene.

The Frontier Orbital Method[2405] As applied to cycloaddition reactions, the rule is that reactions are allowed only when all overlaps between the highest occupied molecular orbital (HOMO) of one reactant and the lowest unoccupied molecular orbital (LUMO) of the other are such that a positive lobe overlaps only with another positive lobe and a negative lobe only with another negative lobe.[2406] Recall that monoalkenes have two π molecular orbitals (Sec. 1.D) and that conjugated dienes have four (Sec. 2.C), as shown in Figure 15.1.

A concerted cyclization of two monoalkenes (a [2 + 2] reaction) is not allowed because it would require that a positive lobe overlap with a negative lobe (Figure 15.2).

[2405] Fukui, K.; Fujimoto, H. *Bull. Chem. Soc. Jpn.* ***1969***, *42*, 3399; Fukui, K. *Acc. Chem. Res.* ***1971***, *4*, 57; Houk, K.N. *Acc. Chem. Res.* ***1975***, *8*, 361. See Chu, S. *Tetrahedron* ***1978***, *34*, 645; Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, ***1999***; Fukui, K. *Angew. Chem. Int. Ed.* ***1982***, *21*, 801.

[2406] For a discussion of molecules with small HOMO-LUMO gaps, see Perepichka, D.F.; Bryce, M.R. *Angew. Chem. Int. Ed.* ***2005***, *44*, 5370.

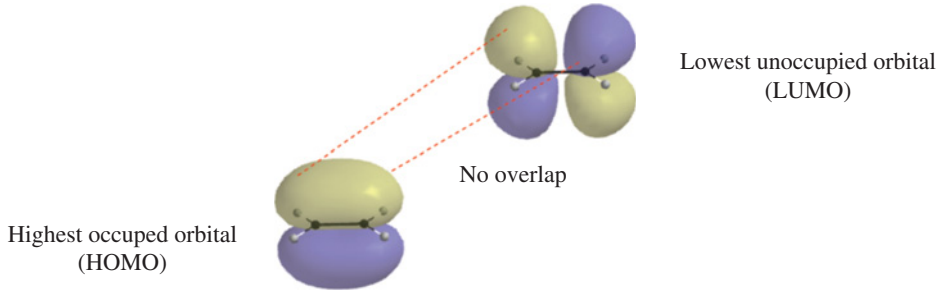


FIGURE 15.2. No overlap of orbitals for a thermal [2 + 2] cycloaddition.

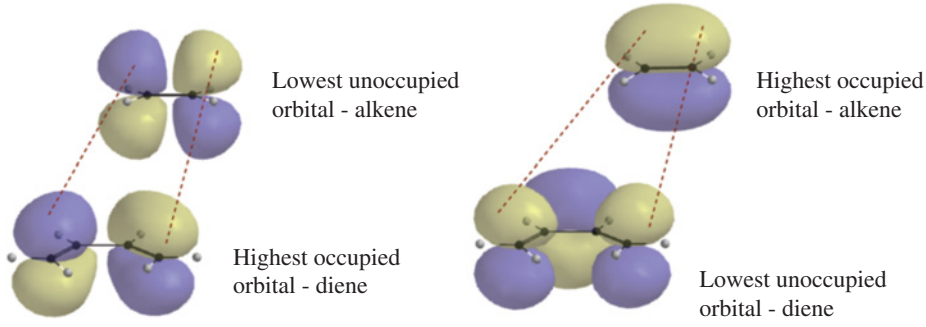


FIGURE 15.3. Two ways for orbitals to overlap in a thermal [4 + 2] cycloaddition.

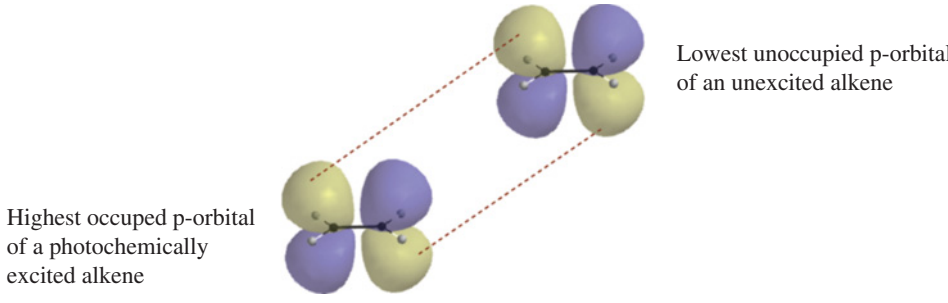


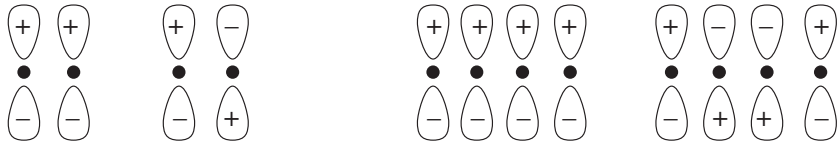
FIGURE 15.4. Overlap of orbitals in a photochemical [2 + 2] cycloaddition.

On the other hand, the Diels-Alder reaction (a [4 + 2] reaction) is allowed, when considered from either direction (Figure 15.3).

These considerations are reversed when the ring closures are photochemically induced since in such cases an electron is promoted to a vacant orbital before the reaction occurs. Obviously, the [2 + 2] reaction is now allowed (Figure 15.4) and the [4 + 2] reaction disallowed.

The reverse reactions follow the same rules, by the principle of microscopic reversibility. In fact, the retro-Diels-Alder reaction is well known, while cleavage of the strained cyclobutanes require more strenuous conditions.[2407]

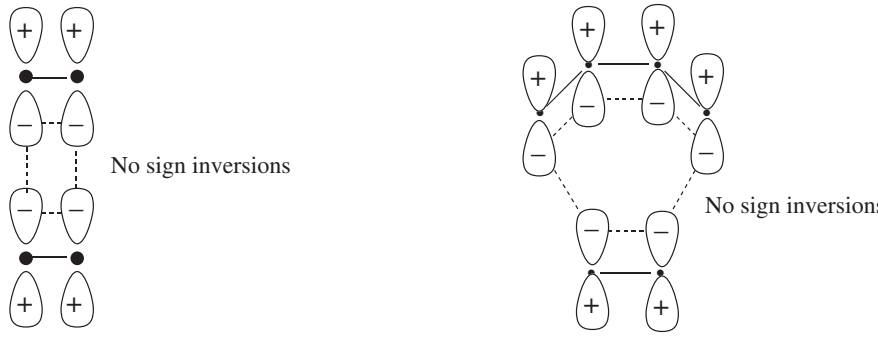
[2407] For the reactivity of strained cycloakenes, see Liu, F.; Paton, R.S.; Kim, S.; Liang, Y.; Houk, K.N. *J. Am. Chem. Soc.* ***2013***, *135*, 15642.



Two basissets for an isolated double bond

Two basissets for a conjugated diene

FIGURE 15.5. Some basis sets.



Transition state for 2 + 2 cyclization (Hückel system)

Transition state for 4 + 2 cyclization (Hückel system)

FIGURE 15.6. Transition states illustrating Hückel-Möbius rules for cycloaddition reactions.

The Möbius-Hückel Method[2408] In this method, the orbital symmetry rules are related to the Hückel aromaticity rule discussed in Chapter 2.[2409] Hückel's rule, which states that a cyclic system of electrons is aromatic (hence, stable) when it consists of $4n + 2$ electrons, applies of course to molecules in their ground states. In applying the orbital symmetry principle, ground states are not of concern, but the focus is on transition states. In the present method, the molecular orbitals themselves are not examined, but rather it is the *p* orbitals before they overlap to form the molecular orbitals that are examined. Such a set of *p* orbitals is called a *basis set* (Figure 15.5).

In investigating the possibility of a concerted reaction, the basis sets are put into the position they would occupy in the transition state, as shown in Figure 15.6 for both the [2 + 2] and the [4 + 2] ring closures, looking for *sign inversions*.

In Figure 15.6 there are no sign inversions in either case. That is, the dashed line connects only lobes with a minus sign. Systems with *zero or an even number* of sign inversions are called *Hückel systems*. Because they have no sign inversions, both of these systems are Hückel systems. Systems with *an odd number* of sign inversions are called *Möbius systems* (because of the similarity to the Möbius strip, which is a mathematical surface, shown in Figure 15.7).[2410]

[2408] Zimmerman, H.E. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 53–107; Zimmerman, H.E *Acc. Chem. Res.* ***1971***, *4*, 272; Dewar, M.J.S. *Angew. Chem. Int. Ed.* ***1971***, *10*, 761; Jefford, C.W.; Burger, U. *Chimia* ***1971***, *25*, 297; Herndon, W.C. *J. Chem. Educ.* ***1981***, *58*, 371.

[2409] See Morao, I.; Cossío, F.P. *J. Org. Chem.* ***1999***, *64*, 1868.

[2410] See Hennigar, K.H.R.; Langler, R.F. *Aust. J. Chem.* ***2010***, *63*, 490.

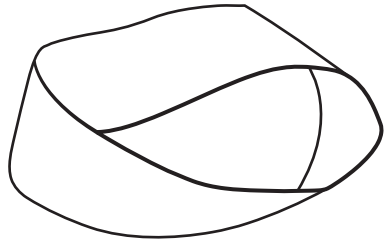


FIGURE 15.7. A Möbius strip. Such a strip is easily constructed by twisting a thin strip of paper 180° and fastening the ends together.

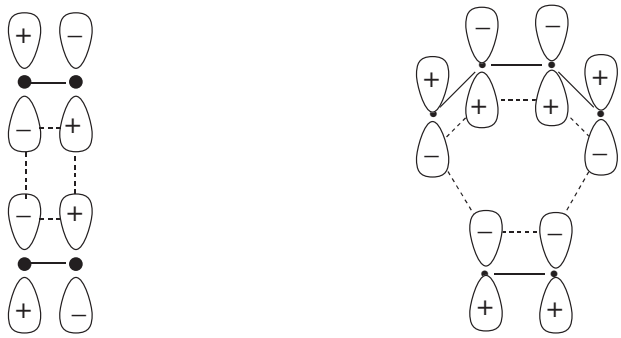


FIGURE 15.8. Transition states of [2 + 2] and [4 + 2] cyclizations involving other basis sets.

Möbius systems do not enter into either of these reactions, but an example of such a system is shown in **18-28**, part B. Double-twist Möbius aromaticity has been invoked in the Diels-Alder transition state for the reaction of a 5,6-di-*tert*-butyl-substituted decapentaene.[2411]

The rule may then be stated: A thermal pericyclic reaction involving a Hückel system is allowed only if the total number of electrons is $4n + 2$. A thermal pericyclic reaction involving a Möbius system is allowed only if the total number of electrons is $4n$. For photochemical reactions these rules are reversed. Since both the [4 + 2] and [2 + 2] cycloadditions are Hückel systems, the Möbius-Hückel method predicts that the [4 + 2] reaction, with 6 electrons, is thermally allowed, but the [2 + 2] reaction is not. On the other hand, the [2 + 2] reaction is allowed photochemically, while the [4 + 2] reaction is forbidden.

Note that both the [2 + 2] and [4 + 2] transition states are Hückel systems no matter what basis sets were chosen. For example, Figure 15.8 shows other basis sets that might have been chosen. In every case there will be zero or an even number of sign inversions.

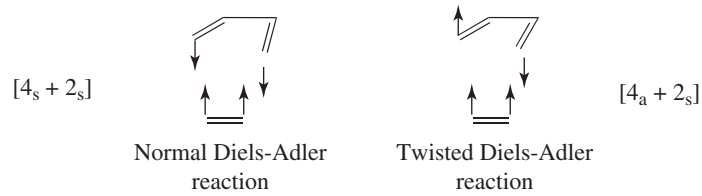
Thus, the FMO and the Hückel-Möbius method (and the correlation diagram method as well) lead to the same conclusions: thermal [4 + 2] cycloadditions and photochemical [2 + 2] cycloadditions (and the reverse ring openings) are allowed, while photochemical [4 + 2] and thermal [2 + 2] ring closings (and openings) are forbidden. In general, cycloaddition reactions allowed thermally are those with $4n + 2$ electrons, while those allowed photochemically have $4n$ electrons.

It must be emphasized once again that the rules apply only to cycloaddition reactions that take place by cyclic mechanisms: e.g., two σ bonds are formed (or broken) at about the same

[2411] Rzepa, H.S. *Chem. Commun.* ***2005***, 5220.

time.[2412] The rule does not apply to cases where one bond is clearly formed (or broken) before the other. It must further be emphasized that the fact that the concerted, thermal Diels-Alder reaction is allowed by the principle of conservation of orbital symmetry does not constitute proof that any given Diels-Alder reaction is also concerted. The principle merely says the mechanism is allowed, not that it must go by this pathway. However, the principle does say that thermal [2 + 2] cycloadditions in which the molecules assume a face to face geometry cannot[2413] take place by a cyclic mechanism because their activation energies would be too high. In **15-58** it will be seen that such reactions largely occur by two-step mechanisms. Similarly, [4 + 2] photochemical cycloadditions are also known, but the fact that they are not stereospecific indicates that they also take place by the two-step diradical mechanism.[2414]

In all of the above discussion it has been assumed that a given molecule forms both the new σ bonds from the same face of the π system. This manner of bond formation, called *suprafacial*, is certainly most reasonable and almost always takes place. The subscript *s* is used to designate this geometry, and a normal Diels-Alder reaction would be called a $[_\pi 2_s + _\pi 4_s]$ cycloaddition (the subscript π indicates that π electrons are involved in the cycloaddition). However, there is another approach in which the newly forming bonds of the diene lie on *opposite* faces of the π system, that is, they point in opposite directions. This type of orientation of the newly formed bonds is called *antarafacial*, and the reaction would be a $[_\pi 2_s + _\pi 4_a]$ cycloaddition (*a* stands for antarafacial).



The FMO shows that this reaction (and consequently the reverse ring-opening reactions) are thermally forbidden and photochemically allowed. Thus in order for a $[_\pi 2_s + _\pi 4_a]$ reaction to proceed, overlap between the highest occupied π orbital of the alkene and the lowest unoccupied π orbital of the diene would have to occur, as shown in Figure 15.9, with a + lobe overlapping a – lobe. Since like signs are no longer overlapping, the thermal reaction is now forbidden.

Similarly, thermal $[_\pi 4_s + _\pi 2_a]$ and $[_\pi 2_s + _\pi 4_a]$ cyclizations are forbidden, while thermal $[_\pi 4_a + _\pi 2_a]$ and $[_\pi 2_s + _\pi 2_a]$ cyclizations are allowed, and these considerations are reversed for the corresponding photochemical processes. Of course, an antarafacial approach is highly unlikely in a [4 + 2] cyclization,[2415] but larger ring closures could take place by such a pathway, and [2 + 2] thermal cyclizations, where the $[_\pi 2_s + _\pi 2_s]$ pathway is forbidden, can also

[2412] See Lehr, R.E.; Marchand, A.P. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 1, Academic Press, NY, ***1977***, pp. 1–51.

[2413] See Baldwin, J.E.; Andrist, A.H.; Pinschmidt Jr., R.K. *Acc. Chem. Res.* ***1972***, *5*, 402; Berson, J.A. *Acc. Chem. Res.* ***1972***, *5*, 406; Baldwin, J.E. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 273–302.

[2414] See Sieber, W.; Heimgartner, H.; Hansen, H.; Schmid, H. *Helv. Chim. Acta* ***1972***, *55*, 3005; Bartlett, P.D.; Helgeson, R.; Wersel, O.A. *Pure Appl. Chem.* ***1968***, *16*, 187; Seeley, D.A. *J. Am. Chem. Soc.* ***1972***, *94*, 4378; Kaupp, G. *Angew. Chem. Int. Ed.* ***1972***, *11*, 313, 718.

[2415] A possible photochemical [4+2] cycloaddition has been reported: Hart, H.; Miyashi, T.; Buchanan, D.N.; Sasson, S. *J. Am. Chem. Soc.* ***1974***, *96*, 4857.

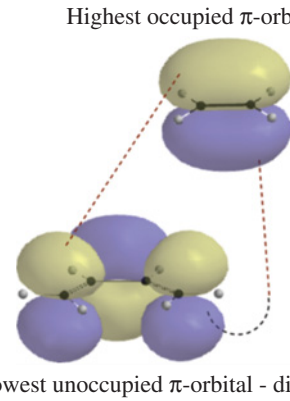


FIGURE 15.9. Overlap of orbitals in an antarafacial thermal [4 + 2] cycloaddition.

do so in certain cases (see **15-59**). Whether a given cycloaddition is allowed or forbidden depends on the geometry of approach of the two molecules involved.

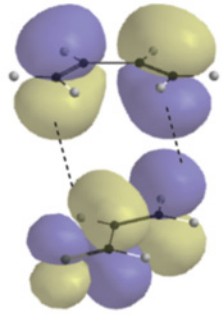
Symmetry considerations have also been advanced to explain predominant *endo* addition.[2416] In the case of [4 + 2] addition of butadiene to acrolein, the approach can be *exo* or *endo*. It can be seen (Figure 15.10) that whether the HOMO of the diene overlaps with the LUMO of acrolein or vice versa, the *endo* orientation is stabilized by additional secondary overlap of orbitals[2417] of like sign (dashed lines between heavy dots). Addition from the *exo* direction has no such stabilization since the sign of the orbitals do not match.

OS **II**, 102; **III**, 310, 807; **IV**, 238, 738, 890, 964; **V**, 414, 424, 604, 985, 1037; **VI**, 82, 196, 422, 427, 445, 454; **VII**, 4, 312, 485; **VIII**, 31, 38, 298, 353, 444, 597; **IX**, 186, 722; **75**, 201; **81**, 171. For a reverse Diels-Alder reaction, see OS **VII**, 339.

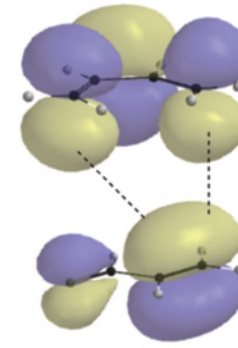
15-57 Heteroatom Diels-Alder Reactions[2418]

Other double bond and triple bond compounds that contain heteroatoms can be dienophiles in *Diels-Alder reactions* and they give rise to heterocyclic compounds[2419] in what is commonly known as the *hetero-Diels-Alder reaction*.[2420] Among these are N≡C–, –N=C–,[2421] iminium salts,[2422] –N=N–, O=N–,[2423] and –C=O compounds[2424] and even molecular

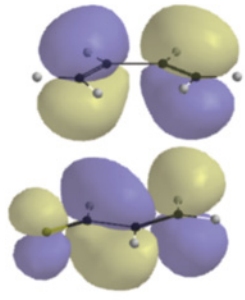
[2416] Hoffmann, R.; Woodward, R.B. *J. Am. Chem. Soc.* ***1965***, *87*, 4388.
[2417] See Ginsburg, D. *Tetrahedron* ***1983***, *39*, 2095; Gleiter, R.; Paquette, L.A. *Acc. Chem. Res.* ***1983***, *16*, 328. See Singleton, D.A. *J. Am. Chem. Soc.* ***1992***, *114*, 6563.
[2418] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 783–791.
[2419] See McCarrick, M.A.; Wu, Y.-D.; Houk, K.N. *J. Org. Chem.* ***1993***, *58*, 3330.
[2420] Eschenbrenner-Lux, V.; Kumar, K.; Waldmann, H. *Angew. Chem. Int. Ed.* ***2014***, *53*, 11146.
[2421] Anniyappan, M.; Muralidharan, D.; Perumal, P.T. *Tetrahedron Lett.* ***2003***, *44*, 3653. For a review, see Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* ***2001***, *57*, 6099.
[2422] See Domingo, L.R. *J. Org. Chem.* ***2001***, *66*, 3211.
[2423] Martin, S.F.; Hartmann, M.; Josey, J.A. *Tetrahedron Lett.* ***1992***, *33*, 3583.
[2424] Boger, D.L.; Weinreb, S.M. *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press, NY, ***1987***; Weinreb, S.M.; Scola, P.M. *Chem. Rev.* ***1989***, *89*, 1525; Kametani, T.; Hibino, S. *Adv. Heterocycl. Chem.* ***1987***, *42*, 245; Desimoni, G.; Tacconi, G. *Chem. Rev.* ***1975***, *75*, 651; Katritzky, A.R.; Dennis, N. *Chem. Rev.* ***1989***, *89*, 827; Schmidt, R.R. *Acc. Chem. Res.* ***1986***, *19*, 250; Boger, D.L. *Chem. Rev.* ***1986***, *86*, 781.



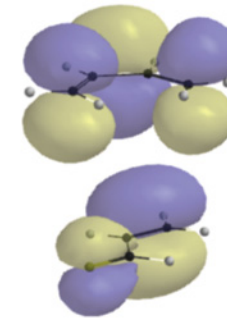
Endo. HOMO diene (top) overlaps with LUMO (acrolein)



Endo. LUMO diene (top) overlaps with HOMO (acrolein)



Exo. HOMO diene (top) shows poor overlap with LUMO (acrolein)



Exo. LUMO diene (top) shows poor overlap with HOMO (acrolein)

FIGURE 15.10. Overlap of orbitals in [4 + 2] cycloaddition of 1,3-butadiene with acrolein.

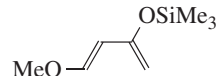
oxygen (**15-58**). Several catalysts can be used, depending on the nature of the heteroatoms incorporated into the alkene or diene.[2425]

Intramolecular cycloaddition with a diene imine substrate leads to pyrrolidines.[2426]

Diels-Alder reactions of carbonyl compounds are well known.[2427] Aldehydes react with suitably functionalized dienes such as **73**, known as *Danishefsky's diene*,[2428] but the reaction usually requires a Lewis acid catalyst.[2429] The Diels-Alder reaction of aldehydes with dienes to give a dihydropyran can be catalyzed by many transition metal compounds, including Co[2430] and In[2431] catalysts.[2432] The Cu-catalyzed reaction of **73** with glyoxals has

[2425] See Molander, G.A.; Rzasa, R.M. *J. Org. Chem.* ***2000***, *65*, 1215.
[2426] Amos, D.T.; Renslo, A.R.; Danhesier, R.L. *J. Am. Chem. Soc.* ***2003***, *125*, 4970.
[2427] Pellissier, H. *Tetrahedron* ***2009***, *65*, 2839.
[2428] See Danishefsky, S.; Schuda, P.F.; Kitahara, T.; Etheredge, S.J. *J. Am. Chem. Soc.* ***1977***, *99*, 6066. Also see Sudo, Y.; Shirasaki, D.; Harada, S.; Nishida, A. *J. Am. Chem. Soc.* ***2008***, *130*, 12588.
[2429] See Zhang, X.; Du, H.; Wang, Z.; Wu, Y.-D.; Ding, K. *J. Org. Chem.* ***2006***, *71*, 2862.
[2430] Kezuka, S.; Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 1333.
[2431] Ali, T.; Chauhan, K.K.; Frost, C.G. *Tetrahedron Lett.* ***1999***, *40*, 5621.
[2432] Liu, L.; Kim, H.; Xie, Y.; Farès, C.; Kaib, P.S.J.; Goddard, R.; List, B. *J. Am. Chem. Soc.* ***2017***, *139*, 13656.

been reported.[2433] Note that the reaction of Danishefsky's diene with an imine,[2434] formed *in situ* by reaction of an aryl aldehyde and an aniline derivative, proceeds without a Lewis acid.[2435]



73

Ketones also react with suitably functionalized dienes.[2436] Hetero-Diels-Alder reactions involving carbonyls have been done in water.[2437] Polymer-supported dienes have been used.[2438]

Hetero-Diels-Alder reactions that proceed with good to excellent asymmetric induction are well known.[2439] Aldehydes react using a chiral Ti,[2440] Zr,[2441] Cu,[2442] Fe,[2443] or Mn[2444] catalysts to give the dihydropyran with good enantioselectivity, and organocatalysts have been used.[2445] Asymmetric chiral 1-aza dienes have been developed as substrates, for example.[2446] Azadienes also react with chiral dienophiles.[2447] Chiral catalysts have been developed.[2448]

Dienes related to **73** are known, and their reactivity has been examined. Amino-substituted dienes undergo what is known as hydrogen bonding-catalyzed reactions.[2449] Imines react with other substrates, such as allenes, to give tetrahydropyridine derivatives with good enantioselectivity in the presence of a chiral ligand.[2450] Azo compounds (—N=N—) react as dienophiles in the presence of an Ag catalyst.[2451] Iminium ions undergo Diels-Alder cycloaddition.[2452]

The Rh/phosphoramidite-catalyzed [4 + 2] cycloaddition of α,β-unsaturated imines and isocyanates gave pyrimidinones.[2453] The chiral phosphoric acid-catalyzed nitroso-Diels-Alder reaction of nitrosoarenes with carbamate dienes gave *cis*-3,6-disubstituted dihydro-1,2-oxazines.[2454] The Cu-catalyzed nitroso Diels-Alder reaction gave

[2433] Li, Y.; Hu, Y.; Zhang, S.; Sun, J.; Li, L.; Zha, Z.; Wang, Z. *J. Org. Chem.* ***2016***, *81*, 2993.
[2434] In an ionic liquid, see Pégot, B.; Vo-Thanh, G. *Synlett* ***2005***, 1409. Also see Babu, G.; Perumal, P.T. *Tetrahedron* ***1998***, *54*, 1627.
[2435] Yuan, Y.; Li, X.; Ding, K. *Org. Lett.* ***2002***, *4*, 3309.
[2436] See Jørgensen, K.A. *Eur. J. Org. Chem.* ***2004***, 2093.
[2437] Lubineau, A.; Augé, J.; Grand, E.; Lubin, N. *Tetrahedron* ***1994***, *50*, 10265.
[2438] Pierres, C.; George, P.; van Hijfte, L.; Ducep, J.-B.; Hibert, M.; Mann, A. *Tetrahedron Lett.* ***2003***, *44*, 3645.
[2439] Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R.G.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***1998***, *120*, 8599.
[2440] Wang, B.; Feng, X.; Huang, Y.; Liu, H.; Cui, X.; Jiang, Y. *J. Org. Chem.* ***2002***, *67*, 2175.
[2441] Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* ***2003***, *125*, 3793.
[2442] Chen, I.-H.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Org. Lett.* ***2008***, *10*, 5151.
[2443] Kuwano, T.; Kurahashi, T.; Matsubara, S. *Chem. Lett.* ***2013***, *42*, 1241.
[2444] Li, L.; Li, Y.; Pang, D.; Liu, F.; Zheng, A.; Zhang, G.; Sun, Y. *Tetrahedron* ***2015***, *71*, 8096.
[2445] Guin, J.; Rabalakos, C.; List, B. *Angew. Chem. Int. Ed.* ***2012***, *51*, 8859; Zhao, X.; Ruhl, K.E.; Rovis, T. *Angew. Chem. Int. Ed.* ***2012***, *51*, 12330.
[2446] Beaudegnies, R.; Ghosez, L. *Tetrahedron: Asymmetry* ***1994***, *5*, 557.
[2447] Wurz, R.P.; Fu, G.C. *J. Am. Chem. Soc.* ***2005***, *127*, 12234.
[2448] See He, M.; Struble, J.R.; Bode, J.W. *J. Am. Chem. Soc.* ***2006***, *128*, 8418.
[2449] Jensen, K.H.; Sigman, M.S. *Angew. Chem. Int. Ed.* ***2008***, *47*, 4748.
[2450] Wurz, R.P.; Fu, G.C. *J. Am. Chem. Soc.* ***2005***, *127*, 12234.
[2451] Kawasaki, M.; Yamamoto, H. *J. Am. Chem. Soc.* ***2006***, *128*, 16482.
[2452] See Sarkar, N.; Banerjee, A.; Nelson, S.G. *J. Am. Chem. Soc.* ***2008***, *130*, 9222.
[2453] Oberg, K.M.; Rovis, T. *J. Am. Chem. Soc.* ***2011***, *133*, 4785.
[2454] Pous, J.; Courant, T.; Bernadat, G.; Iorga, B.I.; Blanchard, F.; Masson, G. *J. Am. Chem. Soc.* ***2015***, *137*, 11950.

3,6-dihydro-1,2-oxazines.[2455] The reaction of $H_2C{=}NH$ and *cis*-buta-1,3-diene was examined by quantum calculations, and the role of an imidazolium catalyst was examined.[2456] Tetrahydropyridazines were prepared by the reaction of ketohydrazones and alkenes, generating azoalkenes by direct oxidative dehydrogenation of ketohydrazones using TEMPO.[2457] The chiral phosphine-catalyzed reaction of an acrylate moiety in an intramolecular [4 + 2] reaction with unsaturated imines gave *N*-heterocycles.[2458]

An oxa analog of the *Povarov reaction* gave 3,4-dihydrobenzopyrans (chromans) via the inverse electron demand [4 + 2] cycloaddition reaction of *in situ*-generated cationic aryl 2-oxadiene oxocarbenium ions with alkenes.[2459] The *Povarov reaction* is the reaction of *N*-arylimines (2-azadienes) with electron-rich alkenes in an inverse electron demand [4 + 2] cycloaddition to give tetrahydroquinolines.[2460]

Dehydrogenative hetero-Diels-Alder reactions (**15-56**) are known. The term has also been used for dehydrogenation of the cycloadduct, as in the nickel-catalyzed reaction of nitriles and alkynes to give pyridine derivatives, done at 130 °C.[2461] The dehydrogenative reaction of imines and alkynes has been reported,[2462] and also of benzylideneaniline derivatives and alkenes.[2463] This method has been applied to the reaction of enamides and alkynes.[2464] A dehydrogenative reaction of formamides and alkynes was reported.[2465]

Azadienes undergo Diels-Alder reactions to form pyridine and dihydro- and tetrahydropyridine derivatives.[2466] In some cases, under the reactions conditions of a thermal Diels-Alder reaction, 1-azadienes isomerize to the more reactive 2-azadiene. Molecular orbital calculations confirm the low reactivity of the unsubstituted 1-azadienes compared to other dienes.[2467] Ultrasound has been used to promote the Diels-Alder reactions of 1-azadienes.[2468] Aza-Diels-Alder reactions have been done in ionic liquids.[2469] *N*-Vinyl lactim ethers undergo Diels-Alder reactions with a limited set of dienophiles.[2470] Brønsted acids can catalyze inverse electron demand aza-Diels-Alder reactions.[2471] Diels-Alder reactions via isomerization of allenamides has been reported.[2472] Functionalized quinolines were prepared by the [4 + 2] cycloaddition of azadienes (generated *in situ* from

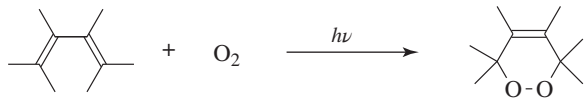
[2455] Maji, B.; Yamamoto, H. *J. Am. Chem. Soc.* ***2015***, *137*, 15957.
[2456] Nziko, V.d.P.N.; Scheiner, S. *J. Org. Chem.* ***2016***, *81*, 2589.
[2457] Yang, X.-L.; Peng, X.-X.; Chen, F.; Han, B. *Org. Lett.* ***2016***, *18*, 2070.
[2458] Jin, Z.; Yang, R.; Du, Y.; Tiwari, B.; Ganguly, R.; Chi, Y.R. *Org. Lett.* ***2012***, *14*, 3226.
[2459] Taylor, R.R.R.; Batey, R.A. *J. Org. Chem.* ***2013***, *78*, 1404.
[2460] Grigos, V.I.; Povarov, L.S.; Mikhailov, B.M. *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)* ***1965***, *12*, 2163; Povarov, L.S.; Grigos, V.I.; Mikhailov, B.M. *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)* ***1966***, *1*, 144; Povarov, L.S. *Russ. Chem. Rev.* ***1967***, *36*, 656; Glushkov, V.A.; Tolstikov, A.G. *Russ. Chem. Rev.* ***2008***, *2*, 137; Kouznetsov, V.V. *Tetrahedron* ***2009***, *65*, 2721. See Fochi, M.; Caruana, L.; Bernardi, L. *Synthesis* ***2014***, *46*, 135.
[2461] Ohashi, M.; Takeda, I.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* ***2011***, *133*, 18018.
[2462] He, R.; Zhi- Huang, T.; Zheng, Q.-Y.; Wang, C. *Angew. Chem. Int. Ed.* ***2014***, *53*, 4950.
[2463] Pérez-Ruiz, R.; Domingo, L.R.; Jiménez, M.C.; Miranda, M.A. *Org. Lett.* ***2011***, *13*, 5116.
[2464] Wu, J.; Xu, W.; Yu, Z.-X.; Wang, J. *J. Am. Chem. Soc.* ***2015***, *137*, 9489.
[2465] Nakao, Y.; Morita, E.; Idei, H.; Hiyama, T. *J. Am. Chem. Soc.* ***2011***, *133*, 3264.
[2466] Fell, J.S.; Martin, B.N.; Houk, K.N. *J. Org. Chem.* ***2017***, *82*, 1912.
[2467] Behforouz, M.; Ahmadian, M. *Tetrahedron* ***2000***, *56*, 5259. See Fell, J.S.; Martin, B.N.; Houk, K.N. *J. Org. Chem.* ***2017***, *82*, 1912.
[2468] Villacampa, M.; Pérez, J.M.; Avendaño, C.; Menéndez, J.C. *Tetrahedron* ***1994***, *50*, 10047.
[2469] Yadav, J.S.; Reddy, B.V.S.; Reddy, J.S.S.; Rao, R.S. *Tetrahedron* ***2003***, *59*, 1599.
[2470] Sheu, J.; Smith, M.B.; Matsumoto, K. *Synth. Commun,* ***1993***, *23*, 253.
[2471] Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* ***2006***, *128*, 13070; Esquivias, J.; Arrayás, R.G.; Carretero, J.C. *J. Am. Chem. Soc.* ***2007***, *129*, 1480.
[2472] Feltenberger, J.B.; Hsung, R.P. *Org. Lett.* ***2011***, *13*, 3114.

o-aminobenzyl alcohol) with internal alkynes.[2473] Ketenes reacted with 1-azadienes, catalyzed by *N*-heterocyclic carbenes, to give 3,4-dihydro-2-pyridones.[2474]

The asymmetric thia-Diels-Alder reaction of dithioesters bearing a chiral auxiliary with buta-1,3-diene derivatives gave the thiopyran derivative.[2475] Thioketones react with dienes to give Diels-Alder cycloadducts.[2476] The carbonyl group of lactams has also been shown to be a dienophile.[2477] Certain heterocyclic aromatic rings (among them furans)[2478] can also behave as dienes in the Diels-Alder reaction. Some hetero dienes that give the reaction are —C=C—C=O, O=C—C=O, and N=C—C=N.[2478] Nitroso compounds of the type *t*-BuO_2C—N=O react with dienes to give the corresponding 2-azadihydropyran.[2479] Conjugated aldehydes react with vinyl ethers, with a chiral Cr catalyst, in an inverse electron demand cycloaddition that gives a dihydropyran with good enantioselectivity.[2480] An organocatalytic inverse electron demand hetero-Diels-Alder reaction has been reported.[2481] Vinyl sulfilimines have been used in chiral Diels-Alder reactions.[2482]

OS **IV**, 311; **V**, 60, 96; **80**, 133. See also, OS **VII**, 326.

15-58 Photooxidation of Dienes (Addition of Oxygen, Oxygen)



Conjugated dienes react with oxygen under the influence of light to give cyclic peroxides.[2483] The reaction has mostly[2484] been applied to cyclic dienes.[2485] Cycloaddition of furan has been reported using singlet oxygen.[2486] The scope extends to certain aromatic compounds such as phenanthrene.[2487] Besides those dienes and aromatic rings that can be photooxidized directly, there is a larger group that gives the reaction in the presence of a

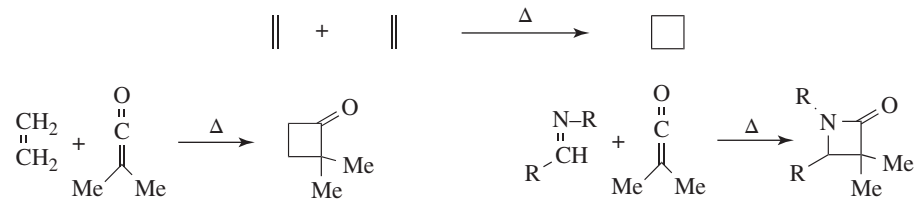
[2473] Saunthwal, R.K.; Patel, M.; Verma, A.K. *Org. Lett.* ***2016***, *18*, 2200.
[2474] Jian, T.-Y.; Shao, P.-L.; Ye, S. *Chem. Commun.* ***2011***, *47*, 2381.
[2475] Dentel, H.; Chataigner, I.; Lohier, J.-F.; Gulea, M. *Tetrahedron* ***2012***, *68*, 2326.
[2476] Schatz, J.; Sauer, J. *Tetrahedron Lett.* ***1994***, *35*, 4767.
[2477] Degnan, A.P.; Kim, C.S.; Stout, C.W.; Kalivretenos, A.G. *J. Org. Chem.* ***1995***, *60*, 7724.
[2478] Katritzky, A.R.; Dennis, N. *Chem. Rev.* ***1989***, *89*, 827; Schmidt, R.R. *Acc. Chem. Res.* ***1986***, *19*, 250; Boger, D.L. *Chem. Rev.* ***1986***, *86*, 781. See Hayashi, Y.; Nakamura, M.; Nakao, S.; Inoue, T.; Shoji, M. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4079.
[2479] Bach, P.; Bols, M. *Tetrahedron Lett.* ***1999***, *40*, 3461.
[2480] Gademann, K.; Chavez, D.E.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3059.
[2481] Hejmanowska, J.; Jasinski, M.; Wojciechowski, J.; Mloston, G.; Albrecht, Ł. *Chem. Commun.* ***2017***, *54*, 11472.
[2482] Ruano, J.L.G.; Clemente, F.R.; Gutiérrez, L.G.; Gordillo, R.; Castro, A.M.M.; Ramos, J.H.R. *J. Org. Chem.* ***2002***, *67*, 2926.
[2483] See Clennan, E.L. *Tetrahedron* ***1991***, *47*, 1343; Wasserman, H.H.; Ives, J.L. *Tetrahedron* ***1981***, *37*, 1825; Denny, R.W.; Nickon, A. *Org. React.* ***1973***, *20*, 133; Schönberg, A. *Preparative Organic Photochemistry*, Springer, NY, ***1968***, pp. 382–397.
[2484] Matsumoto, M.; Dobashi, S.; Kuroda, K.; Kondo, K. *Tetrahedron* ***1985***, *41*, 2147.
[2485] See Saito, I.; Nittala, S.S. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 311–374; Balci, M. *Chem. Rev.* ***1981***, *81*, 91; Adam, W.; Bloodworth, A.J. *Top. Curr. Chem.* ***1981***, *97*, 121.
[2486] Onitsuka, S.; Nishino, H.; Kurosawa, K. *Tetrahedron* ***2001***, *57*, 6003.
[2487] In Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, see the articles by Wasserman, H.H.; Lipshutz, B.H. pp. 429–509; Saito, I.; Matsuura, T. pp. 511–574. Rigaudy, J. *Pure Appl. Chem.* ***1968***, *16*, 169.

photosensitizer (Sec. 7.A.vi, category 5) such as eosin (a red xanthene dye). Among these is α-terpinene, which is converted to ascaridole.[2488]

As in **14-6**, it is not the ground-state oxygen (the triplet), that reacts, but the excited singlet state,[2489] so the reaction is actually a *Diels-Alder reaction* (see **15-56**) with singlet oxygen as dienophile:[2490] Like **15-56**, this reaction is reversible.

As previously discussed, the reaction of singlet oxygen with double bond compounds gave hydroperoxides (**14-6**). However, singlet oxygen can also react with double bonds in another way to give a 1,2-dioxetane intermediate[2491] which usually cleaves to aldehydes or ketones[2492] but has been isolated.[2493] Both the six-membered cyclic peroxides[2494] and the four-membered dioxetane[2495] have been formed from oxygenation reactions that do not involve singlet oxygen. If cyclic peroxides are desired, better reagents[2496] are triphenyl phosphite ozonide $(PhO)_3PO_3$ and triethylsilyl hydrotrioxide ($Et_3SiOOOH$), but yields are not high.[2497]

15-59 [2 + 2] Cycloadditions[2498]



Two alkene molecules react under thermal conditions to give cyclobutane derivatives in what is known as a [2 + 2] cycloaddition. The cycloaddition occurs when the alkenes are the same or different, but the reaction is not general for all alkenes.[2499] Variations include

[2488] Schenck, G. O.; Ziegler, K. *Naturwissenschaften* ***1944***, *32*, 157.

[2489] Frimer, A.A. *Singlet O_2*, 4 Vols., CRC Press, Boca Raton, FL, ***1985***; See Frimer, A.A. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 201–234; Gorman, A.A.; Rodgers, M.A.J. *Chem. Soc. Rev.* ***1981***, *10*, 205; Ohloff, G. *Pure Appl. Chem.* ***1975***, *43*, 481; Kearns, D.R. *Chem. Rev.* ***1971***, *71*, 395; Wayne, R.P. *Adv. Photochem.* ***1969***, *7*, 311. Adam, W.; Cilento, G. *Chemical and Biological Generation of Excited States*, Academic Press, NY, ***1982***.

[2490] Monroe, B.M. *J. Am. Chem. Soc.* ***1981***, *103*, 7253. See also O'Shea, K.E.; Foote, C.S. *J. Am. Chem. Soc.* ***1988***, *110*, 7167.

[2491] Adam, W.; Cilento, G. *Angew. Chem. Int. Ed.* ***1983***, *22*, 529; Schaap, A.; Zaklika, K.A. in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 173–242; Bartlett, P.D. *Chem. Soc. Rev.* ***1976***, *5*, 149. For discussions of the mechanisms, see Frimer, A.A. *Chem. Rev.* ***1979***, *79*, 359; Clennan, E.L.; Nagraba, K. *J. Am. Chem. Soc.* ***1988***, *110*, 4312.

[2492] Kearns, D.R. *Chem. Rev.* ***1971***, *71*, 395, pp. 422–424; Foote, C.S. *Pure Appl. Chem.* ***1971***, *27*, 635.

[2493] Adam, W. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 829–920; Bartlett, P.D.; Landis, M.E. in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 243–286; Adam, W. *Adv. Heterocycl. Chem.* ***1977***, *21*, 437. See also, Adam, W.; Encarnación, L.A.A. *Chem. Ber.* ***1982***, *115*, 2592; Adam, W.; Baader, W.J. *Angew. Chem. Int. Ed.* ***1984***, *23*, 166.

[2494] See Nelson, S.F.; Teasley, M.F.; Kapp, D.L. *J. Am. Chem. Soc.* ***1986***, *108*, 5503.

[2495] See Nelson, S.F. *Acc. Chem. Res.* ***1987***, *20*, 269.

[2496] See Curci, R.; Lopez, L.; Troisi, L.; Rashid, S.M.K.; Schaap, A.P. *Tetrahedron Lett.* ***1987***, *28*, 5319.

[2497] Posner, G.H.; Weitzberg, M.; Nelson, W.M.; Murr, B.L.; Seliger, H.H. *J. Am. Chem. Soc.* ***1987***, *109*, 278.

[2498] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 801–817.

[2499] Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Elmsford, NY, ***1990***; Roberts, J.D.; Sharts, C.M. *Org. React.* ***1962***, *12*, 1; Gilchrist, T.L.; Storr, R.C. *Organic Reactions and Orbital Symmetry*, 2nd ed., Cambridge University Press, Cambridge, ***1979***, pp. 173–212; Dilling, W.L. *Chem. Rev.* ***1983***, *83*, 1. For a

the reaction of ketenes with alkenes to give cyclobutanones or the reaction of ketenes with imines to give β-lactams. Theses reactions can be carried out at 100–225 °C, under pressure, although the reactions of alkene substrates shown in section 4 (see below) occur under milder conditions. Solvents are not necessary for [2 + 2] cycloadditions. However, the choice of solvent can control the distribution of products in photochemical [2 + 2] cycloaddition.[2500] Certain transition metal complexes can catalyze the cycloaddition.[2501]

Many variations of the basic reaction have been examined. The Ru-catalyzed [2 + 2] intramolecular cycloaddition of molecules that contain both an allene and an alkene moiety gave bicyclo[3.2.0]heptane skeletons that have a cyclobutane ring.[2502] Arene alkene cycloaddition reactions have been reviewed.[2503] Iron dinitrogen compounds catalyzed the intermolecular [2 + 2] cycloaddition of ethene and buta-1,3-diene to form vinylcyclobutane.[2504] Benzynes undergo cycloaddition to give biphenylene derivatives.[2505] Activated alkenes and certain methylenecyclopropanes also react.[2506] Alkenes react with alkynes[2507] or with activated alkynes, with a Ru[2508] or a Rh[2509] catalyst, to give cyclobutenes.[2510] Dimerization of allenes leads to bis(alkylidene) cyclobutanes.[2511]

Different alkenes combine as follows:

1. $F_2C{=}CX_2$ (X = F or Cl), especially $F_2C{=}CF_2$, form cyclobutanes with many alkenes. Compounds of this type even react with conjugated dienes to give four-membered rings rather than undergoing normal *Diels-Alder reactions*.[2512]
2. Allenes[2513] and ketenes[2514] react with activated alkenes and alkynes. Ketenes give 1,2-addition, even with conjugated dienes, to give cyclobutanone derivatives.[2515] Ketenes also add to unactivated alkenes if sufficiently long reaction times are

list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 546–647, 1341–1344.

[2500] Ng, S.M.; Bader, S.J.; Snapper, M.L. *J. Am. Chem. Soc.* ***2006***, *128*, 7315.

[2501] See Fructos, M.R.; Prieto, A. *Tetrahedron* ***2016***, *72*, 355; Schmidt, V.A.; Hoyt, J.M.; Margulieux, G.W.; Chirik, P.J. *J. Am. Chem. Soc.* ***2015***, *137*, 7903.

[2502] Gulías, M.; Collado, A.; Trillo, B.; López, F.; Oñate, E.; Esteruelas, M.A.; Mascareñas, J.L. *J. Am. Chem. Soc.* ***2011***, *133*, 7660.

[2503] Remy, R.; Bochet, C.G. *Chem. Rev.* ***2016***, *116*, 9816.

[2504] Russell, S.K.; Lobkovsky, E.; Chirik, P.J. *J. Am. Chem. Soc.* ***2011***, *133*, 8858.

[2505] See Mariet, N.; Ibrahim-Ouali, M.; Santelli, M. *Tetrahedron Lett.* ***2002***, *43*, 5789.

[2506] Dolbier Jr., W.R.; Lomas, D.; Garza, T.; Harmon, C.; Tarrant, P. *Tetrahedron* ***1972***, *28*, 3185.

[2507] López-Carrillo, V.; Echavarren, A.M. *J. Am. Chem. Soc.* ***2010***, *132*, 9292.

[2508] Jordan, R.W.; Tam, W. *Org. Lett.* ***2000***, *2*, 3031.

[2509] Sakai, K.; Kochi, T.; Kakiuchi, F. *Org. Lett.* ***2013***, *15*, 1024.

[2510] See Luparia, M.; Audisio, D.; Maulide, N. *Synlett* ***2011***, *22*, 735.

[2511] Saito, S.; Hirayama, K.; Kabuto, C.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2000***, *122*, 10776.

[2512] De Cock, C.; Piettre. S.; Lahousse, F.; Janousek, Z.; Merényi, R.; Viehe, H.G. *Tetrahedron* ***1985***, *41*, 4183.

[2513] Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 286–317; Hopf, H. in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, pp. 525–562; Ghosez, L.; O'Donnell, M.J. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 79–140; Conner, M.L.; Brown, M.K. *J. Org. Chem.* ***2016***, *81*, 8050; Li, X.-X.; Zhu, L.-L.; Zhou, W.; Chen, Z. *Org. Lett.* ***2012***, *14*, 436.

[2514] Ghosez, L.; O'Donnell, M.J. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***; Brady, W.T. *Synthesis* ***1971***, 415; Snider, B.B. *Chem. Rev.* ***1988***, *88*, 793. See Ussing, B.R.; Hang, C.; Singleton, D.A. *J. Am. Chem. Soc.* ***2006***, *128*, 7594.

[2515] See Huisgen, R.; Feiler, L.A.; Otto, P. *Chem. Ber.* ***1969***, *102*, 3475; Corey, E.J.; Ravindranathan, T.; Terashima, S. *J. Am. Chem. Soc.* ***1971***, *93*, 4326; See de Faria, A.R.; Matos, C.R.; Correia, C.R.D. *Tetrahedron Lett.* ***1993***, *34*, 27. For a review of ketene equivalents, see Ranganathan, S.; Ranganathan, D.; Mehrotra, A.K. *Synthesis* ***1977***, 289.

used.[2516] Allenes and ketenes also add to each other,[2517] and substituted ketenes can dimerize to give cyclobutenone derivatives, although ketene itself dimerizes in a different manner, to give an unsaturated β-lactone (**16-89**).[2518] Lewis acid-catalyzed ketene alkene reactions are known,[2519] and intermolecular cycloadditions are well known.[2520] A typical reaction of dimethylketene and ethene gives 2,2-dimethylcyclobutanone.[2521] Ketimines[2522] and also imines[2523] reacted with allenoates to give azetidines. A chiral NHC was used to catalyze the asymmetric [2 + 2] cycloaddition of alkylarylketenes with aldehydes to give stereodefined β-lactones.[2524]

3. Enamines[2525] form four-membered rings with *Michael-type* alkenes[2526] and ketenes.[2527] In both cases, only enamines from aldehydes give stable four-membered rings. Generating the ketene *in situ* from an acyl halide and a tertiary amine is a convenient way to carry out the reaction of enamines with ketenes.
4. Alkenes with electron-withdrawing groups may form cyclobutanes with alkenes containing electron-donating groups.[2528] The enamine reactions, mentioned above, are examples of this, but it has also been accomplished with tetracyanoethylene and similar molecules, which give substituted cyclobutanes when treated with alkenes of the form C═C─A, where A may be OR,[2529] SR (enol and thioenol ethers),[2530] cyclopropyl,[2531] or certain aryl groups.[2532]

Ketenes react with imines via a [2 + 2] cycloaddition to produce β-lactams, in what is commonly known as the *Staudinger reaction*, via a nonphotochemical [2 + 2] cycloaddition.[2533] See **19-70** for a discussion of reactions that give β-lactams. Ketenes have been generated using flow conditions (Sec. 7.D).[2534] Chiral *N*-heterocyclic carbenes catalyze

[2516] Bak, D.A.; Brady, W.T. *J. Org. Chem.* ***1979***, *44*, 107.
[2517] Gras, J.; Bertrand, M. *Nouv. J. Chim.* ***1981***, *5*, 521.
[2518] Dehmlow, E.V.; Pickardt, J.; Slopianka, M.; Fastabend, U.; Drechsler, K.; Soufi, J. *Liebigs Ann. Chem.* ***1987***, 377.
[2519] Rasik, C.M.; Brown, M.K. *Synlett* ***2014***, *25*, 760.
[2520] Martin, P.; Greuter, H.; Bellus, D. *Helv. Chim. Acta.,* ***1984***, *64*, 64.
[2521] Sustmann, R.; Ansmann, A.; Vahrenholt, F. *J. Am. Chem. Soc.* ***1972***, *94*, 8099; Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G.P. *Natural Product Synthesis Through Pericyclic Reactions*, American Chemical Society, Washington, ***1983***, pp. 119–254.
[2522] Takizawa, S.; Arteaga, F.A.; Yoshida, Y.; Suzuki, M.; Sasai, H. *Org. Lett.* ***2013***, *15*, 4142.
[2523] Denis, J.-B; Masson, G.; Retailleau, P.; Zhu, J. *Angew. Chem. Int. Ed.* ***2011***, *50*, 5356.
[2524] Douglas, J.; Taylor, J.E.; Churchill, G.; Slawin, A.M.Z.; Smith, A.D. *J. Org. Chem.* ***2013***, *78*, 3925.
[2525] Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, pp. 347–440.
[2526] Brannock, K.C.; Bell, A.; Goodlett, V.W.; Thweatt, J.G. *J. Org. Chem.* ***1964***, *29*, 813.
[2527] Hasek, R.H.; Gott, P.G.; Martin, J.C. *J. Org. Chem.* ***1966***, *31*, 1931.
[2528] See Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* ***2005***, *127*, 3668.
[2529] Scheeren, J.W. *Recl. Trav. Chim. Pays-Bas* ***1986***, *105*, 71–84.
[2530] Williams, J.K., Wiley, D.W.; McKusick, B.C. *J. Am. Chem. Soc.* ***1962***, *84*, 2210.
[2531] Nishida, S.; Moritani, I.; Teraji, T. *J. Org. Chem.* ***1973***, *38*, 1878.
[2532] Shirota, Y.; Yoshida, K.; Nogami, T.; Mikawa, H. *Chem. Lett.* ***1973***, 1271.
[2533] Brown, M.J. *Heterocycles* ***1989***, *29*, 2225; Isaacs, N.S. *Chem. Soc. Rev.* ***1976***, *5*, 181; Wright, S., Li, J.J. (Ed.) *Name Reactions for Carbocyclic Ring Formations*, Wiley, Hoboken, NJ, ***2010***, pp. 45, 47; Cossio, F.P.; Arrieta, A.; Sierra, M.G. *Acc. Chem. Res.* ***2008***, *41*, 925; Liang, Y.; Jiao, L.; Zhang, S.; Yu, Z.-X.; Xu, J. *J. Am. Chem. Soc.* ***2009***, *131*, 1542. See Zavar, S.; Zarei, M.; Saraei, M. *Synth. Commun.* ***2016***, *46*, 2031. Xie, P.; Qian, B.; Huang, H.; Xia, C. *Tetrahedron Lett.* ***2012***, *53*, 1613.
[2534] Hafner, A.; Ley, S.V. *Synlett* ***2015***, *26*, 1470.

the Staudinger reaction of ketenes with imines to form β-lactam derivatives.[2535] The Rh-catalyzed cycloaddition of terminal alkynes and imines gave β-lactams.[2536] Cycloaddition of an imine with a conjugated ester in the presence of Et_3MeSiH and an Ir catalyst also gives a β-lactam.[2537] Ketene iminum salts reacted with akenes[2538] to give azetidines and they reacted with alkynes to give dihydroacetidine.[2539] The *sulfa-Staudinger cycloaddition* (or *thio-Staudinger reaction*),[2540] based on the reaction of sulfonyl chlorides and imines with electron-donating N and C substituents, gave primarily *cis*-β-sultams, whereas C electron-withdrawing substituents on the imine gave more of the *trans*-β-sultam.[2541]

Enantioselective [2 + 2] cycloaddition reactions are known. Chiral organocatalysts lead to chiral cyclobutane derivatives.[2542] An enantiomeric photocycloadditon between an alkene with a (+)-camphor substituent and a conjugated ketone gave the polycyclic product.[2543]

Intramolecular [2 + 2] cycloadditions are common in which a diene is converted to a bicyclic compound with a four-membered ring fused to another ring. Heating *N*-vinyl imines, where the vinyl moiety is a silyl enol, gives β-lactams.[2544] Transition metal-catalyzed reactions have been reported, including the use of Fe complexes.[2545] Apart from photochemical initiation of such reactions (see below), intramolecular cycloaddition of two conjugated ketone units, in the presence of $PhMeSiH_2$ and catalyzed by Co compounds, leads to the bicyclic compound with two ketone substituents.[2546]

Thermal cycloadditions leading to four-membered rings can also take place between a cyclopropane ring and an alkene or alkyne bearing electron-withdrawing groups.[2547] These reactions are $[_\pi 2 +_s 2]$ cycloadditions. Ordinary cyclopropanes do not undergo the reaction, but it has been accomplished with strained systems such as bicyclo[1.1.0]butanes[2548] and bicyclo[2.1.0]pentanes. For example, bicyclo[2.1.0]pentane reacts with maleonitrile (or fumaronitrile) to give all three isomers of 2,3-dicyanonorbornane, as well as four other products.[2549] The lack of stereospecificity and the negligible effect of solvent on the rate indicate a diradical mechanism.[2550]

[2535] Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett.* ***2008***, *10*, 277; Hans, M.; Wouters, J.; Demonceau, A.; Delaude, L. *Chem. Eur. J.* ***2015***, *21*, 10870. For a mechanistic insight, see Hans, M.; Wouters, J.; Demonceau, A.; Delaude, L. *Chem. Eur. J.* ***2013***, *19*, 9668.

[2536] Kim, I.; Roh, S.W.; Lee, D.G.; Lee, C. *Org. Lett.* ***2014***, *16*, 2482.

[2537] Townes, J.A.; Evans, M.A.; Queffelec, J.; Taylor, S.J.; Morken, J.P. *Org. Lett.* ***2002***, *4*, 2537.

[2538] For the preparation of aminocyclobutanes, see Kolleth, A.; Lumbroso, A.; Tanriver, G.; Catak, S.; Sulzer-Mossé, S.; De Mesmaeker, A. *Tetrahedron Lett.* ***2016***, *57*, 2697. For an Fe-catalyzed reaction to give aminocyclobutanes, see Florian de Nanteuil, F.; Waser, J. *Angew. Chem. Int. Ed.* ***2013***, *52*, 9009.

[2539] Domingo, L.R.; Ríos-Gutiérrez, M.; Pérez, P. *Tetrahedron* ***2015***, *71*, 2421.

[2540] Hem, W.; Zhuang, J.; Yang, Z.; Xu, J. *Org. Biomol. Chem.* ***2017***, *15*, 5541.

[2541] Yang, Z.; Xu, J. *Tetrahedron* ***2015***, *71*, 2844.

[2542] See Ishihara, K.; Fushimi, M. *J. Am. Chem. Soc.* ***2008***, *130*, 7532; Albrecht, Ł.; Dickmeiss, G.; Acosta, F.C.; Rodríguez-Escrich, C.; Davis, R.L.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2012***, *134*, 2543.

[2543] Zhao, G.; Yang, C.; Sun, H.; Lin, R.; Xia, W. *Org. Lett.* ***2012***, *14*, 776.

[2544] Bandin, E.; Favi, G.; Martelli, G.; Panunzio, M.; Piersanti, G. *Org. Lett.* ***2000***, *2*, 1077.

[2545] Bouwkamp, M.W.; Bowman, A.C.; Lobkovsky, E.; Chirik, P.J. *J. Am. Chem. Soc.* ***2006***, *128*, 13340.

[2546] Baik, T.-G.; Luis, A.L.; Wang, L.-C.; Krische, M.J. *J. Am. Chem. Soc.* ***2001***, *123*, 6716.

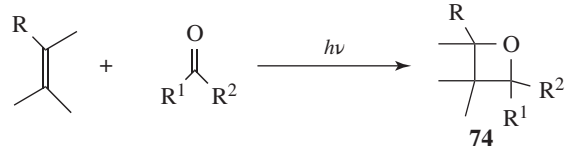
[2547] For a review, see Gassman, P.G. *Acc. Chem. Res.* ***1971***, *4*, 128.

[2548] Cairncross, A.; Blanchard, E.P. *J. Am. Chem. Soc.* ***1966***, *88*, 496.

[2549] Gassman, P.G.; Mansfield, K.T.; Murphy, T.J. *J. Am. Chem. Soc.* ***1969***, *91*, 1684.

[2550] For a reaction that involved reversible diradical formation, see Cinar, M.E.; Vavilala, C.; Fan, J.; Schmittel, M. *Org. Biomol. Chem.* ***2011***, *9*, 3776.

It has been found that certain [2 + 2] cycloadditions that do not occur thermally can be made to take place without photochemical initiation using certain catalysts, usually transition metal compounds.[2551] Visible light mediates cycloaddition in the presence of a Rh catalyst.[2552] The role of the catalyst is not certain and may be different in each case. One possibility is that the presence of the catalyst causes a forbidden reaction to become allowed, through coordination of the catalyst to the π or σ bonds of the substrate.[2553] In such a case, the reaction would of course be a concerted [$_{s}2 + _{s}2$] process.[2554] However, the available evidence is more consistent with nonconcerted mechanisms involving metal–carbon σ-bonded intermediates, at least in most cases.[2555] For example, such an intermediate was isolated in the dimerization of norbornadiene, catalyzed by Ir complexes.[2556] Photochemical [$_{\pi}2 + _{s}2$] cycloadditions[2557] have also been reported. The [2 + 2] photocycloaddition of cinnamates has been reported using flow conditions (Sec. 7.D).[2558] Some reverse cyclobutane ring openings can also be catalytically induced (**18-38**).



74

The photochemical cycloaddition of a carbonyl, generally from an aldehyde or ketone, and an alkene is called the *Paternò-Büchi reaction.*[2559] This [2 + 2] cycloaddition gives an oxetane (**74**) and the reaction is believed to proceed via a diradical intermediate. Silyl enol ethers react with aldehydes under nonphotochemical conditions using $ZnCl_2$ at 25 °C or $SnCl_4$ at − 78 °C.[2560] A synthesis of stable oxetenes ha been reported via the Pd-catalyzed [2 + 2] cycloaddition of alkynes with trifluoropyruvate.[2561] Quinones also react to give spirocyclic oxetanes.[2562]

[2551] Treutwein, J.; Hilt, G. *Angew. Chem. Int. Ed.* ***2008***, *47*, 6811. See Yamazaki, S.; Fujitsuka, H.; Yamabe, S.; Tamura, H. *J. Org. Chem.* ***1992***, *57*, 5610.

[2552] Ischay, M.A.; Anzovino, M.E.; Du, J.; Yoon, T.P. *J. Am. Chem. Soc.* ***2008***, *130*, 12886.

[2553] See Mango, F.D. *Top. Curr. Chem.* ***1974***, *45*, 39; *Tetrahedron Lett.* ***1973***, 1509.

[2554] See Bachrach, S.M.; Gilbert, J.C. *J. Org. Chem.* ***2004***, *69*, 6357; Ozkan, I.; Kinal, A. *J. Org. Chem.* ***2004***, *69*, 5390.

[2555] See Grubbs, R.H.; Miyashita, A.; Liu, M.M.; Burk, P.L. *J. Am. Chem. Soc.* ***1977***, *99*, 3863.

[2556] Fraser, A.R.; Bird, P.H.; Bezman, S.A.; Shapley, J.R.; White, R.; Osborn, J.A. *J. Am. Chem. Soc.* ***1973***, *95*, 597.

[2557] See Poplata, S.; Tröster, A.; Zou, Y.-Q.; Bach, T. *Chem. Rev.* ***2016***, *116*, 9748.

[2558] Telmesani, R.; Park, S.H.; Lynch-Colameta, T.; Beeler, A.B. *Angew. Chem. Int. Ed.* ***2015***, *54*, 11521; Pagirek, S.K.; Hossain, A.; Traub, L.; Kerres, S.; Reiser, O. *Chem. Commun.* ***2017***, *54*, 12072.

[2559] Paternò, E.; Chieffi, C. *Gazz. Chim. Ital.* ***1909***, *39*, 341; Büchi, G.; Inman, C.G.; Lipinsky, E.S. *J. Am. Chem. Soc.* ***1954***, *76*, 4327. See García-Expósito, E.; Bearpark, M.J.; Ortuño, R.M.; Robb, M.A.; Branchadell, V. *J. Org. Chem.* ***2002***, *67*, 6070; Ninomiya, I.; Naito, T. *Photochemical Synthesis*, Academic Press, NY, ***1989***, pp. 138–152; Carless, H.A.J. in Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***, pp. 95–117; Carless, H.A.J. in Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, ***1984***, pp. 425–487; Jones II, M. *Org. Photochem.* ***1981***, *5*, 1.

[2560] Wang, Y.; Zhao, C.; Romo, D. *Org. Lett.* ***1999***, *1*, 1197.

[2561] Aikawa, K.; Hioki, Y.; Shimizu, N.; Mikami, K. *J. Am. Chem. Soc.* ***2011***, *133*, 20092.

[2562] Ciufolini, M.A.; Rivera-Fortin, M.A.; Byrne, N.E. *Tetrahedron Lett.* ***1993***, *34*, 3505.

In general, the mechanism consists of the addition of an excited state of the carbonyl compound to the ground state of the alkene. Both singlet (S_1)[2563] and n,π^* triplet[2564] states have been shown to add to alkenes to give oxetanes. A diradical intermediate[2565] •O—C—C—C• has been detected by spectroscopic methods.[2566] The reaction can be highly diastereoselective,[2567] and allylic alcohols were shown to react with aldehydes to give an oxetane with *syn* selectivity.[2568] There are several side reactions. When the reaction proceeds through a triplet state, it can in general be successful only when the alkene possesses a triplet energy comparable to, or higher than, the carbonyl compound; otherwise energy transfer from the excited carbonyl group to the ground-state alkene can take place (triplet–triplet photosensitization, Sec. 7.A.vi).[2569] Aldehydes and ketones also add photochemically to allenes to give the corresponding alkylidene oxetanes and dioxaspiro compounds.[2570] Aldehydes add to silyl enol ethers.[2571] An intramolecular reaction of ketones was reported to give a bicyclic oxetane via photolysis on the solid state.[2572]

A "transposed Paternò-Büchi" reaction used the π–π^* excited state of an alkene in an intramolecular reaction with an aldehyde chromophore to give the oxetane moiety.[2573]

Many, although by no means all, double bond compounds react *when photochemically excited* (either directly or by a photosensitizer, Sec. 7.A.vi, category 5), even if they are not in the above categories.[2574] Simple alkenes absorb in the far UV (Sec. 7.A.iii), which is difficult to reach experimentally, although this problem can sometimes be overcome by the use of suitable photosensitizers. The reaction has been applied to strained compounds such as cyclopropenes and cyclobutenes,[2575] but more often the double bond compounds involved are conjugated dienes,[2576] α,β-unsaturated ketones,[2577] conjugated acids or acid derivatives, and quinones. Such conjugated compounds absorb at longer wavelengths (Sec. 7.A.iii).

[2563] Turro, N.J. *Pure Appl. Chem.* ***1971***, *27*, 679; Barltrop, J.A.; Carless, H.A.J. *J. Am. Chem. Soc.* ***1972***, *94*, 1951, 8761.

[2564] Arnold, D.R.; Hinman, R.L.; Glick, A.H. *Tetrahedron Lett.* ***1964***, 1425; Yang, N.C.; Nussim, M.; Jorgenson, M.J.; Murov, S. *Tetrahedron Lett.* ***1964***, 3657.

[2565] See references cited in Griesbeck, A.G.; Stadmüller, S. *J. Am. Chem. Soc.* ***1990***, *112*, 1281. See also, Kutateladze, A.G. *J. Am. Chem. Soc.* ***2001***, *123*, 9279.

[2566] See Griesbeck, A.G.; Mauder, H.; Stadmüller, S. *Accts. Chem. Res.* ***1994***, *27*, 70.

[2567] Adam, W.; Stegmann, V.R. *J. Am. Chem. Soc.* ***2002***, *124*, 3600. See Ciufolini, M.A.; Rivera-Fortin, M.A.; Zuzukin, V.; Whitmire, K.H. *J. Am. Chem. Soc.* ***1994***, *116*, 1272.

[2568] Greisbeck, A.G.; Bondock, S. *J. Am. Chem. Soc.* ***2001***, *123*, 6191. See also, Adam, W.; Stegmann, V.R. *Synthesis* ***2001***, 1203.

[2569] For a spin-directed reaction, see Griesbeck, A.G.; Fiege, M.; Bondock, S.; Gudipati, M.S. *Org. Lett.* ***2000***, *2*, 3623.

[2570] Howell, A.R.; Fan, R.; Truong, A. *Tetrahedron Lett.* ***1996***, *37*, 8651. See Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 317–326.

[2571] Abe, M.; Tachibana, K.; Fujimoto, K.; Nojima, M. *Synthesis* ***2001***, 1243.

[2572] Kang, T.; Scheffer, J.R. *Org. Lett.* ***2001***, *3*, 3361.

[2573] Kumarasamy, E.; Raghunathan, R.; Kandappa, S.K.; Sreenithya, A.; Jockusch, S.; Sunoj, R.B.; Sivaguru, J. *J. Am. Chem. Soc.* ***2017***, *139*, 655.

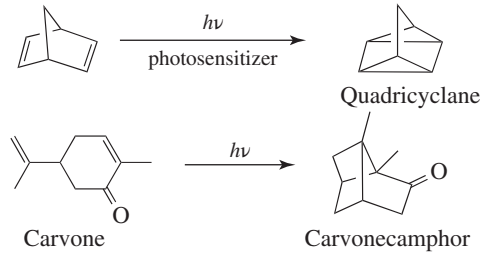
[2574] Demuth, M.; Mikhail, G. *Synthesis* ***1989***, 145; Ninomiya, I.; Naito, T. *Photochemical Synthesis*, Academic Press, NY, ***1989***, pp. 58–109; Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* ***1987***, *87*, 433; Wender, P.A. in Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***, pp. 163–188; Schreiber, S.L. *Science* ***1985***, *227*, 857; Baldwin, S.W. *Org. Photochem.* ***1981***, *5*, 123.

[2575] See Yamazaki, H.; Cvetanovic, R.J. *J. Am. Chem. Soc.* ***1969***, *91*, 520.

[2576] See Dilling, W.L. *Chem. Rev.* ***1969***, *69*, 845.

[2577] Schuster, D.I.; Lem, G.; Kaprinidis, N.A. *Chem. Rev.* ***1993***, *93*, 3; Cossy, J.; Carrupt, P.; Vogel, P. in Patai, S. *The Chemistry of Double-Bonded Functional Groups, Supplement A*, Vol. 2, pt. 2, Wiley, NY, ***1989***, pp. 1369–1565; Eaton, P.E. *Acc. Chem. Res.* ***1968***, *1*, 50; Erickson, J.A.; Kahn, S.D. *Tetrahedron* ***1993***, *49*, 9699.

Both dimerizations and mixed additions are common. Photochemical [2 + 2] cycloadditions can also take place intramolecularly if a molecule has two double bonds that are properly oriented.[2578] Two examples are the preparation of quadricyclane[2579] and of carvonecamphor from carvone.[2580]



However, attempted cyclizations of this kind are not always successful. In many cases, polymeric or other side products are obtained instead of the desired product.

It is possible that some of these photochemical cycloadditions take place by a $[{}_{\pi}2_{s} + {}_{\pi}2_{s}]$ mechanism (which is of course allowed by orbital symmetry); when and if they do, one of the molecules must be in the excited singlet state (S_1) and the other in the ground state. *Reactions between two excited molecules are extremely rare.* The nonphotosensitized dimerizations of *cis*- and *trans*-2-butene are stereospecific,[2581] making it likely that the $[{}_{\pi}2_{s} + {}_{\pi}2_{s}]$ mechanism is operating in these reactions. However, in most cases it is a triplet excited state that reacts with the ground-state molecule; in these cases the diradical (or in certain cases, the diionic) mechanism is taking place.[2582] In one intramolecular case, the intermediate diradical has been trapped.[2583] Photosensitized $[2\pi + 2\pi]$ cycloadditions almost always involve the triplet state and hence a diradical (or diionic) mechanism.

The photochemical diradical mechanism is not quite the same as the thermal diradical mechanism. In the thermal mechanism the initially formed diradical must be a singlet, but in the photochemical process a triplet excited state is adding to a ground state (which is of course a singlet). Thus, in order to conserve spin,[2584] the initially formed diradical must be a triplet; that is, the two electrons must have the same spin. Consequently the second, or ring-closing, step of the mechanism cannot take place at once, because a new bond cannot form from a combination of two electrons with the same spin, and the diradical has a reasonably long lifetime before collisions with molecules in the environment allow a spin inversion to take place and the diradical to cyclize. The prediction is nonstereospecificity, and that is what is found.[2585] It has been believed that at least some [2 + 2] photocycloadditions take

[2578] See Becker, D.; Haddad, N. *Org. Photochem.* ***1989***, *10*, 1–162; Crimmins, M.T. *Chem. Rev.* ***1988***, *88*, 1453; Oppolzer, W. *Acc. Chem. Res.* ***1982***, *15*, 135.

[2579] Hammond, G.S.; Turro, N.J.; Fischer, A. *J. Am. Chem. Soc.* ***1961***, *83*, 4674; Dauben, W.G.; Cargill, R.L. *Tetrahedron* ***1961***, *15*, 197. See also, Cristol, S.J.; Snell, R.L. *J. Am. Chem. Soc.* ***1958***, *80*, 1950.

[2580] Ciamician, G.; Silber, P. *Ber.* ***1908***, *41*, 1928; Büchi, G.; Goldman, I.M. *J. Am. Chem. Soc.* ***1957***, *79*, 4741.

[2581] See Lewis, F.D.; Kojima, M. *J. Am. Chem. Soc.* ***1988***, *110*, 8660.

[2582] Maradyn, D.J.; Weedon, A.C. *Tetrahedron Lett.* ***1994***, *35*, 8107.

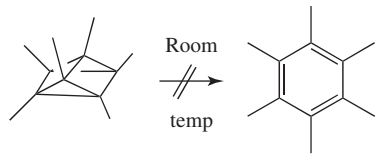
[2583] Becker, D.; Haddad, N.; Sahali, Y. *Tetrahedron Lett.* ***1989***, *30*, 2661.

[2584] This is an example of the *Wigner spin conservation rule* (Sec. 7.A.vi, category 5). Note that spin conservation is something entirely different from symmetry conservation.

[2585] See, for example, Kramer, B.D.; Bartlett, P.D. *J. Am. Chem. Soc.* ***1972***, *94*, 3934.

place by way of exciplex intermediates[2586] [an *exciplex*[2587] is an excited EDA complex (Sec. 7.A.vii) that is dissociated in the ground state; in this case one double bond is the donor and the other the acceptor], but there is evidence against this.[2588]

In **15-56**, the principle of conservation of orbital symmetry was used to explain why certain reactions take place readily and others do not. The orbital symmetry principle can also explain why certain molecules are stable although highly strained. Quadricyclane and hexamethylprismane[2589] are thermodynamically much less stable (because they are much more strained), for example, than their corresponding isomeric dienes, norbornadiene and hexamethylbicyclo[2.2.0]hexadiene (a Dewar benzene).[2590] Yet these two compounds can be kept indefinitely at room temperature, although in the absence of orbital symmetry considerations it is not easy to understand why the electrons simply do not move over to give the more stable diene isomers. The reason is that both these reactions involve the conversion of a cyclobutane ring to a pair of double bonds ($a_s2 + {}_s2$ process) and, as seen previously, a thermal process of this sort is forbidden by the *Woodward-Hoffmann rules*. The process is allowed photochemically, so both quadricyclane and hexamethylprismane are photochemically converted to the respective dienes at room temperature or below.[2591] Although simple bond rearrangements can be imagined where hexamethylprismane is converted to hexamethylbenzene, which of course is far more stable, this rearrangement does not occur.



It has been calculated that hexamethylbenzene is at least 90 kcal mol^{-1} (380 kJ mol^{-1}) more stable than hexamethylprismane. A correlation diagram for this reaction[2592] discloses that it too is a symmetry forbidden process. Some "forbidden" reactions can take place when the compounds are heated, but the diradical mechanism is likely under these conditions.[2592]

Bicyclo[2.2.0]hexadienes and prismanes are *valence isomers* of benzenes.[2593] These compounds actually have the structures that were proposed for benzenes in the nineteenth century. Prismanes have the Ladenburg formula, and bicyclo[2.2.0]hexadienes have the Dewar formula. Because of this, bicyclo[2.2.0]hexadiene is often called Dewar benzene. In the paragraph prior to Sec. 2.A, it was mentioned that Dewar formulas are canonical forms (although not very important) of benzenes. Yet they also exist as separate compounds in which the positions of the nuclei are different from those of benzenes.

[2586] See Caldwell, R.A.; Creed, D. *Acc. Chem. Res.* ***1980***, *13*, 45; Mattes, S.L.; Farid, S. *Acc. Chem. Res.* ***1982***, *15*, 80; Swapna, G.V.T.; Lakshmi, A.B.; Rao, J.M.; Kunwar, A.C. *Tetrahedron* ***1989***, *45*, 1777.

[2587] For a review of exciplexes, see Davidson, R.S. *Adv. Phys. Org. Chem.* ***1983***, *19*, 1–130.

[2588] Schuster, D.I.; Heibel, G.E.; Brown, P.B.; Turro, N.J.; Kumar, C.V. *J. Am. Chem. Soc.* ***1988***, *110*, 8261.

[2589] See Schäfer, W.; Criegee, R.; Askani, R.; Grüner, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 78.

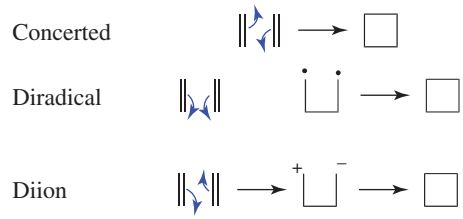
[2590] See Schäfer, W.; Hellmann, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 518.

[2591] With transition metal catalysts: Landis, M.E.; Gremaud, D.; Patrick, T.B. *Tetrahedron Lett.* ***1982***, *23*, 375; Maruyama, K.; Tamiaki, H. *Chem. Lett.* ***1987***, 683.

[2592] See Oth, J.F.M. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 1185.

[2593] Kobayashi, Y.; Kumadaki, I. *Adv. Heterocycl. Chem.* ***1982***, *31*, 169; *Acc. Chem. Res.* ***1981***, *14*, 76; van Tamelen, E.E. *Acc. Chem. Res.* ***1972***, *5*, 186; *Angew. Chem. Int. Ed.* ***1965***, *4*, 738; Schäfer, W.; Hellmann, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 518.

Three mechanisms have been proposed for [2 + 2] cycloaddition.[2594]



The three mechanisms are a concerted pericyclic process, and two-step reactions involving, respectively, a diradical or a diion intermediate. As in **15-56**, a diradical intermediate must be a singlet. In searching for ways to tell which mechanism is operating in a given case, the diion mechanism is expected to be sensitive to changes in solvent polarity, while the concerted and the diradical mechanisms should be insensitive. The concerted mechanism is expected to be stereospecific, while the other two mechanisms probably would not be stereospecific. However, if the second step of these processes takes place very rapidly, before the diradical or the diion have a chance to rotate about the newly formed single bond, stereospecificity might be observed. Because of entropy considerations, such rapid ring closure might be more likely here than in a [4 + 2] cycloaddition.

There is evidence that the reactions can take place by all three mechanisms, depending on the structure of the reactants. A thermal $[_{\pi}2_{s} + _{\pi}2_{s}]$ mechanism is ruled out for most of these substrates by the orbital symmetry rules, but a $[_{\pi}2_{s} + _{\pi}2_{a}]$ mechanism is allowed (see above), and there is much evidence that ketenes and certain other linear molecules[2595] in which the steric hindrance to such an approach is minimal can and often do react by this mechanism. In a $[_{\pi}2_{s} + _{\pi}2_{a}]$ cycloaddition the molecules must approach each other in such a way (Figure 15.11a) that the HOMO/LUMO overlap requires that the groups of one molecule project *into* the plane of the other. This does not happen with ordinary alkenes,[2596] but if one molecule is a ketene (Figure 15.11b), a group on carbon of the C=C unit is missing (relative to an alkene) and the $[_{\pi}2_{s} + _{\pi}2_{a}]$ reaction can take place.

Among the evidence[2597] for this mechanism[2598] is the following:

1. The reactions are stereospecific.[2599]
2. The isomer that forms is the *more-hindered one*. Thus the reaction of methylketene plus cyclopentadiene gave only the *endo* product (**75**, A = H, R = CH_3).[2600] Even

[2594] For a review, see Bartlett, P.D. *Q. Rev. Chem. Soc.* ***1970***, *24*, 473. See Check, C.E.; Gilbert, T.M. *J. Org. Chem.* ***2005***, *70*, 9828.

[2595] See Gilbert, J.C.; Baze, M.E. *J. Am. Chem. Soc.* ***1984***, *106*, 1885.

[2596] See Bartlett, P.D.; Cohen, G.M.; Elliott, S.P.; Hummel, K.; Minns, R.A.; Sharts, C.M.; Fukunaga, J.Y. *J. Am. Chem. Soc.* ***1972***, *94*, 2899.

[2597] Also see Gheorghiu, M.D.; Pârvulescu, L.; Drâghici, C.; Elian, M. *Tetrahedron* ***1981***, *37 Suppl.*, 143. See, however, Holder, R.W.; Graf, N.A.; Duesler, E.; Moss, J.C. *J. Am. Chem. Soc.* ***1983***, *105*, 2929.

[2598] See, however, Wang, X.; Houk, K.N. *J. Am. Chem. Soc.* ***1990***, *112*, 1754; Bernardi, F.; Bottoni, A.; Robb, M.A.; Venturini, A. *J. Am. Chem. Soc.* ***1990***, *112*, 2106; Valentí, E.; Pericàs, M.A.; Moyano, A. *J. Org. Chem.* ***1990***, *55*, 3582.

[2599] Bertrand, M.; Gras, J.L.; Goré, J. *Tetrahedron* ***1975***, *31*, 857; Marchand-Brynaert, J.; Ghosez, L. *J. Am. Chem. Soc.* ***1972***, *94*, 2870; Huisgen, R.; Mayr, H. *Tetrahedron Lett.* ***1975***, 2965, 2969.

[2600] Rey, M.; Roberts, S.; Dieffenbacher, A.; Dreiding, A.S. *Helv. Chim. Acta* ***1970***, *53*, 417. See Rey, M.; Roberts, S.M.; Dreiding, A.S.; Roussel, A.; Vanlierde, H.; Toppet, S.; Ghosez, L. *Helv. Chim. Acta* ***1982***, *65*, 703.

FIGURE 15.11. Steric interactions in $[_\pi 2_s + _\pi 2_s]$ cycloaddition between (a) two alkene molecules and (b) a ketene and an alkene.

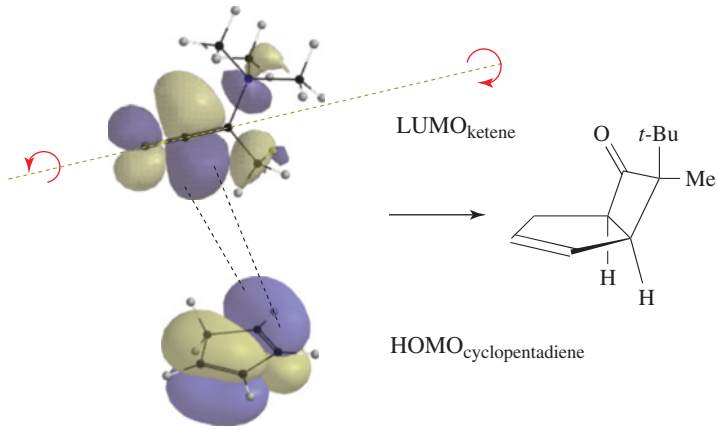
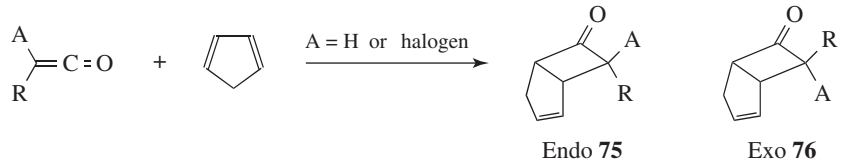


FIGURE 15.12. Orbital overlap in the reaction of a ketene with cyclopentadiene. Reproduced from Brook, P.R.; Harrison, J.M.; Duke, A.J. *J. Chem. Soc., D* ***1970***, 589 with permission from the Royal Society of Chemistry.

more remarkably, when haloalkyl ketenes RXC═C═O were treated with cyclopentadiene, the *endo*/*exo* ratio of the product (**75**/**76**, A = halogen) actually *increased* substantially when R was changed from Me to *i*-Pr to *t*-Bu![2601]



One would expect preferential formation of the *exo* products (**76**) from $[_\pi 2_s + _\pi 2_s]$ cycloadditions where the molecules approach each other face to face. However, a $[_\pi 2_s + _\pi 2_a]$ process leads to *endo* products because the ketene molecule (which for steric reasons would approach with its smaller group, methyl in the figure, directed toward the alkene) must twist as shown in Figure 15.12[2602] (*tert*-butyl = larger; methyl = smaller group) in order for the + lobes to interact. This process swings the larger group (*tert*-butyl) into the *endo* position.[2602] The experimental results in which the amount of *endo* isomer increases with the increasing size of the R group appears to be contrary to what would be expected from steric hindrance

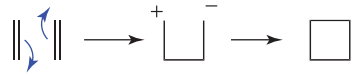
[2601] Brady, W.T.; Roe Jr., R. *J. Am. Chem. Soc.* ***1970***, *92*, 4618.
[2602] Brook, P.R.; Harrison, J.M.; Duke, A.J. *J. Chem. Soc. D* ***1970***, 589.

considerations (called *masochistic steric effects*), but they are just what is predicted for a $[_{\pi}2_{s} + _{\pi}2_{a}]$ reaction.

3. There is only moderate polar solvent acceleration.[2603]
4. The rate of the reaction is not very sensitive to the presence of electron-withdrawing or electron-donating substituents.[2604] Because cycloadditions involving allenes are often stereospecific, it has been suggested that these also take place by the $[_{\pi}2_{s} + _{\pi}2_{a}]$ mechanism,[2605] but the evidence in these cases is more consistent with the diradical mechanism *b*.[2606]

The diradical mechanism is most prominent in the reactions involving fluorinated alkenes.[2607] These reactions are generally not stereospecific[2608] and are insensitive to solvent effects. Further evidence that a diion is not involved is that head to head coupling is found when an unsymmetrical molecule is dimerized. Thus dimerization of $F_2C{=}CFCl$ gives 1,2-dichloro-1,2,3,3,4,4-hexafluorocyclobutane, not 1,3-dichloro-1,2,2,3,4,4-hexafluorocyclobutane. If one pair of electrons moved before the other, the positive end of one molecule would be expected to attack the negative end of the other.[2609]

The diion mechanism[2610] has been reported for at least some of the reactions[2611] in categories 3 and 4 (see above),[2612] as well as some ketene dimerizations.[2613]



The rate of the reaction between 1,2-bis(trifluoromethyl)-1,2-dicyanoethene and ethyl vinyl ether, for example, was strongly influenced by changes in solvent polarity.[2614] Some of these reactions are nonstereospecific, but others are stereospecific.[2615] As previously indicated, it is likely that in the latter cases the diionic intermediate closes before rotation

[2603] Brady, W.T.; O'Neal, H.R. *J. Org. Chem.* ***1967***, *32*, 612; Huisgen, R.; Feiler, L.A.; Otto, P. *Tetrahedron Lett.* ***1968***, 4485; *Chem. Ber.* ***1969***, *102*, 3444; Sterk, H. *Z. NaturForsch. Teil B* ***1972***, *27*, 143.

[2604] Isaacs, N.S.; Stanbury, P. *J. Chem. Soc., Perkin Trans. 2* ***1973***, 166.

[2605] See Baldwin, J.E.; Roy, U.V. *Chem. Commun.* ***1969***, 1225; Moore, W.R.; Bach, R.D.; Ozretich, T.M. *J. Am. Chem. Soc.* ***1969***, *91*, 5918.

[2606] Dolbier Jr., W.R.; Weaver, S.L. *J. Org. Chem.* ***1990***, *55*, 711; Becker, D.; Denekamp, C.; Haddad, N. *Tetrahedron Lett.* ***1992***, *33*, 827.

[2607] See, however, Roberts, D.W. *Tetrahedron* ***1985***, *41*, 5529.

[2608] Bartlett, P.D.; Hummel, K.; Elliott, S.P.; Minns, R.A. *J. Am. Chem. Soc.* ***1972***, *94*, 2898.

[2609] See De Cock, C.; Piettre. S.; Lahousse, F.; Janousek, Z.; Merényi, R.; Viehe, H.G. *Tetrahedron* ***1985***, *41*, 4183; Doering, W. von E.; Guyton, C.A. *J. Am. Chem. Soc.* ***1978***, *100*, 3229.

[2610] See Huisgen, R. *Acc. Chem. Res.* ***1977***, *10*, 117, 199.

[2611] See Gompper, R. *Angew. Chem. Int. Ed.* ***1969***, *8*, 312.

[2612] The reactions of ketenes with enamines are apparently not concerted but take place by the diionic mechanism: Otto, P.; Feiler, L.A.; Huisgen, R. *Angew. Chem. Int. Ed.* ***1968***, *7*, 737.

[2613] See Moore, H.W.; Wilbur, D.S. *J. Am. Chem. Soc.* ***1978***, *100*, 6523.

[2614] Proskow, S.; Simmons, H.E.; Cairns, T.L. *J. Am. Chem. Soc.* ***1966***, *88*, 5254. See also, Huisgen, R. *Pure Appl. Chem.* ***1980***, *52*, 2283.

[2615] Huisgen, R.; Steiner, G. *J. Am. Chem. Soc.* ***1973***, *95*, 5054, 5055.

can take place. Such rapid ring closure is more likely for a diion than for a diradical because of the attraction between the opposite charges. Other evidence for the diion mechanism in these cases is that reaction rates are greatly dependent on the presence of electron-donating groups and electron-withdrawing groups and that it is possible to trap the diionic intermediates.

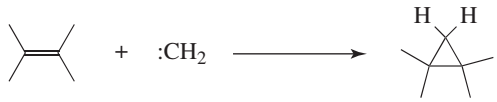
Whether a given alkene reacts by the diradical or diion mechanism depends, among other things, on the groups attached to it. For example, phenyl and vinyl groups at the α positions of diradical $\bullet CH_2CH_2CH_2CH_2\bullet$ or diion $^+CH_2CH_2CH_2CH_2^-$ help to stabilize the diradical,while donors such as oxygen and nitrogen favor a diion (they stabilize the positively charged end).[2616] A table published elsewhere (Ref. 2616, p. 451) shows which mechanism is more likely for [2 + 2] cycloadditions of various pairs of alkenes.

Thermal cleavage of cyclobutanes[2617] to give two alkene molecules (*cycloreversion*,[2618] the reverse of [2 + 2] cycloaddition) operates by the diradical mechanism, and the $[_\sigma 2_s + _\sigma 2_a]$ pathway has not been found[2619] (the subscripts σ indicate that σ bonds are involved in this reaction).

In some cases, double bonds add to triple bonds to give cyclobutenes, apparently at about the same rate that they add to double bonds. The addition of triple bonds to triple bonds would give cyclobutadienes, and this has not been observed, except where these rearrange before they can be isolated (see **15-61**)[2620] or in the presence of a suitable coordination compound, so that the cyclobutadiene is produced in the form of a complex (Sec. 2.K.ii).[2621]

OS **V**, 54, 235, 277, 297, 370, 393, 424, 459, 528; **VI**, 378, 571, 962, 1002, 1024, 1037; **VII**, 177, 256, 315; **VIII**, 82, 116, 306, 377; **IX**, 28, 275; **80**, 160. For the reverse reaction, see OS **V**, 734.

15-60 The Addition of Carbenes and Carbenoids to Double and Triple Bonds



Carbenes and substituted carbenes add to double bonds to give cyclopropane derivatives by what can be considered as a formal [1 + 2] cycloaddition.[2622] Many carbene derivatives

[2616] Hall Jr., H.K. *Angew. Chem. Int. Ed.* ***1983***, *22*, 440.

[2617] See Frey, H.M. *Adv. Phys. Org. Chem.* ***1966***, *4*, 147 (see pp. 170–175, 180–183).

[2618] See Schaumann, E.; Ketcham, R. *Angew. Chem. Int. Ed.* ***1982***, *21*, 225. See also, Reddy, G.D.; Wiest, O.; Hudlicky, T.; Schapiro, V.; Gonzalez, D. *J. Org. Chem.* ***1999***, *64*, 2860.

[2619] See Paquette, L.A.; Carmody, M.J. *J. Am. Chem. Soc.* ***1976***, *98*, 8175. See, however, Doering, W. von E.; Roth, W.R.; Breuckmann, R.; Figge, L.; Lennartz, H.; Fessner, W.; Prinzbach, H. *Chem. Ber.* ***1988***, *121*, 1.

[2620] See Fuks, R.; Viehe, H.G. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 435–442.

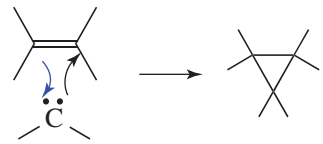
[2621] D'Angelo, J.; Ficini, J.; Martinon, S.; Riche, C.; Sevin, A. *J. Organomet. Chem.* ***1979***, *177*, 265. See Hogeveen, H.; Kok, D.M. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1983***, pp. 981–1013.

[2622] In Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, Wiley, NY, ***1987***, see the reviews by Tsuji, T.; Nishida, S. pt. 1, pp. 307–373; Verhé, R.; De Kimpe, N. pt. 1, pp. 445–564; Marchand, A.P. in Patai, S. *The Chemistry of Double-Bonded Functional Groups, Supplement A*, pt. 1, Wiley, NY, ***1977***, pp. 534–607, 625–635; Kirmse, W. *Carbene Chemistry*, 2nd ed.; Academic Press, NY, ***1971***, pp. 85–122, 267–406. For a review of certain intramolecular additions, see Burke, S.D.; Grieco, P.A. *Org. React.* ***1979***, *26*, 361. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 135–153. Xu, L.; Doubleday, C.E.; Houk, K.N. *J. Am. Chem. Soc.* ***2011***, *133*, 17848.

have been added to double bonds, but the reaction is often performed with CH_2 itself, with halo and dihalocarbenes,[2623] and with carbalkoxycarbenes[2624] (generated from diazoacetic esters). Alkylcarbenes HCR have been added to alkenes,[2625] but more often these rearrange to give alkenes (Sec. 5.D.ii, category 4). The carbene can be generated in any of the ways normally used (Sec. 5.D.ii). However, most reactions in which a cyclopropane is formed by treatment of an alkene with a carbene "precursor" do not actually involve free carbene intermediates. In some cases it is certain that free carbenes are not involved, and in other cases there is doubt. Because of this, the term *carbene transfer* is often used to cover all reactions in which a double bond is converted to a cyclopropane, whether a carbene or a carbenoid (Sec. 5.D.ii) is actually involved.

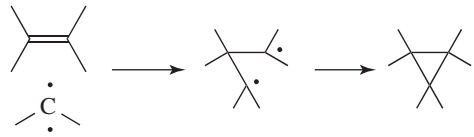
Carbene itself ($:CH_2$) is extremely reactive and gives many side reactions, especially insertion reactions (**12-21**), which greatly reduce yields. This competition is also true with Rh-catalyzed diazoalkane cyclopropanations[2626] (see below). When:CH_2 must be added for preparative purposes, a free carbene is not used, but the Simmons-Smith procedure (see structure **79** later in this section) or some other method that does not involve free carbenes is employed instead. Halocarbenes are less active than carbenes, and this reaction proceeds quite well, since insertion reactions do not interfere.[2627] Vinyldiazolactone is a vinylcarbene precursor for a reaction with alkenes to give spirolactones.[2628]

Most carbenes are electrophilic, and, in accord with this, electron-donating substituents on the alkene increase the rate of the reaction, and electron-withdrawing groups decrease it,[2629] although the range of relative rates is not very great.[2630] The activation energies of carbene addition to alkenes has been estimated.[2631] As discussed in Sec. 5.D.i, carbenes in the singlet state (which is the most common state) react stereospecifically and *syn*,[2632] probably by a one-step mechanism.[2633] Infrared spectra of a carbene and the cyclopropane product have been observed in an argon matrix at 12–45 K.[2634]



Carbenes in the triplet state react nonstereospecifically,[2635] probably by a diradical mechanism.

[2623] See Parham, W.E.; Schweizer, E.E. *Org. React.* ***1963***, *13*, 55. Aouf, C.; Santelli, M. *Tetrahedron Lett.* ***2011***, *52*, 688.
[2624] See Dave, V.; Warnhoff, E.W. *Org. React.* ***1970***, *18*, 217.
[2625] See Frey, H.M. *J. Chem. Soc.* ***1962***, 2293.
[2626] For a review, see Merlic, C.A.; Zechman, A.L. *Synthesis* ***2003***, 1137.
[2627] Moss, R.A. *Acc. Chem. Res.* ***1989***, *22*, 15; Kostikov, R.R.; Molchanov, A.P.; Khlebnikov, A.F. *Russ. Chem. Rev.* ***1989***, *58*, 654.
[2628] Bykowski, D.; Wu, K.-H.; Doyle, M.P. *J. Am. Chem. Soc.* ***2006***, *128*, 16038.
[2629] Mitsch, R.A.; Rodgers, A.S. *Int. J. Chem. Kinet.* ***1969***, *1*, 439.
[2630] Moss, R.A. in Jones Jr., M.; Moss, R.A. *Carbenes*, Vol. 1, Wiley, NY, ***1973***, pp. 153–304. See also, Cox, D.P.; Gould, I.R.; Hacker, N.P.; Moss, R.A.; Turro, N.J. *Tetrahedron Lett.* ***1983***, *24*, 5313.
[2631] Moss, R.A.; Krogh-Jespersen, K. *Tetrahedron Lett.* ***2016***, *57*, 611.
[2632] Ando, W.; Hendrick, M.E.; Kulczycki Jr., A.; Howley, P.M.; Hummel, K.F.; Malament, D.S. *J. Am. Chem. Soc.* ***1972***, *94*, 7469.
[2633] See Giese, B.; Lee, W.; Neumann, C. *Angew. Chem. Int. Ed.* ***1982***, *21*, 310.
[2634] Nefedov, O.M.; Zuev, P.S.; Maltsev, A.K.; Tomilov, Y.V. *Tetrahedron Lett.* ***1989***, *30*, 763.
[2635] Skell, P.S.; Klebe, J. *J. Am. Chem. Soc.* ***1960***, *82*, 247. See also, Jones Jr., M.; Tortorelli, V.J.; Gaspar, P.P.; Lambert, J.B. *Tetrahedron Lett.* ***1978***, 4257.



For carbenes or carbenoids of the type R—C—R′ with alkene systems ABC═CDM, where A and D are *trans* in the alkene and in the cyclopropane product, there is another aspect of stereochemistry.[2636] When these species are added to all but symmetrical alkenes, two isomers are possible, (R is *cis* to A or R is *trans* to A) even if the four groups originally on the double bond carbons maintain their configurations. Which isomer is predominantly formed depends on R, on R′, and on the method by which the carbene or carbenoid is generated. Most studies have been carried out on monosubstituted species (R′ = H), and in these studies it is found that aryl groups generally prefer the more substituted side (*syn* addition) while carbethoxy groups usually show *anti* stereoselectivity. When R = halogen, free halocarbenes show little or no stereochemical preference, while halocarbenoids exhibit a preference for *syn* addition. Beyond this, it is difficult to make simple generalizations.

The absolute rate constant for addition of selected alkoxychlorocarbenes to butenes has been measured to range from 330 to 1×10^4 M^{-1} s^{-1}.[2637] Both entropy and enthalpy play a role in addition of some carbenes.[2638] A few of the many ways[2639] in which halocarbenes or carbenoids are generated are the reaction of organolithium reagents with dichloromethane, the photolysis of N_2CHBr, the reaction of chloroform with hydroxide,[2640] the thermolysis of $PhHgCCl_2Br$,[2641] the reaction of NaI with Me_3SnCF_3,[2642] and the electrolysis of 2,2-dibromopropane.[2643] An equilibration between halocarbene and halocarbanions has been observed.[2644] A trifluoromethylcarbene source has been developed.[2645] Difluorocarbene has been generated using continuous flow techniques (Sec. 7.D).[2646]

The reaction between $CHCl_3$ and HO^- is often carried out under phase-transfer conditions.[2647] It has been shown that the reaction between $PhCHCl_2$ and *t*-BuOK produces a carbenoid, but when the reaction is run in the presence of a crown ether, the carbene Ph(Cl)C:

[2636] Moss, R.A. *Sel. Org. Transform.* ***1970***, *1*, 35–88; Closs, G.L. *Top Stereochem.* ***1968***, *3*, 193–235. For a discussion of enantioselectivity in this reaction, see Nakamura, A. *Pure Appl. Chem.* ***1978***, *50*, 37.

[2637] Moss, R.A.; Ge, C.-S.; Wlostowska, J.; Jang, E.G.; Jefferson, E.A.; Fan, H. *Tetrahedron Lett.* ***1995***, *36*, 3083.

[2638] Moss, R.A.; Wang, L.; Zhang, M.; Skalit, C.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* ***2008***, *130*, 5634.

[2639] Seyferth, D.; Haas, C.K.; Dagani, D. *J. Organomet. Chem.* ***1976***, *104*, 9.

[2640] See also Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 313–319; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 135–143.

[2641] See Seyferth, D. *Acc. Chem. Res.* ***1972***, *5*, 65; Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 341–380.

[2642] Seyferth, D. in Moss, R.A.; Jones Jr., M. *Carbenes*, Vol. 2, Wiley, NY, ***1975***, pp. 101–158; Sheppard, W.A.; Sharts, C.M. *Organic Fluorine Chemistry*, W.A. Benjamin, NY, ***1969***, pp. 237–270.

[2643] Léonel, É.; Paugam, J.P.; Condon-Gueugnot, S.; Nédélec, Y.-Y. *Tetrahedron* ***1998***, *54*, 3207.

[2644] Wang, L.; Moss, R.A.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* ***2012***, *134*, 17459.

[2645] Duan, Y.; Lin, J.-H.; Xiao, J.-C.; Gu, Y.-C. *Org. Lett.* ***2016***, *18*, 2471.

[2646] White, J.D.; Shaw, S. *Org. Lett.* ***2014***, *16*, 3880. For difluorocarbene used in nonflow conditions, see Duan, Y.; Lin, J.-H.; Xiao, J.-C.; Gu, Y.-C. *Chem. Commun.* ***2017***, *53*, 3870.

[2647] See Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***, pp. 224–268; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 18–43, 58–62. For a discussion of the mechanism, see Gol'dberg, Yu.Sh.; Shimanskaya, M.V. *J. Org. Chem. USSR* ***1984***, *20*, 1212.

is formed instead.[2648] The reaction of iodoform and $CrCl_2$ leads to iodocyclopropanes upon reaction with alkenes.[2649] Dihalocyclopropanes are very useful compounds[2650] that can be reduced to cyclopropanes, treated with Mg or Na to give allenes (**18-3**), or converted to a number of other products.

Alkenes of all types can be converted to cyclopropane derivatives by this reaction, but difficulty may be encountered with sterically hindered ones.[2651] Even tetracyanoethylene, which responds very poorly to electrophilic attack, gives cyclopropane derivatives with carbenes.[2652] Conjugated dienes give 1,2-addition to give a vinylcyclopropane.[2653] Addition of a second molar equivalent gives bicyclopropyl derivatives.[2654] 1,4-Addition is rare but has been reported in certain cases.[2655] Carbene adds to ketene to give cyclopropanone.[2656] Allenes react with carbenes to give cyclopropanes with an exocyclic double bond.[2657] A second equivalent gives spiropentanes. In fact, any size ring with an exocyclic double bond can be converted by a carbene to a spiro compound.[2658]

The *Büchner ring expansion* is a two-step C—C bond-forming reaction that gives seven-membered rings. The *retro-Büchner reaction* of 7-substituted 1,3,5-cycloheptatrienes, promoted by cationic gold, gave gold(I) carbenes and reaction with alkenes gave the cyclopropane.[2659]

Free carbenes can also be avoided by using transition metal/carbene complexes $L_nM{=}CRR'$ (L = a ligand, M = a metal),[2660] which add the group CRR′ to double bonds.[2661] An example is the reaction of an iron carbene ($Cp(CO)_2Fe{=}CHMe$) that reacted with styrene to give 3-methyl-1-phenylcyclopropane.[2662] These complexes can be isolated in some cases; in others they are generated *in situ* from appropriate precursors, of which diazo compounds are among the most important. Chromium complexes have been used for the cyclopropanation of alkenes.[2663]

[2648] Moss, R.A.; Lawrynowicz, W. *J. Org. Chem.* ***1984***, *49*, 3828.
[2649] Takai, K.; Toshikawa, S.; Inoue, A.; Kokumai, R. *J. Am. Chem. Soc.* ***2003***, *125*, 12990.
[2650] Banwell, M.G.; Reum, M.E. *Adv. Strain Org. Chem.* ***1991***, *1*, 19–64; Kostikov, R.R.; Molchanov, A.P.; Hopf, H. *Top. Curr. Chem.* ***1990***, *155*, 41–80.
[2651] Dehmlow, E.V.; Eulenberger, A. *Liebigs Ann. Chem.* ***1979***, 1112.
[2652] Cairns, T.L.; McKusick, B.C. *Angew. Chem.* ***1961***, *73*, 520.
[2653] Woodworth, R.C.; Skell, P.S. *J. Am. Chem. Soc.* ***1957***, *79*, 2542.
[2654] See Skattebøl, L. *J. Org. Chem.* ***1964***, *29*, 2951.
[2655] See Hudlicky, T.; Seoane, G.; Price, J.D.; Gadamasetti, K.G. *Synlett* ***1990***, 433; Lambert, J.B.; Ziemnicka-Merchant, B.T. *J. Org. Chem.* ***1990***, *55*, 3460.
[2656] Rothgery, E.F.; Holt, R.J.; McGee Jr., H.A. *J. Am. Chem. Soc.* ***1975***, *97*, 4971; Wasserman, H.H.; Berdahl, D.R.; Lu, T. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, Wiley, NY, ***1987***, pt. 2, pp. 1455–1532.
[2657] Landor, S.R. in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, pp. 351–360; Binger, P.; Büch, H.M. *Top. Curr. Chem.* ***1987***, *135*, 77.
[2658] See Krapcho, A.P. *Synthesis* ***1978***, 77–126.
[2659] Solorio-Alvarado, C.R.; Wang, Y.; Echavarren, A.M. *J. Am. Chem. Soc.* ***2011***, *133*, 11952. Buchner, E.; Curtius, T. *Ber. Dtsch. Chem. Ges.* ***1885***, *18*, 2377; Buchner, E.; Curtius, T. *Ber. Dtsch. Chem. Ges.* ***1885***, *18*, 2371.
[2660] Doyle, M.P.; McKervey, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, NY, ***1998***.
[2661] See Helquist, P. *Adv. Met.-Org. Chem.* ***1991***, *2*, 143; Brookhart, M.; Studabaker, W.B. *Chem. Rev.* ***1987***, *87*, 411; Syatkovskii, A.I.; Babitskii, B.D. *Russ. Chem. Rev.* ***1984***, *53*, 672.
[2662] Brookhart, M.; Tucker, J.R.; Husk, G.R. *J. Am. Chem. Soc.* ***1983***, *105*, 258.
[2663] Barluenga, J.; Aznar, F.; Gutiérrez, I.; García-Granda, S.; Llorca-Baragaño, M.A. *Org. Lett.* ***2002***, *4*, 4233.

Diazo compounds, including CH_2N_2 and other diazoalkanes, react with metals or metal salts (Cu, Pd,[2664] Ag,[2665] La,[2666] and Rh[2667] are commonly used) to give the carbene complexes that add:CRR′ to double bonds.[2668] The synergistic effect of additives on the cyclopropanation of alkenes has been discussed.[2669] Polymer-supported benzenesulfonyl azides have been developed as a safe diazo-transfer reagent.[2670] Diazoketones and diazo esters react with alkenes to give the cyclopropane derivative, usually with a transition metal catalyst such as a Cu complex.[2671] The Ru-,[2672] Cu/Fe-,[2673] Ag-,[2674] or Au-catalyzed[2675] reaction of diazo esters with an alkyne gives a cyclopropene. An X-ray structure of an Os catalyst intermediate has been determined.[2676] Electron-rich alkenes react faster than simple alkenes.[2677] Diazo esters have been generated and used using flow techniques (Sec. 7.D).[2678] α-Diazo-β-ketonitriles gave intramolecular cyclopropanation of tri- and tetrasubstituted alkenes as well as arene cyclopropanation.[2679] The Cu-catalyzed diazo ester cyclopropanation was reported in an ionic liquid.[2680] Fischer carbene compounds (see **15-54**) react with enolate anions to give cyclopropane derivatives.[2681] A Cr-promoted cyclopropanation of conjugated amides has been reported.[2682] The synthesis of [3.1.0] and [4.1.0] bicyclic molecules was reported via a Ru-catalyzed intramolecular cyclopropanation

[2664] Beaufort, L.; Demonceau, A.; Noels, A.F. *Tetrahedron* ***2005***, *61*, 9025. Also see Rodríguez-García, C.; Oliva, A.; Ortuño, R.M.; Branchadell, V. *J. Am. Chem. Soc.* ***2001***, *123*, 6157.

[2665] Thompson, J.L.; Davies, H.M.L. *J. Am. Chem. Soc.* ***2007***, *129*, 6090.

[2666] Nishiyama, Y.; Tanimizu, H.; Tomita, T. *Tetrahedron Lett.* ***2007***, *48*, 6405.

[2667] See Panne, P.; DeAngelis, A.; Fox, J.M. *Org. Lett.* ***2008***, *10*, 2987; Rosenberg, M.L.; Vlašaná, K.; Gupta, N.S.; Wragg, D.; Tilset, M. *J. Org. Chem.* ***2011***, *76*, 2465; Verdecchia, M.; Tubaro, C.; Biffis, A. *Tetrahedron Lett.* ***2011***, *52*, 1136.

[2668] See Adams, J.; Spero, D.M. *Tetrahedron* ***1991***, *47*, 1765; Maas, G. *Top. Curr. Chem.* ***1987***, *137*, 75; Doyle, M.P. *Chem. Rev.* ***1986***, *86*, 919; *Acc. Chem. Res.* ***1986***, *19*, 348; Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 401–407; Wulfman, D.S.; Poling, B. *React. Intermed. (Plenum)* ***1980***, *1*, 321; Müller, E.; Kessler, H.; Zeeh, B. *Fortschr. Chem. Forsch.* ***1966***, *7*, 128.

[2669] Cheng, D.; Huang, D.; Shi, Y. *Org. Biomol. Chem.* ***2013***, *11*, 5588.

[2670] Green, G.M.; Peet, N.P.; Metz, W.A. *J. Org. Chem.* ***2001***, *66*, 2509.

[2671] Díaz-Requejo, M.M.; Belderraín, T.R.; Trofimenko, S.; Pérez, P.J. *J. Am. Chem. Soc.* ***2001***, *123*, 3167. See Bühl, M.; Terstegen, F.; Löffler, F.; Meynhardt, B.; Kierse, S.; Müller, M.; Näther, C.; Lüning, U. *Eur. J. Org. Chem.* ***2001***, 2151.

[2672] Panne, P.; Fox, J.M. *J. Am. Chem. Soc.* ***2007***, *129*, 22; Chanthamath, S.; Iwasa, S. *Acc. Chem. Res.* ***2016***, *49*, 2080.

[2673] For a magnetically recoverable catalyst, see Ishikawa, S.; Hudson, R.; Masnadi, M.; Bateman, M.; Castonguay, A.; Braidy, N.; Moores, A.; Li, C.-J. *Tetrahedron* ***2014***, *70*, 6162.

[2674] See Briones, J.F.; Davies, H.M.L. *Org. Lett.* ***2011***, *13*, 3984. For a Ag-catalyzed reaction using mechanochemical conditions, see Chen, L.; Bovee, M.O.; Lemma, B.E.; Keithley, K.S.M.; Pilson, S.L.; Coleman, M.G.; Mack, J. *Angew. Chem. Int. Ed.* ***2015***, *54*, 11084.

[2675] Briones, J.F.; Davies, H.M.L. *J. Am. Chem. Soc.* ***2012***, *134*, 11916.

[2676] Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M. *J. Am. Chem. Soc.* ***2001***, *123*, 4843.

[2677] See Davies, H.M.L.; Xiang, B.; Kong, N.; Stafford, D.G. *J. Am. Chem. Soc.* ***2001***, *123*, 7461.

[2678] Müller, S.T.R.; Smith, D.; Hellier, P.; Wirth, T. *Synlett* ***2014***, *25*, 871; Roda, N.M.; Tran, D.N.; Battilocchio, C.; Labes, R.; Ingham, R.J.; Hawkins, J.M.; Ley, S.V. *Org. Biomol. Chem.* ***2015***, *13*, 2550.

[2679] Nani, R.R.; Reisman, S.E. *J. Am. Chem. Soc.* ***2013***, *135*, 7304.

[2680] Fraile, J.M.; García, J.I.; Herrerías, C.I.; Mayoral, J.A.; Carrié, D.; Vaultier, M. *Tetrahedron: Asymmetry* ***2001***, *12*, 1891.

[2681] Barluenga, J.; Suero, M.G.; Pérez-Sánchez, I.; Flórez, J. *J. Am. Chem. Soc.* ***2008***, *130*, 2708.

[2682] Concellón, J.M.; Rodríguez-Solla, H.; Méjica, C.; Blanco, E.G.; García-Granda, S.; Diaz, M.R. *Org. Lett.* ***2008***, *10*, 349.

reaction of enynols that have a propargyl alcohol moiety, which functions as β-oxocarbene precursors.[2683]

Asymmetric cyclopropanation reactions are a growing area of interest,[2684] and chiral complexes have been used for enantioselective cyclopropane synthesis.[2685] Decomposition of diazoalkanes in the presence of chiral Rh,[2686] Cu,[2687] Ir,[2688] Co,[2689] Au,[2690] or Ru[2691] complexes leads to optically active cyclopropanes. The Rh-catalyzed cycloaddition using chiral ligands leads to formation of cyclopropanes with good enantioselectivity.[2692] The use of chiral additives or auxiliaries with a metal complex also leads to cyclopropanes enantioselectively.[2693] An important chiral species is Rh_2(*S*-DOSP)$_4$,[2694] which leads to cyclopropanes with excellent enantioselectivity in carbene cyclopropanation reactions.[2695] Chiral organocatalysts have been used.[2696] Engineered myoglobin-based catalysts have been developed.[2697] Organocatalytic enantioselective cyclopropanation has been reported using continuous flow techniques (Sec. 7.D).[2698] Asymmetric, intramolecular cyclopropanation reactions have been reported.[2699] It is noted that the reaction of a diazo ester with a chiral dirhodium catalyst leads to β-lactones with modest enantioselectivity.[2700]

Triple bond compounds[2701] react with carbenes to give cyclopropenes, except that in the case of acetylene itself, the cyclopropenes first formed cannot be isolated because they

[2683] Trost, B.M.; Breder, A.; O'Keefe, B.M.; Rao, M.; Franz, A.W. *J. Am. Chem. Soc.* ***2011***, *133*, 4766.

[2684] Pellissier, H. *Tetrahedron* ***2008***, *64*, 7041; Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Synthesis* ***2014***, *46*, 879.

[2685] Singh, V.K.; DattaGupta, A.; Sekar, G. *Synthesis* ***1997***, 137; Davies, H.M.L.; Bruzinski, P.R.; Fall, M.J. *Tetrahedron Lett.* ***1996***, *37*, 4133.

[2686] Davies, H.M.L.; Rusiniak, L. *Tetrahedron Lett.* ***1998***, *39*, 8811; Ichiyanagi, T.; Shimizu, M.; Fujisawa, T. *Tetrahedron* ***1997***, *53*, 9599; Fukuda, T.; Katsuki, T. *Tetrahedron* ***1997***, *53*, 7201.

[2687] Bayardon, J.; Holczknecht, O.; Pozzi, G.; Sinou, D. *Tetrahedron: Asymmetry* ***2006***, *17*, 1568.

[2688] Suematsu, H.; Kanchiku, S.; Uchida, T.; Katsuki, T. *J. Am. Chem. Soc.* ***2008***, *130*, 10327.

[2689] Chen, Y.; Ruppel, J.V.; Zhang, X.P. *J. Am. Chem. Soc.* ***2007***, *129*, 12074; Doyle, M.P. *Angew. Chem. Int. Ed.* ***2009***, *48*, 850; White, J.D.; Shaw, S. *Org. Lett.* ***2014***, *16*, 3880.

[2690] Prieto, A.; Fructos, M.R.; Díaz-Requejo, M.M.; Pérez, P.J.; Pérez-Galán, P.; Delpont, N.; Echavarren, A.M. *Tetrahedron* ***2009***, *65*, 1790.

[2691] Iwasa, S.; Takezawa, F.; Tuchiya, Y.; Nishiyama, H. *Chem. Commun.* ***2001***, 59. For a discussion of the mechanism, see Oxgaard, J.; Goddard III, W.A. *J. Am. Chem. Soc.* ***2004***, *126*, 442.

[2692] Adly, F.G.; Gardiner, M.G.; Ghanem, A. *Chem. Eur. J.* ***2016***, *22*, 3447–3461. For a discussion of the mechansim and origin of enantioselectivity, see Nowlan III, D.T.; Singleton, D.A. *J. Am. Chem. Soc.* ***2005***, *127*, 6190. Also see Jiao, L.; Ye, S.; Yu, Z.-X. *J. Am. Chem. Soc.* ***2008***, *130*, 7178.

[2693] Ferreira, V.F.; Leão, R.A.C.; da Silva, F. de C.; Pinheiro, S.; Lhoste, P.; Sinou, D. *Tetrahedron: Asymmetry* ***2007***, *18*, 1217; Miller, J.A.; Gross, B.A.; Zhuravel, M.A.; Jin, W.; Nguyen, S.B.T. *Angew. Chem. Int. Ed.* ***2005***, *44*, 3885.

[2694] Doyle, M.P. *Pure Appl. Chem.* ***1998***, *70*, 1123; Davies, H.M.L.; Hansen, T.; Churchill, M.R. *J. Am. Chem. Soc.* ***2000***, *122*, 3063. See also, Davies, H.M.L.; Lee, G.H. *Org. Lett.* ***2004***, *6*, 2117.

[2695] Davies, H.M.L.; Townsend, R.J. *J. Org. Chem.* ***2001***, *66*, 6595.

[2696] Johansson, C.C.C.; Bremeyer, N.; Ley, S.V.; Owen, D.R.; Smith, S.C.; Gaunt, M.J. *Angew. Chem. Int. Ed.* ***2006***, *45*, 6024.

[2697] Bordeaux, M.; Tyagi, V.; Fasan, R. *Angew. Chem. Int. Ed.* ***2015***, *54*, 1744.

[2698] Llanes, P.; Rodríguez-Escrich, C.; Sayalero, S.; Pericàs, M.A. *Org. Lett.* ***2016***, *18*, 6292.

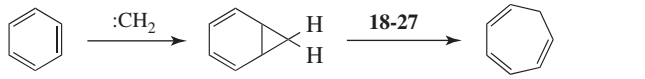
[2699] See Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* ***2003***, *125*, 2860.

[2700] Doyle, M.P.; May, E.J. *Synlett* ***2001***, 967.

[2701] See Fuks, R.; Viehe, H.G. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 427–434; Closs, G.L. *Adv. Alicyclic Chem.* ***1966***, *1*, 53–127 (pp. 58–65).

rearrange to allenes.[2702] Cyclopropenones (Sec. 2.K.i) are obtained by hydrolysis of dihalocyclopropenes.[2703] Transition metal-catalyzed reactions are well known.[2704]

Carbenes are so reactive that they add to the "double bonds" of aromatic rings.[2705] The products are usually unstable and rearrange to give ring expansion. Carbene reacts with benzene to give cyclohepta-1,3,5-triene:[2706]

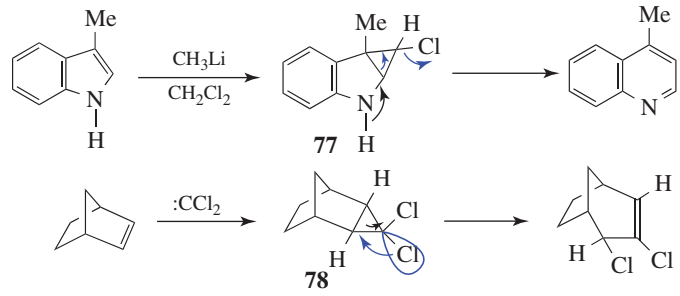


Norcaradiene Cyclohepta-1,3,5-triene

The norcaradiene intermediate cannot be isolated in this case[2707] as it undergoes an electrocyclic rearrangement (**18-27**). However, certain substituted norcaradienes, for example, the product of addition of $:C(CN)_2$ to benzene,[2708] have been isolated.[2709] Not all carbenes are reactive enough to add to benzene. With $:CH_2$, insertion is a major side reaction, and, for example, benzene gives toluene as well as cycloheptatriene. A method of adding $:CH_2$ to benzene rings without the use of free carbene is the catalytic decomposition of diazomethane (CH_2N_2) in the aromatic compound as solvent with CuCl or CuBr.[2710] By this method better yields of cycloheptatrienes are obtained without insertion side products. *Picosecond optical grating calorimetry* has been used to investigate the photochemical decomposition of diazomethane in benzene, and it appears that a transient intermediate is formed that is consistent with a weak complex between singlet methylene and benzene.[2711] Chlorocarbene, :CHCl, is active enough to add to benzene, but dihalocarbenes do not add to benzene or toluene, only to rings with greater electron density. The activation parameters of arylchlorocarbenes for their electrophilicity with regard to additions to alkenes has been reported.[2712]

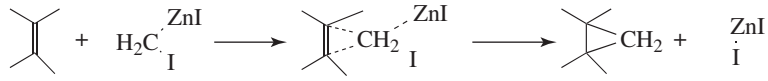
The Pd-catalyzed cyclopropanation of heterocycles is known.[2713] Pyrroles and indoles can be expanded, respectively, to pyridines and quinolines by treatment with halocarbenes[2714] via the initially formed adduct **77** in the case of the indole. In such cases, a side reaction that sometimes occurs is expansion of the *six-membered* ring. Ring expansion can occur even with nonaromatic compounds, especially when the driving force is supplied by relief of strain (see **78**).[2715]

[2702] Frey, H.M. *Chem. Ind. (London)* ***1960***, 1266.
[2703] Vol'pin, M.E.; Koreshkov, Yu.D.; Kursanov, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1959***, 535.
[2704] Torres, Ò.; Pla-Quintana, A. *Tetrahedron Lett.* ***2016***, *57*, 3881.
[2705] See Giese, C.M.; Hadad, C.M. *J. Org. Chem.* ***2002***, *67*, 2532.
[2706] Doering, W. von E.; Knox, L.H. *J. Am. Chem. Soc.* ***1951***, *75*, 297.
[2707] It has been detected by UV spectroscopy: Rubin, M.B. *J. Am. Chem. Soc.* ***1981***, *103*, 7791.
[2708] Ciganek, E. *J. Am. Chem. Soc.* ***1967***, *89*, 1454.
[2709] See Kawase, T.; Iyoda, M.; Oda, M. *Angew. Chem. Int. Ed.* ***1987***, *26*, 559.
[2710] Wittig, G.; Schwarzenbach, K. *Liebigs Ann. Chem.* ***1961***, *650*, 1; Müller, E.; Fricke, H. *Liebigs Ann. Chem.* ***1963***, *661*, 38; Müller, E.; Kessler, H.; Fricke, H.; Kiedaisch, W. *Liebigs Ann. Chem.* ***1961***, *675*, 63.
[2711] Khan, M.I.; Goodman, J.L. *J. Am. Chem. Soc.* ***1995***, *117*, 6635.
[2712] Wang, L.; Krogh-Jespersen, K.; Moss, R.A. *J. Org. Chem.* ***2015***, *80*, 7590.
[2713] Wu, X.; Lei, C.; Yue, G.; Zhou, J. *Angew. Chem. Int. Ed.* ***2015***, *54*, 9601.
[2714] See Rees, C.W.; Smithen, C.E. *Adv. Heterocycl. Chem.* ***1964***, *3*, 57–78.
[2715] Jefford, C.W.; Gunsher, J.; Hill, D.T.; Brun, P.; Le Gras, J.; Waegell, B. *Org. Synth.* ***VI***, 142. For a review of the addition of halocarbenes, see Jefford, C.W. *Chimia* ***1970***, *24*, 357–363.



As previously mentioned, free carbene is not very useful for additions to double bonds since it gives too many side products. The *Simmons-Smith procedure* accomplishes the same result without a free carbene intermediate and without insertion side products.[2716] This is known as a *carbenoid* reaction. Intramolecular variations are known.[2717] The Simmons-Smith procedure involves treatment of the double bond compound with CH_2I_2 and a Zn/Cu couple and leads to cyclopropane derivatives in good yields.[2718] The Zn/Cu couple can be prepared in several ways,[2719] and heating Zn dust with CuCl in ether under nitrogen[2720] is particularly convenient. The reaction has also been done with unactivated Zn and ultrasound.[2721] When $TiCl_4$ is used along with Zn and CuCl, CH_2I_2 can be replaced by the cheaper CH_2Br_2.[2722] Borocyclopropanation of allylic ethers used boromethyzinc carbenoids.[2723] The effect of additives on certain zinc carbenoid reactions has been discussed.[2724]

The actual attacking species is an organozinc intermediate, probably $(ICH_2)_2Zn{\bullet}ZnI_2$, which is stable enough for isolable solutions.[2725] An X-ray crystallographic investigation of the intermediate, complexed with a diether, has been reported.[2726] The addition is stereospecifically *syn*, and a concerted mechanism is likely,[2727] perhaps involving **79**.[2728]



79

[2716] See Simmons, H.E.; Cairns, T.L.; Vladuchick, S.A.; Hoiness, C.M. *Org. React.* ***1973***, *20*, 1–131; Furukawa, J.; Kawabata, N. *Adv. Organomet. Chem.* ***1974***, *12*, 83–134 (pp. 84–103); Lévesque, É.; Goudreau, S.R.; Charette, A.B. *Org. Lett.* ***2014***, *16*, 1490.

[2717] Bull, J.A.; Charette, A.B. *J. Am. Chem. Soc.* ***2010***, *132*, 1895.

[2718] Simmons, H.E.; Smith, R.D. *J. Am. Chem. Soc.* ***1959***, *81*, 4256. See Cheng, K.; Carroll, P.J.; Walsh, P.J. *Org. Lett.* ***2011***, *13*, 2346. For another role of Cu, see Fujii, K.; Misaki, T.; Sugimura, T. *Chem. Lett.* ***2014***, *43*, 634.

[2719] LeGoff, E. *J. Org. Chem.* ***1964***, *29*, 2048; Denis, J.M.; Girard, C.; Conia, J.M. *Synthesis* ***1972***, 549.

[2720] Rawson, R.J.; Harrison, I.T. *J. Org. Chem.* ***1970***, *35*, 2057.

[2721] Repič, O.; Lee, P.G.; Giger, U. *Org. Prep. Proced. Int.* ***1984***, *16*, 25.

[2722] Friedrich, E.C.; Lunetta, S.E.; Lewis, E.J. *J. Org. Chem.* ***1989***, *54*, 2388.

[2723] Benoit, G.; Charette, A.B. *J. Am. Chem. Soc.* ***2017***, *139*, 1364.

[2724] Ramirez, A.; Truc, C.; Lawler, M.; Ye, Y.K.; Wang, J.; Wang, C.; Chen, S.; Laporte, T.; Liu, N.; Kolotuchin, S.; Jones, S.; Bordawekar, S.; Tummala, S.; Waltermire, R.E.; Kronenthal, D. *J. Org. Chem.* ***2014***, *79*, 6233.

[2725] Blanchard, E.P.; Simmons, H.E. *J. Am. Chem. Soc.* ***1964***, *86*, 1337. For an analysis by density functional theory, see Fang, W.-H.; Phillips, D.L.; Wang, D.-q.; Li, Y.-L. *J. Org. Chem.* ***2002***, *67*, 154.

[2726] Denmark, S.E.; Edwards, J.P.; Wilson, S.R. *J. Am. Chem. Soc.* ***1991***, *113*, 723.

[2727] Dargel, T.K.; Koch, W. *J. Chem. Soc., Perkin Trans. 2* ***1996***, 877.

[2728] Simmons, H.E.; Blanchard, E.P.; Smith, R.D. *J. Am. Chem. Soc.* ***1964***, *86*, 1347. For the transition state and intermediate, see Bernardi, F.; Bottoni, A.; Miscione, G.P. *J. Am. Chem. Soc.* ***1997***, *119*, 12300.

An iodomethylzinc phosphate has also been used for cyclopropanation reactions.[2729] Diiodomethane gives cyclopropanes in a reaction mediated by indium.[2730] Asymmetric induction is possible when chiral additives are used.[2731] Chiral complexes also lead to enantioselectivity in the cyclopropanation reaction.[2732] Organocatalysts have been used.[2733] With the Simmons-Smith procedure, as with free carbenes, conjugated dienes give 1,2-addition,[2734] and allenes give methylenecyclopropanes or spiropentanes.[2735]

An alternative way of carrying out the Simmons-Smith reaction is by treatment of the substrate with CH_2I_2 or another dihalomethane and Et_2Zn in ether.[2736] The reaction of diethylzinc and diiodomethane gave ketones that were chain extended by one carbon.[2737] This method can be adapted to the introduction of RCH and ArCH by the use of $RCHI_2$ or $ArCHI_2$ instead of the dihalomethane.[2738] The reaction is compatible with other functionality in the carbenoid complex. The reaction of RCO_2CH_2I with diethyl zinc and an alkene under photolysis conditions give a cyclopropane.[2739] Samarium and CH_2I_2 has been used for the cyclopropanation of conjugated amides.[2740] For the conversion of enolate anions to cyclopropanols, CH_2I_2 has been used along with SmI_2.[2741] Diodomethane in the presence of isopropylmagnesium chloride has been used to cyclopropanate allyl alcohols.[2742]

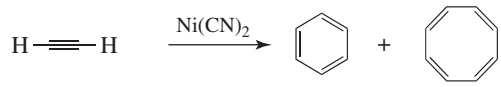
The *Simmons-Smith reaction* is the basis of a method for the indirect α methylation of a ketone.[2743] The ketone is first converted to an enol ether, an enamine (**16-12**), or a silyl enol ether[2744] (**12-17**), and cyclopropanation via the Simmons-Smith reaction is followed by hydrolysis to give the α-methylated ketone. In another variation, phenols can be *ortho*-methylated in one laboratory step, by treatment with Et_2Zn and CH_2I_2.[2745]

Stable two-coordinate acyclic silylenes have been prepared.[2746]

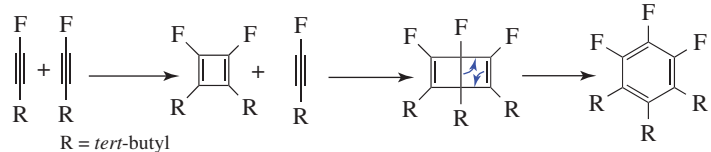
OS **V**, 306, 855, 859, 874; **VI**, 87, 142, 187, 327, 731, 913, 974; **VII**, 12, 200, 203; **VIII**, 124, 196, 321, 467; **IX**, 422; **76**, 86.

[2729] Lacasse, M.-C.; Poulard, C.; Charette, A.B. *J. Am. Chem. Soc.* ***2005***, *127*, 12440.
[2730] Virender; Jain, S.L.; Sain, B. *Tetrahedron Lett.* ***2005***, *46*, 37.
[2731] Balsells, J.; Walsh, P.J. *J. Org. Chem.* ***2000***, *65*, 5005; Du, H.; Long, J.; Shi, Y. *Org. Lett.* ***2006***, *8*, 2827; Long, J.; Du, H.; Li, K.; Shi, Y. *Tetrahedron Lett.* ***2005***, *46*, 2737.
[2732] Shitama, H.; Katsuki, T. *Angew. Chem. Int. Ed.* ***2008***, *47*, 2450; Zimmer, L.E.; Charette, A.B. *J. Am. Chem. Soc.* ***2009***, *131*, 15624.
[2733] Long, J.; Xu, L.; Du, H.; Li, K.; Shi, Y. *Org. Lett.* ***2009***, *11*, 5226.
[2734] Overberger, C.G.; Halek, G.W. *J. Org. Chem.* ***1963***, *28*, 867.
[2735] Charette, A.B.; Jolicoeur, E.; Bydlinski, G.A.S. *Org. Lett.* ***2001***, *3*, 3293.
[2736] See Zhao, C.; Wang, D.; Phillips, D.L. *J. Am. Chem. Soc.* ***2002***, *124*, 12903. For a Ni-catalyzed version of this reaction, see Xu, J.; Samsuri, N.B.; Duong, H.A. *Chem. Commun.* ***2016***, *52*, 3372.
[2737] Brogan, J.B.; Zercher, C.K. *J. Org. Chem.* ***1997***, *62*, 6444.
[2738] Friedrich, E.C.; Biresaw, G. *J. Org. Chem.* ***1982***, *47*, 1615.
[2739] Charette, A.B.; Beauchemin, A.; Francoeur, S. *J. Am. Chem. Soc.* ***2001***, *123*, 8139.
[2740] Concellón, J.M.; Rodríguez-Solla, H.; Gómez, C. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1917.
[2741] Imamoto, T.; Takiyama, N. *Tetrahedron Lett.* ***1987***, *28*, 1307. See also, Molander, G.A.; Harring, L.S. *J. Org. Chem.* ***1989***, *54*, 3525.
[2742] Bolm, C.; Pupowicz, D. *Tetrahedron Lett.* ***197***, *38*, 7349.
[2743] For the enol ether procedure, see Wenkert, E.; Mueller, R.A.; Reardon Jr., E.J.; Sathe, S.S.; Scharf, D.J.; Tosi, G. *J. Am. Chem. Soc.* ***1970***, *92*, 7428; for the enamine procedure, see Kuehne, M.E.; King, J.C. *J. Org. Chem.* ***1973***, *38*, 304; for the silyl ether procedure, see Conia, J.M. *Pure Appl. Chem.* ***1975***, *43*, 317–326.
[2744] See Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* ***1976***, *41*, 2073; *Org. Synth.* ***VI***, 327.
[2745] Lehnert, E.K.; Sawyer, J.S.; Macdonald, T.L. *Tetrahedron Lett.* ***1989***, *30*, 5215.
[2746] Protchenko, A.V.; Birjkumar, K.H.; Dange, D.; Schwarz, A.D.; Vidovic, D.; Jones, C.; Kaltsoyannis, N.; Mountford, P.; Aldridge, S. *J. Am. Chem. Soc.* ***2012***, *134*, 6500.

15-61 Trimerization and Tetramerization of Alkynes



Aromatic compounds can be prepared by cyclotrimerization of alkynes[2747] or triynes. Cyclotrimerization is possible by heating to 450–600 °C with no catalyst.[2748] The *spontaneous* (no catalyst) trimerization of *t*-BuC≡CF gave 1,2,3-tri-*tert*-butyl-4,5,6-trifluorobenzene (**81**), the first time three adjacent *tert*-butyl groups had been put onto a benzene ring.[2749] The fact that this is a head to head joining allows formation of **81** from two alkynes. The fact that **80** (a Dewar benzene) was also isolated lends support to this scheme.[2750]



When acetylene is heated with nickel cyanide, other Ni(II) or Ni(0) compounds, or similar catalysts, it gives benzene and cyclooctatetraene.[2751] It is possible to get more of either product by a proper choice of catalyst. Substituted acetylenes give substituted benzenes,[2752] and this reaction has been used to prepare very crowded molecules. Dialkylalkynes were trimerized over $CO_2(CO)_8$[2753] and over $Hg[Co(CO)_4]_2$ to give hexaisopropylbenzene.[2754] The six isopropyl groups are not free to rotate but are lined up perpendicular to the plane of the benzene ring. Highly substituted benzene derivatives have also been prepared via cyclotrimerization using Rh,[2755] Ni,[2756] Ti,[2757] Mo,[2758] Ru,[2759] In,[2760] Fe,[2761]

[2747] For a review, see Rubin, M.; Sromek, A.W.; Gevorgyan, V. *Synlett* ***2003***, 2265.
[2748] Kociolek, M.G.; Johnson, R.P. *Tetrahedron Lett.* ***1999***, *40*, 4141.
[2749] Viehe, H.G.; Merényi, R.; Oth, J.F.M.; Valange, P. *Angew. Chem. Int. Ed.* ***1964***, *3*, 746; Viehe, H.G.; Merényi, R.; Oth, J.F.M.; Senders, J.R.; Valange, P. *Angew. Chem. Int. Ed.* ***1964***, *3*, 755.
[2750] See also, Wingert, H.; Regitz, M. *Chem. Ber.* ***1986***, *119*, 244.
[2751] See Winter, M.J. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 3, Wiley, NY, ***1985***, pp. 259–294; Vollhardt, K.P.C. *Angew. Chem. Int. Ed.* ***1984***, *23*, 539; *Acc. Chem. Res.* ***1977***, *10*, 1; Schore, N.E. *Chem. Rev.* ***1988***, *88*, 1081. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 198–201.
[2752] Sigman, M.S.; Fatland, A.W.; Eaton, B.E. *J. Am. Chem. Soc.* ***1998***, *120*, 5130; Larock, R.C.; Tian, Q. *J. Org. Chem.* ***1998***, *63*, 2002.
[2753] Yong, L.; Butenschön, H. *Chem. Commun.* ***2002***, 2852; Marchueta, I.; Olivella, S.; Solà, L.; Moyano, A.; Pericàs, M.A.; Riera, A. *Org. Lett.* ***2001***, *3*, 3197. See also, Agenet, N.; Gandon, V.; Vollhardt, K.P.C.; Malacria, M.; Aubert, C. *J. Am. Chem. Soc.* ***2007***, *129*, 8860.
[2754] See Hopff, H.; Gati, A. *Helv. Chim. Acta* ***1965***, *48*, 509.
[2755] See Yoshida, K.; Morimoto, I.; Mitsudo, K.; Tanaka, H. *Chem. Lett.* ***2007***, *36*, 998.
[2756] See Pal, S.; Uyeda, C. *J. Am. Chem. Soc.* ***2015***, *137*, 8042.
[2757] Tanaka, R.; Nakano, Y.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* ***2002***, *124*, 9682.
[2758] Nishida, M.; Shiga, H.; Mori, M. *J. Org. Chem.* ***1998***, *63*, 8606.
[2759] Yamamoto, Y.; Ishii, J.-i.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* ***2004***, *126*, 3712.
[2760] Xu, Y.-l.; Pan, Y.-m.; Wu, Q.; Wang, H.-s.; Liu, P.-z. *J. Org. Chem.* ***2011***, *76*, 8472.
[2761] Lipschutz, M.I.; Chantarojsiri, T.; Dong, Y.; Tilley, T.D. *J. Am. Chem. Soc.* ***2015***, *137*, 6366.

Co,[2762] or Pd[2763] catalysts. Alkynes react with allenes and a Ni catalyst to give highly substituted benzene derivatives.[2764] Conjugated ketones react with internal alkynes with Me_3Al and a Ni catalyst[2765] to give an aromatic ring fused to a cyclic ketone after reaction with DBU and air.[2766] *N*-Aryl chloroimines react with alkynes and a Rh catalyst to give quinolines,[2767] as do *N*-aryl alkynyl imines with a W complex.[2768]

Intramolecular cyclotrimerizations have been reported by condensation of a diyne[2769] with an alkyne in the presence of a Pd,[2770] Mo,[2771] Ni,[2772] Rh,[2773] Ir,[2774] Ag,[2775] Au/Ag,[2776] Co,[2777] or Ru catalyst.[2778] Triynes have been similarly condensed with a Rh[2779] or a Co[2780] catalyst. Note that this type of cyclization has been labeled as a [2 + 2 + 2] cycloaddition reaction, which is discussed in reaction **15-62**. The internal cyclotrimerization of a triyne, utilizing a siloxy tether and a Co catalyst, has been reported.[2781] Fused-ring aromatic compounds are prepared by this method. Similar results were obtained from diynes and allenes with a Ni catalyst.[2782] A Ni-catalyzed cross cyclotrimerization and dimerization of allenes and alkynes has been reported.[2783] Solid-supported cyclotrimerizations have been reported.[2784] Benzene derivatives with *ortho* alkyne units can be converted to naphthalene derivatives in aqueous NaOH with hydrazine, Te, $NaBH_4$, and sonication.[2785] Vinyl and alkyne substituents with a Ru catalyst lead to naphthalene derivatives.[2786] Cyclotrimerization occurs with alkynyl boronic esters.[2787]

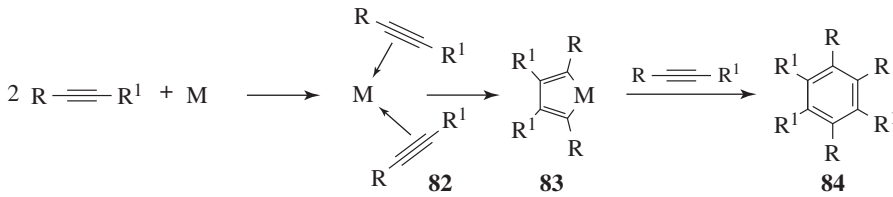
There are many variations of this basic approach. Imino and iodo substituents with a silyl alkyne and a Pd catalyst lead to an isoquinoline.[2788] Benzene derivatives having *ortho*

[2762] Sugihara, T.; Wakabayashi, A.; Nagai, Y.; Takao, H.; Imagawa, H.; Nishizawa, M. *Chem. Commun.* ***2002***, 576; Eichman, C.C.; Bragdon, J.P.; Stambuli, J.P. *Synlett* ***2011***, *22*, 1109.
[2763] Gevorgyan, V.; Quan, L.G.; Yamamoto, Y. *J. Org. Chem.* ***2000***, *65*, 568. Also see Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* ***2003***, *68*, 6836; Li, J.-H.; Xie, Y.-X. *Synth. Commun.* ***2004***, *34*, 1737.
[2764] Shanmugasundaram, M.; Wu, M.-S.; Cheng, C.-H. *Org. Lett.* ***2001***, *3*, 4233.
[2765] Ikeda, S.; Kondo, H.; Arii, T.; Odashima, K. *Chem. Commun.* ***2002***, 2422.
[2766] Mori, N.; Ikeda, S.-i.; Sato, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 2722.
[2767] Amii, H.; Kishikawa, Y.; Uneyama, K. *Org. Lett.* ***2001***, *3*, 1109.
[2768] Sangu, K.; Fuchibe, K.; Akiyama, T. *Org. Lett.* ***2004***, *6*, 353.
[2769] See Kawathar, S.P.; Schreiner, P.R. *Org. Lett.* ***2002***, *4*, 3643.
[2770] Gevorgyan, V.; Radhakrishnan, U.; Takeda, A.; Rubina, M.; Rubin, M.; Yamamoto, Y. *J. Org. Chem.* ***2001***, *66*, 2835. See also, Tsukada, N.; Sugawara, S.; Nakaoka, K.; Inoue, Y. *J. Org. Chem.* ***2003***, *68*, 5961.
[2771] Hara, R.; Guo, Q.; Takahashi, T. *Chem. Lett.* ***2000***, 140.
[2772] Jeevanandam, A.; Korivi, R.P.; Huang, I.-w.; Cheng, C.-H. *Org. Lett.* ***2002***, *4*, 807.
[2773] Witulski, B.; Zimmermann, A. *Synlett* ***2002***, 1855.
[2774] Shibata, T.; Fujimoto, T.; Yokota, K.; Takagi, K. *J. Am. Chem. Soc.* ***2004***, *126*, 8382.
[2775] Zhao, J.; Hughes, C.O.; Toste, F.D. *J. Am. Chem. Soc.* ***2006***, *128*, 7436.
[2776] Zhang, D.-H.; Yao, L.-F.; Wei, Y.; Shi, M. *Angew. Chem. Int. Ed.* ***2011***, *50*, 2583.
[2777] Hilt, G.; Vogler, T.; Hess, W.; Galbiati, F. *Chem. Commun.* ***2005***, 1474.
[2778] Yamamoto, Y.; Hattori, K.; Nishiyama, H. *J. Am. Chem. Soc.* ***2006***, *128*, 8336.
[2779] Kinoshita, H.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* ***2003***, *125*, 7784.
[2780] Jungk, P.; Fischer, F.; Thiel, I.; Hapke, M. *J. Org. Chem.* ***2015***, *80*, 9781.
[2781] Chouraqui, G.; Petit, M.; Aubert, C.; Malacria, M. *Org. Lett.* ***2004***, *6*, 1519.
[2782] Shanmugasundaram, M.; Wu, M.-S.; Jeganmohan, M.; Huang, C.-W.; Cheng, C.-H. *J. Org. Chem.* ***2002***, *67*, 7724.
[2783] Sakashita, K.; Shibata, Y.; Tanaka, K. *Angew. Chem. Int. Ed.* ***2016***, *55*, 6753.
[2784] Young, D.D.; Senaiar, R.S.; Deiters, A. *Chem. Eur. J.* ***2006***, *12*, 5563.
[2785] Landis, C.A.; Payne, M.M.; Eaton, D.L.; Anthony, J.E. *J. Am. Chem. Soc.* ***2004***, *126*, 1338.
[2786] Klumpp, D.A.; Beauchamp, P.S.; Sanchez Jr., G.V.; Aguirre, S.; de Leon, S. *Tetrahedron Lett.* ***2001***, *42*, 5821.
[2787] Gandon, V.; Leca, D.; Aechtner, T.; Vollhardt, K.P.C.; Malacria, M.; Aubert, C. *Org. Lett.* ***2004***, *6*, 3405.
[2788] Roesch, K.R.; Larock, R.C. *J. Org. Chem.* ***2002***, *67*, 86.

imine and alkyne substituents give an isoquinoline when treated with iodine[2789] or with a Pd catalyst.[2790] Diynes with nitriles and a Ru catalyst lead to isoquinolines.[2791] Isocyanides and alkynes also react with a phosphine catalyst to give pyrroles.[2792] α,β-Unsaturated oxime pivalates in the presence of cationic Rh complexes reacted with alkenes via irreversible migratory insertion to give 2,3-dihydropyridine products.[2793]

Nitriles react with 2 molar equivalents of acetylene, in the presence of a Co catalyst, to give 2-substituted pyridines.[2794] Propargyl amines react with cyclohexanone derivatives and a Au complex give tetrahydroquinolines.[2795] Treatment of alkynes with Cp_2ZrEt_2 followed by reaction with acetonitrile and then a second alkyne, with a Ni catalyst, gives a highly substituted pyridine.[2796] This reaction can be done intramolecularly using a photochemically induced reaction with a Co catalyst and *p*-TolCN to give pyridines incorporated into macrocycles.[2797] Diynes react with *N*-heterocyclic carbenes in the presence of a Ni catalyst to give pyridines.[2798] Alkynyl esters react with enamino esters with a $ZnBr_2$ catalyst to give substituted pyridines.[2799]

In contrast to the spontaneous reaction, the catalyzed process seldom gives the 1,2,3-trisubstituted benzene isomer from an acetylene RC≡CH. The chief product is usually the 1,2,4 isomer,[2800] with lesser amounts of the 1,3,5 isomer also generally obtained, but little if any of the 1,2,3 isomer.



The mechanism of the catalyzed reaction to form benzenes[2801] is believed to go through a species **82**, in which two molecules of alkyne coordinate with the metal, and another species **83**, a five-membered heterocyclic intermediate.[2802] Such intermediates (where M = Rh, Ir, Zr,[2803] or Ni) have been isolated and shown to give benzenes (**84**) when treated with

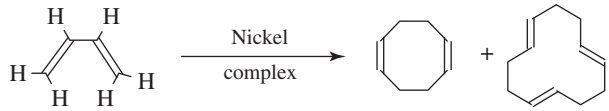
[2789] Huang, Q.; Hunter, J.A.; Larock, R.C. *Org. Lett.* ***2001***, *3*, 2973.
[2790] See Dai, G.; Larock, R.C. *J. Org. Chem.* ***2003***, *68*, 920.
[2791] Varela, J.A.; Castedo, L.; Saá, C. *J. Org. Chem.* ***2003***, *68*, 8595.
[2792] Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *Tetrahedron Lett.* ***2005***, *46*, 2563.
[2793] Romanov-Michailidis, F.; Sedillo, K.F.; Neely, J.M.; Rovis, T. *J. Am. Chem. Soc.* ***2015***, *137*, 8892.
[2794] Heller, B.; Oehme, G. *J. Chem. Soc., Chem. Commun.* ***1995***, 179.
[2795] Abbiati, G.; Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *J. Org. Chem.* ***2003***, *68*, 6959.
[2796] Takahashi, T.; Tsai, F.Y.; Kotora, M. *J. Am. Chem. Soc.* ***2000***, *122*, 4994.
[2797] Moretto, A.F.; Zhang, H.-C.; Maryanoff, B.E. *J. Am. Chem. Soc.* ***2001***, *123*, 3157.
[2798] McCormick, M.M.; Duong, H.A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* ***2005***, *127*, 5030.
[2799] Bagley, M.C.; Dale, J.W.; Hughes, D.D.; Ohnesorge, M.; Philips, N.G.; Bower, J. *Synlett* ***2001***, 1523.
[2800] See Saito, S.; Kawasaki, T.; Tsuboya, N.; Yamamoto, Y. *J. Org. Chem.* ***2001***, *66*, 796.
[2801] See Lawrie, C.J.; Gable, K.P.; Carpenter, B.K. *Organometallics* ***1989***, *8*, 2274.
[2802] Colborn, R.E.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* ***1981***, *103*, 6259; Kochi, J.K. *Organometallic Mechanisms and Catalysis*, Academic Press, NY, ***1978***, pp. 428–432; Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA, ***1987***, pp. 870–877; Eisch, J.J.; Sexsmith, S.R. *Res. Chem. Intermed.* ***1990***, *13*, 149–192.
[2803] Takahahsi, T.; Ishikawa, M.; Huo, S. *J. Am. Chem. Soc.* ***2002***, *124*, 388.

alkynes.[2804] Note that this pathway accounts for the predominant formation of the 1,2,4 isomer. Two possibilities for the last step are a *Diels-Alder reaction,* and a ring expansion, each followed by extrusion of the metal:[2805] In at least one case the mechanism is different, going through a cyclobutadiene/Ni complex (Sec. 2.K.ii), which has been isolated.[2806] Similar results were obtained with a Ti complex.[2807] Using a mixture of $PdCl_2$ and $CuCl_2$, however, aliphatic alkynes are converted to the 1,3,5-trialkyl benzene derivative.[2808]

Alkoxy Cr carbenes (*Fischer carbene complexes*, see **15-54**) react with phenyl alkynes to give naphthalene derivatives.[2809] These Cr carbenes react with alkynyl boronates, cerium (IV) compounds, and then PhBr and a Pd catalyst to give a naphthoquinone.[2810] Diynes react to give cyclotrimerization.[2811] It is noted that vinyl Cr carbenes react directly with alkynes to give spirocyclic compounds (spiro[4.4]nona-1,3,6-trienes).[2812] Benzofurans can be prepared using methoxy carbenes.[2813] Imino-substituted Cr carbenes react with alkynes to give pyrrole derivatives.[2814] Fischer carbene complexes react with alkynes to give the *Dötz benzannulation*,[2815] giving *p*-alkoxylphenol derivatives. Modification of this basic technique can lead to eight-membered ring carbocycles (see **15-62**).[2816]

OS **VII**, 256; **IX**, 1; **80**, 93.

15-62 Other Cycloaddition Reactions



Cycloaddition reactions other than [4 + 2], [3 + 2], or [2 + 2] are possible, often providing synthetically useful routes to cyclic compounds. The Cu-catalyzed [3 + 1] cycloaddition of alkenyl diazoacetates and iminoiodinanes gave 2-azetines.[2817] A [3 + 3] annulation reaction was used to prepare 1-alkylquinolines.[2818] Tetrahydroquinolines have also been prepared.[2819] The enantioselective [3 + 3] cycloaddition of 2,3-disubstituted indoles and acrolein has been reported.[2820] Triazinines and azetidines have been prepared by [3 + 3]

[2804] See Eisch, J.J.; Galle, J.E. *J. Organomet. Chem.* ***1975***, *96*, C23; McAlister, D.R.; Bercaw, J.E.; Bergman, R.G. *J. Am. Chem. Soc.* ***1977***, *99*, 1666.
[2805] See, however, Bianchini, C.; Caulton, K.G.; Chardon, C.; Eisenstein, O.; Folting, K.; Johnson, T.J.; Meli, A.; Peruzzini, M.; Raucher, D.J.; Streib, W.E.; Vizza, F. *J. Am. Chem. Soc.* ***1991***, *113*, 5127.
[2806] Mauret, P.; Alphonse, P. *J. Organomet. Chem.* ***1984***, *276*, 249. See also, Pepermans, H.; Willem, R.; Gielen, M.; Hoogzand, C. *Bull. Soc. Chim. Belg.* ***1988***, *97*, 115.
[2807] Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* ***2001***, *123*, 7925.
[2808] Li, J.; Jiang, H.; Chen, M. *J. Org. Chem.* ***2001***, *66*, 3627.
[2809] Jackson, T.J.; Herndon, J.W. *Tetrahedron* ***2001***, *57*, 3859.
[2810] Davies, M.W.; Johnson, C.N.; Harrity, J.P.A. *J. Org. Chem.* ***2001***, *66*, 3525.
[2811] Jiang, M.X.-W.; Rawat, M.; Wulff, W.D. *J. Am. Chem. Soc.* ***2004***, *126*, 5970.
[2812] Schirmer, H.; Flynn, B.L.; de Meijere, A. *Tetrahedron* ***2000***, *56*, 4977.
[2813] Herndon, J.W.; Zhang, Y.; Wang, H.; Wang, K. *Tetrahedron Lett.* ***2000***, *41*, 8687.
[2814] Campos, P.J.; Sampedro, D.; Rodríquez, M.A. *J. Org. Chem.* ***2003***, *68*, 4674.
[2815] Dötz, K.H. *Angew. Chem. Int. Ed.* ***1975***, *14*, 644.
[2816] Barluenga, J.; Aznar, F.; Palomero, M.A. *Angew. Chem. Int. Ed.* ***2000***, *39*, 4346.
[2817] Barluenga, J.; Riesgo, L.; Lonzi, G.; Tomás, M.; López, L.A. *Chem. Eur. J.* ***2012***, *18*, 9221.
[2818] Shan, G.; Sun, X.; Xia, Q.; Rao, Y. *Org. Lett.* ***2011***, *13*, 5770.
[2819] Das, S.; Chakrabarty, S.; Daniliuc, C.G.; Studer, A. *Org. Lett.* ***2016***, *18*, 2784.
[2820] Huang, J.; Zhao, L.; Liu, Y.; Cao, W.; Wu, X. *Org. Lett.* ***2013***, *15*, 4338.

cycloaddition reactions.[2821] Tetrahydropyridazines have been prepared by a [3 + 3] cycloaddition.[2822]

The reaction of a conjugated carbonyl compound with a diazo ester, in the presence of a Cu catalyst, leads to a dihydropyran in what is labeled a [4 + 1] cycloaddition.[2823] Dienes react with nitriles in a Ti-mediated [4 + 1] cycloaddition.[2824] Reaction with a chiral Rh catalyst converts dienes and diazo compounds to cycloheptadienes.[2825] The intramolecular [4 + 1] cycloaddition of a dialkoxycarbene and an electron-deficient diene gave 5–5, 6–5, and 7–5 fused *O*-heterocyclic compounds, where the stereoselectivity is dependent on the length of the tether.[2826] A spirophosphine-catalyzed [4 + 1] annulation of amines with allenes gave dihydropyrroles.[2827] The reaction of 3-bromooxindoles, α,β-unsaturated *N*-tosylimines, and 2′-methyl α-isocupreine led to α-substituted ammonium ylids, which gave spirocyclic oxindoles.[2828] The Rh-catalyzed [4 + 1] annulation reaction of α,α-difluoromethylene alkyne, as a nontraditional one-carbon reaction partner, with *N*-methoxybenzamide derivatives gave isoindolin-1-one derivatives.[2829] Propargyl acetates of the type $RCH(OAc)C{\equiv}CC(CH_3){=}CH_2$ undergo [4 + 1] cycloaddition with CO, with a Rh catalyst, to give cyclopentenones.[2830] Methylenecyclopropanes reacted with enones via [4 + 1] cycloaddition using a Ni catalyst to give dihydrofurans.[2831] 2,5-Dihydrofurans were prepared by the gold-catalyzed [4 + 1] cycloaddition of α-diazo esters and propargyl alcohols.[2832] The enantioselective [4 + 1] annulation of pyrazolones and 2-(acetoxymethyl)buta-2,3-dienoates, catalyzed by amino acid-derived phosphines, gave spiropyrazolones.[2833]

A Cu-catalyzed [5 + 1] annulation of 2-ethynylanilines with an *N*,*O*-acetal gave quinoline derivatives with 2-carboalkyl substituent.[2834] An Fe-mediated [5 + 1] cycloaddition of vinylcyclopropanes (VCPs) and CO gave α,β-cyclohexenones.[2835] Dihydrofuro[3,2-*c*]pyridine was prepared by the reaction of ammonium acetate and 1-acyl-1-[(dimethylamino)alkenoyl]cyclopropanes via [5C + 1N] annulation.[2836]

The Rh-catalyzed intramolecular cycloaddition of a furan with a conjugated diazo ester gave a [4 + 3] cycloadduct.[2837] The suprafacial thermal addition of an allylic cation to a diene (a [4 + 3] cycloaddition) is allowed by the *Woodward-Hoffmann rules* (this reaction

[2821] Zhang, H.-H.; Luo, Y.-C.; Wang, H.-P.; Chen, W.; Xu, P.-F. *Org. Lett.* ***2014***, *16*, 4896.
[2822] Garve, L.K.B.; Petzold, M.; Jones, P.G.; Werz, D.B. *Org. Lett.* ***2016***, *18*, 564.
[2823] Son, S.; Fu, G.C. *J. Am. Chem. Soc.* ***2007***, *129*, 1046.
[2824] Laroche, C.; Bertus, P.; Szymoniak, J. *Chem. Commun.* ***2005***, 3030.
[2825] Deng, L.; Giessert, A.J.; Gerlitz, O.O.; Dai, X.; Diver, S.T.; Davies, H.M.L. *J. Am. Chem. Soc.* ***2005***, *127*, 1342.
[2826] Beaumier, F.; Dupuis, M.; Spino, C.; Legault, C.Y. *J. Am. Chem. Soc.* ***2012***, *134*, 5938.
[2827] Kramer, S.; Fu, G.C. *J. Am. Chem. Soc.* ***2015***, *137*, 3803.
[2828] Zheng, P.-F.; Ouyang, Q.; Niu, S.-L.; Shuai, L.; Yuan, Y.; Jiang, K.; Liu, T.-Y.; Chen, Y.-C. *J. Am. Chem. Soc.* ***2015***, *137*, 9390.
[2829] Wang, C.-Q.; Ye, L.; Feng, C.; Loh, T.-P. *J. Am. Chem. Soc.* ***2017***, *139*, 1762.
[2830] Chen, W.; Tay, J.-H.; Yu, X.-Q.; Pu, L. *J. Org. Chem.* ***2012***, *77*, 6215.
[2831] Inami, T.; Sako, S.; Kurahashi, T.; Matsubara, S. *Org. Lett.* ***2011***, *13*, 3837.
[2832] Wang, J.; Yao, X.; Wang, T.; Han, J.; Zhang, J.; Zhang, X.; Wang, P.; Zhang, Z. *Org. Lett.* ***2015***, *17*, 5124.
[2833] Han, X.; Yao, W.; Wang, T.; Tan, Y.R.; Yan, Z.; Kwiatkowski, J.; Lu, Y. *Angew. Chem. Int. Ed.* ***2014***, *53*, 5643.
[2834] Sakai, N.; Tamura, K.; Shimamura, K.; Ikeda, R.; Konakahara, T. *Org. Lett.* ***2012***, *14*, 836.
[2835] Liu, C.-H.; Zhuang, Z.; Bose, S.; Yu, Z.-X. *Tetrahedron* ***2016***, *72*, 2752.
[2836] Huang, P.; Zhang, R.; Liang, Y.; Dong, D. *Org. Lett.* ***2012***, *14*, 5196.
[2837] Davies, H.M.L.; Calvo, R.L.; Townsend, R.-J.; Ren, P.; Churchill, R.M. *J. Org. Chem.* ***2000***, *65*, 4261. For reviews of [3+4] cycloadditions, see Mann, J. *Tetrahedron* ***1986***, *42*, 4611; Hoffmann, H.M.R. *Angew. Chem. Int. Ed.* ***1984***, *23*, 1; ***1973***, *12*, 819; Noyori, R. *Acc. Chem. Res.* ***1979***, *12*, 61.

would be expected to follow the same rules as the *Diels-Alder reaction*[2838]). Pyrroles react with allylic diazo compounds, in the presence of a Rh catalyst, to give bicyclic amines in a [4 + 3] cycloaddition.[2839] A different [4 + 3] cycloaddition involves the intramolecular reaction of a diene with an alkylidenecyclopropane unit, in the presence of a Pd catalyst, to give a seven-membered ring as part of a bicyclic system.[2840] Chiral cations have been used in [4 + 3] cycloadditions.[2841] An aza [4 + 3] cycloaddition of cyclic dienes and aza-oxyallyl cationic intermediates, generated *in situ* by the dehydrohalogenation of α-haloamides, gave a bicyclic product.[2842] The [4 + 3] cycloaddition of aromatic conjugated aldehydes or ketones with epoxides, catalyzed by a Lewis acid, gave seven-membered ring oxacycles.[2843] Diaza [4 + 3] cycloadditions of cyclic dienes via diaza-oxyallyl cationic intermediates led to the 1,4-diamination of cyclic dienes.[2844] An aza [4 + 3] cycloaddition, Rh catalyzed, of vinyl aziridines and dienes gave azeprines.[2845] Indolizines have been prepared by an aza [4 + 3] annulation.[2846]

Conjugated dienes can be dimerized or trimerized at the 1,4-positions (formally [4 + 4] and [4 + 4 + 4] cycloadditions) by treatment with certain complexes or other transition metal compounds.[2847] Thus buta-1,3-diene gives 1,5-cyclooctadiene and 1,5,9-cyclododecatriene.[2848] The relative amount of each product can be controlled by use of the proper catalyst. Initial [4 + 4] photocycloaddition of an enyne with an pyridone yields a 1,2,5-cyclooctatriene; subsequent photooxidation gives a cyclopropanone and subsequent photoextrusion of carbon monoxide gave the observed 1,4-cycloheptadiene product.[2849]

A [5 + 2] cycloaddition[2850] of vinylcyclopropanes and alkenes, in the presence of a Rh catalyst, leads to seven-membered rings.[2851] A dual thiourea catalyst system was developed for an intramolecular oxidopyrylium [5 + 2] cycloaddition that gave tricyclic structures enantioselectively.[2852]

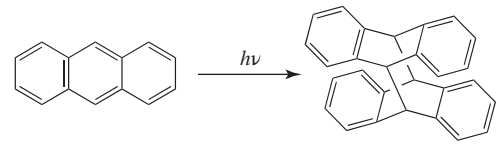
Cycloheptatriene reacts with terminal alkynes, using complex catalysts involving Co and Zn compounds, to give a bicyclic triene via a [6 + 2] cycloaddition.[2853] Eight-membered rings were formed by the Rh-catalyzed [6 + 2] cycloaddition of 4-allenals and alkynes.[2854] Tricyclopentanoids were prepared using organocatalysts via a [6 + 2] cycloaddition.[2855] The intramolecular Rh-catalyzed [6 + 2] cycloaddition of 4-allenals and alkynes or alkenes gave

[2838] Garst, M.E.; Roberts, V.A.; Houk, K.N.; Rondan, N.G. *J. Am. Chem. Soc.* ***1984***, *106*, 3882.
[2839] Reddy, R.P.; Davies, H.M.L. *J. Am. Chem. Soc.* ***2007***, *129*, 10312.
[2840] Gulías, M.; Durán, J.; López, F.; Castedo, L.; Mascareñas, J.L. *J. Am. Chem. Soc.* ***2007***, *129*, 11026.
[2841] Huang, J.; Hsung, R.P. *J. Am. Chem. Soc.* ***2005***, *127*, 50. See Harmata, M. *Chem. Commun.* ***2010***, 8886, 8904.
[2842] Jeffrey, C.S.; Barnes, K.L.; Eickhoff, J.A.; Carson, C.R. *J. Am. Chem. Soc.* ***2011***, *133*, 7688.
[2843] Zhou, Y.-Q.; Wang, N.-X.; Zhou, S.-B.; Huang, Z.; Cao, L. *J. Org. Chem.* ***2011***, *76*, 669.
[2844] Jeffrey, C.S.; Anumandla, D.; Carson, C.R. *Org. Lett.* ***2012***, *14*, 5764.
[2845] Zhu, C.-Z.; Feng, J.J.; Zhang, J. *Angew. Chem. Int. Ed.* ***2017***, *56*, 1351.
[2846] Buchanan, G.S.; Dai, H.; Hsung, R.P.; Gerasyuto, A.I.; Scheinebeck, C.M. *Org. Lett.* ***2011***, *13*, 4402.
[2847] Wilke, G. *Angew. Chem. Int. Ed.* ***1988***, *27*, 186; Baker, R. *Chem. Rev.* ***1973***, *73*, 487 (see pp. 489–512); Semmelhack, M.F. *Org. React.* ***1972***, *19*, 115 (pp. 128–143).
[2848] See Rona, P. *Intra-Sci. Chem. Rep.* ***1971***, *5*, 105.
[2849] Kulyk, S.; Khatri, B.B.; Sieburth, S.McN. *Angew. Chem. Int. Ed.* ***2017***, *56*, 319.
[2850] See Yoo, E.J. *Synlett* ***2015***, *26*, 2189; Ylijoki, K.E.O.; Stryker, J.M. *Chem. Rev.* ***2013***, *113*, 2244.
[2851] Wender, P.A.; Haustedt, L.O.; Lim, J.; Love, J.A.; Williams, T.J.; Yoon, J.-Y. *J. Am. Chem. Soc.* ***2006***, *128*, 6302.
[2852] Burns, N.Z.; Witten, M.R.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2011***, *133*, 14578.
[2853] Achard, M.; Tenaglia, A.; Buono, G. *Org. Lett.* ***2005***, *7*, 2353.
[2854] Oonishi, Y.; Hosotani, A.; Sato, Y. *Angew. Chem. Int. Ed.* ***2012***, *51*, 11548.
[2855] Hayashi, Y.; Gotoh, H.; Honma, M.; Sankar, K.; Kumar, I.; Ishikawa, H.; Konno, K.; Yui, H.; Tsuzuki, S.; Uchimaru, T. *J. Am. Chem. Soc.* ***2011***, *133*, 20175.

6–8-fused bicyclic ketone derivatives.[2856] A Cu/ferrocene-catalyzed [6 + 3] cycloaddition of tropone and azomethine ylids gave piperidine-fused bicyclic heterocycles.[2857] Chromium catalysts are available for [6 + 4] cycloadditions.[2858]

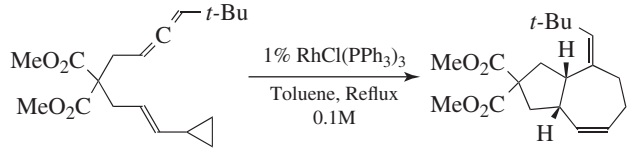
As seen in **15-56**, the *Woodward-Hoffmann rules* allow suprafacial concerted cycloadditions to take place thermally if the total number of electrons is [4*n* + 2] and photochemically if the number is 4*n*. Furthermore, forbidden reactions become allowed if one molecule reacts antarafacially. It would thus seem that syntheses of many large rings could easily be achieved. However, when the newly formed ring is eight-membered or greater, concerted mechanisms, although allowed by orbital symmetry for the cases stated, become difficult to achieve. Due to the entropy factor, the two ends of one system must simultaneously encounter the two ends of the other, unless one or both components are cyclic, in which case the molecule has many fewer possible conformations. There have been a number of reports of cycloaddition reactions leading to eight-membered and larger rings, some thermally and some photochemically induced, but (apart from the dimerization and trimerization of butadienes mentioned above, which are known not to involve direct [4 + 4] or [4 + 4 + 4] cycloaddition) in most cases evidence is lacking to indicate whether they are concerted or stepwise processes. Some examples are shown here:

4 + 4



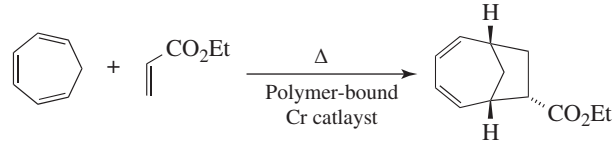
Ref. 2859

5 + 2



Ref. 2860

6 + 2



Ref. 2861

[2856] Oonishi, Y.; Hosotani, A.; Sato, Y. *J. Am. Chem. Soc.* ***2011***, *133*, 10386.

[2857] Liu, H.; Wu, Y.; Zhao, Y.; Li, Z.; Zhang, L.; Yang, W.; Jiang, H.; Jing, C.; Yu, H.; Wang, B.; Xiao, Y.; Guo, H. *J. Am. Chem. Soc.* ***2014***, *136*, 2625; Teng, H.-L.; Yao, L.; Wang, C.-J. *J. Am. Chem. Soc.* ***2014***, *136*, 4075.

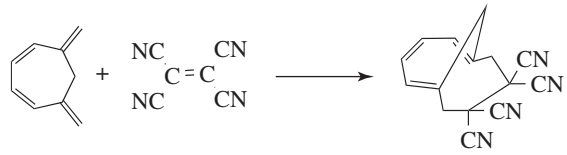
[2858] Kündig, E.P.; Robvieux, F.; Kondratenko, M. *Synthesis* ***2002***, 2053.

[2859] Shönberg, A. *Preparative Organic Photochemistry*, Springer, NY, ***1968***, pp. 97–99. Also see Zhu, M.; Qiu, Z.; Hiel, G.P.; Sieburth, S.Mc.N. *J. Org. Chem.* ***2002***, *67*, 3487.

[2860] Wender, P.A.; Gamber, G.G.; Scanio, M.J.C. *Angew. Chem. Int. Ed.* ***2001***, *40*, 3895; Wender, P.A.; Pedersen, T.M.; Scanio, M.J.C. *J. Am. Chem. Soc.* ***2002***, *124*, 15154; Wender, P.A.; Love, J.A.; Williams, T.J. *Synlett* ***2003***, 1295.

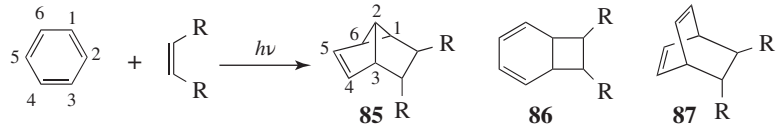
[2861] Rigby, J.H.; Mann, L.W.; Myers, B.J. *Tetrahedron Lett.* ***2001***, *42*, 8773. See Rigby, J.H.; Ateeq, H.S.; Charles, N.R.; Henshilwood, J.A.; Short, K.M.; Sugathapala, P.M. *Tetrahedron* ***1993***, *49*, 5495.

8 + 2



Ref. 2862

Benzene rings can undergo photochemical cycloaddition with alkenes.[2863] The major product is usually the 1,3-addition product **85** (in which a three-membered ring has also been formed), although some of the 1,2-product **86** (**15-59**) is sometimes formed as well. (**86** is usually the main product where the alkene bears electron-withdrawing groups and the aromatic compound electron-donating groups, or vice versa.) The 1,4-product **87** is rarely formed. The reaction has also been run with benzenes substituted with alkyl, halo, OR, CN, and other groups, and with acyclic and cyclic alkenes bearing various groups.[2864]



85 **86** **87**

Alkynes and isocyanates react with CO in the presence of a Ru catalyst to give imides,[2865] and other [2 + 2 + 1] cycloadditions are known.[2866] A [2 + 2 + 1] annulation of a terminal alkyne, a nitrile, and an oxygen atom from reaction of Au/carbene intermediates gave 2,5-disubstituted oxazoles,[2867] although PhIO with TfOH or Tf_2NH has also been used to give an oxazole.[2868] The Ru-catalyzed [2 + 2 + 1] reaction of α,ω-diynes with DMSO gave bicyclic furans.[2869] A free radical-mediated [2 + 2 + 1] cycloaddition reaction of acetylenes, amidines, and CO gave five-membered α,β-unsaturated lactams.[2870] The Ni-catalyzed [2 + 2 + 1] carbonylative cycloaddition reaction of imines and alkynes or norbornene used phenyl formate as a CO source to give *N*-benzenesulfonyl, -tosyl, and -phosphoryl-substituted γ-lactams.[2871]

[2 + 2 + 2] cycloaddition reactions are known[2872] (also see **15-61**), usually with diynes, enynes, or intermolecular reactions of alkynes or alkenes[2873] with an alkyne, and facilitated

[2862] Farrant, G.C.; Feldmann, R. *Tetrahedron Lett.* ***1970***, 4979.

[2863] See Wender, P.A.; Ternansky, R.; deLong, M.; Singh, S.; Olivero, A.; Rice, K. *Pure Appl. Chem.* ***1990***, *62*, 1597; Gilbert, A. in Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, ***1984***, pp. 1–60. For a review of this and related reactions, see McCullough, J.J. *Chem. Rev.* ***1987***, *87*, 811.

[2864] See the table in Wender, P.A.; Siggel, L.; Nuss, J.M. *Org. Photochem.* ***1989***, *10*, 357 (pp. 384–415).

[2865] Kondo, T.; Nomura, M.; Ura, Y.; Wada, K.; Mitsudo, T.-a. *J. Am. Chem. Soc.* ***2006***, *128*, 14816.

[2866] Knölker, H.-J.; Braier, A.; Bröcher, D.J.; Jones, P.G.; Piotrowski, H. *Tetrahedron Lett.* ***1999***, *40*, 8075; Chatani, N.; Tobisu, M.; Asaumi, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* ***1999***, *121*, 7160; Iwata, T.; Inagaki, F.; Mukai, C. *Angew. Chem. Int. Ed.* ***2013***, *52*, 11138.

[2867] He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* ***2011***, *133*, 8482.

[2868] Saito, A.; Taniguchi, A.; Kambara, Y.; Hanzawa, Y. *Org. Lett.* ***2013***, *15*, 267.

[2869] Yamashita, K.; Yamamoto, Y.; Nishiyama, H. *J. Am. Chem. Soc.* ***2012***, *134*, 7660. For a Rh-catalyzed reaction that gave cyclopentenones, see Kim, J.H.; Song, T.; Chung, Y.K. *Org. Lett.* ***2017***, *19*, 1248.

[2870] Fukuyama, T.; Nakashima, N.; Okada, T.; Ryu, I. *J. Am. Chem. Soc.* ***2013***, *135*, 1006.

[2871] Hoshimoto, Y.; Ohata, T.; Sasaoka, Y.; Ohashi, M.; Ogoshi, S. *J. Am. Chem. Soc.* ***2014***, *136*, 15877.

[2872] For reviews, see Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* ***2005***, 4741; Broere, D.L.J.; Ruijter, E. *Synthesis* ***2012***, *44*, 2639. Beeck, S.; Wegner, H.A. *Synlett* ***2017***, *28*, 1018. Also see Tran-Van, A.-F.; Götz, S.; Neuburger, M.; Wegner, H.A. *Org. Lett.* ***2014***, *16*, 2410.

[2873] Domínguez, G.; Pérez-Castells, J. *Chem. Eur. J.* ***2016***, *22*, 6720.

by Ni,[2874] Pd,[2875] Rh,[2876] Rh/Ag,[2877] Nb,[2878] Ir,[2879] Ru,[2880] or a Co catalyst.[2881] A mechanistic density functional study has been reported for this reaction.[2882] With a Co,[2883] Rh,[2884] Nb,[2885] Cu,[2886] Fe,[2887] Ru,[2888] Ir,[2889] or pyrylium salt[2890] catalyst, or under metal-free conditions,[2891] an intramolecular [2 + 2 + 2] cycloaddition with nitriles gave pyridines. Alkenyl isocyanates and alkynes react via [2 + 2 + 2] cycloaddition, in the presence of a Ru catalyst, to form bicyclic conjugated lactams.[2892] Pyridines can also be prepared by metal-catalyzed [2 + 2 + 2] cycloaddition.[2893] The Ni-catalyzed reaction of two molecules of an isocyanate with one molecule of a 1,3-diene gave a 6-substituted dihydropyrimidine-2,4-dione.[2894]

A Cu-catalyzed [3 + 1 + 1]-type condensation reaction of oximes, anhydrides, and potassium thiocyanate (KSCN) gave thiazoles.[2895] A Ru/iminium co-catalyzed asymmetric [3 + 1 + 1] cycloaddition reaction of diazoacetophenones, anilines, and enals gave multisubstituted pyrrolidines.[2896] A Rh-catalyzed carbonylative [3 + 2 + 1] cycloaddition of alkyne-tethered alkylidenecyclopropanes gave bicyclic phenols.[2897] The Lewis acid-catalyzed [3 + 1 + 1] cycloaddition of azomethine ylids and isocyanide gave pyridine derivatives.[2898]

[2874] Komagawa, S.; Wang, C.; Morokuma, K.; Saito, S.; Uchiyama, M. *J. Am. Chem. Soc.* ***2013***, *135*, 14508; Kumar, R.; Tokura, H.; Nishimura, A.; Mori, T.; Hoshimoto, Y.; Ohashi, M.; Ogoshi, S. *Org. Lett.* ***2015***, *17*, 6018; Wang, G.; You, X.; Gan, Y.; Liu, Y. *Org. Lett.* ***2017***, *19*, 110; Xue, F.; Loh, Y.K.; Song, X.; Teo, W.J.; Chua, J.Y.D.; Zhao, J.; Hor, T.S.A. *Chem. Asian J.* ***2017***, *12*, 168.

[2875] Zhou, P.; Zheng, M.; Jiang, H.; Li, X.; Qi, C. *J. Org. Chem.* ***2011***, *76*, 4759.

[2876] See Yoshizaki, S.; Nakamura, Y.; Masutomi, K.; Yoshida, T.; Noguchi, K.; Shibata, Y.; Tanaka, K. *Org. Lett.* ***2016***, *18*, 388.

[2877] Brusoe, A.T.; Edwankar, R.V.; Alexanian, E.J. *Org. Lett.* ***2012***, *14*, 6096.

[2878] Satoh, Y.; Obora, Y. *Org. Lett.* ***2011***, *13*, 2568; Simon, C.; Amatore, M.; Aubert, C.; Petit, M. *Org. Lett.* ***2015***, *17*, 844.

[2879] Auvinet, A.-L.; Michelet, V.; Ratovelomanana-Vidal, V. *Synthesis* ***2013***, *45*, 2003.

[2880] See Tanaka, D.; Sato, Y.; Mori, M. *J. Am. Chem. Soc.* ***2007***, *129*, 7730; Mallagaray, Á.; Medina, S.; Domínguez, G.; Pérez-Castells, J. *Synlett* ***2010***, 2114.

[2881] Hilt, G.; Paul, A.; Harms, K. *J. Org. Chem.* ***2008***, *73*, 5187.

[2882] Varela, J.A.; Rubín, S.G.; Castedo, L.; Saá, C. *J. Org. Chem.* ***2008***, *73*, 1320.

[2883] Boñaga, L.V.R.; Zhang, H.-C.; Moretto, A.F.; Ye, H.; Gauthier, D.A.; Li, J.; Leo, G.C.; Maryanoff, B.E. *J. Am. Chem. Soc.* ***2005***, *127*, 3473.

[2884] Shibata, Y.; Tanaka, K. *Synthesis* ***2012***, *44*, 323. Amatore, M.; Lebœuf, D.; Malacria, M.; Gandon, V.; Aubert, C. *J. Am. Chem. Soc.* ***2013***, *135*, 4576.

[2885] Satoh, Y.; Obora, Y. *J. Org. Chem.* ***2013***, *78*, 7771.

[2886] Sheng, J.; Wang, Y.; Su, X.; He, R.; Chen, C. *Angew. Chem. Int. Ed.* ***2017***, *56*, 4824.

[2887] Spahn, N.A.; Nguyen, M.H.; Renner, J.; Lane, T.K.; Louie, J. *J. Org. Chem.* ***2017***, *82*, 234; Wang, C.; Li, X.; Wu, F.; Wan, B. *Angew. Chem. Int. Ed.* ***2011***, *50*, 7162.

[2888] Medina, S.; Domínguez, G.; Pérez-Castells, J. *Org. Lett.* ***2012***, *14*, 4982; García-Rubín, S.; González-Rodríguez, C.; García-Yebra, C.; Varela, J.A.; Esteruelas, M.A.; Saá, C. *Angew. Chem. Int. Ed.* ***2014***, *53*, 1841.

[2889] See Hashimoto, T.; Kato, K.; Yano, R.; Natori, T.; Miura, H.; Takeuchi, R. *J. Org. Chem.* ***2016***, *81*, 5393.

[2890] Wang, K.; Meng, L.-G.; Wang, L. *Org. Lett.* ***2017***, *19*, 1958.

[2891] Wang, Y.; Song, L.-J.; Zhang, X.; Sun, J. *Angew. Chem. Int. Ed.* ***2016***, *55*, 9704; Hapke, M. *Tetrahedron Lett.* ***2016***, *57*, 5719.

[2892] See Yu, R.T.; Rovis, T. *J. Am. Chem. Soc.* ***2006***, *128*, 12370.

[2893] Varela, J.A.; Saá, C. *Synlett* ***2008***, 2571.

[2894] Morimoto, M.; Nishida, Y.; Miura, T.; Murakami, M. *Chem. Lett.* ***2013***, *42*, 550.

[2895] Tang, X.; Yang, J.; Zhu, Z.; Zheng, M.; Wu, W.; Jiang, H. *J. Org. Chem.* ***2016***, *81*, 11461.

[2896] Li, M.; Chu, R.; Chen, J.; Wu, X.; Zhao, Y.; Liu, S.; Hu, W. *Org. Lett.* ***2017***, *19*, 1290.

[2897] Kim, S.; Chung, Y.K. *Org. Lett.* ***2014***, *16*, 4352.

[2898] Soeta, T.; Miyamoto, Y.; Fujinami, S.; Ukaji, Y. *Tetrahedron* ***2014***, *70*, 6623.

A [3 + 2 + 2] cycloaddition was reported with an alkyne and an alkene alkylidenecyclopropane substrate, in the presence of a Rh catalyst.[2899]

Yne dienes undergo [4 + 2 + 1] cycloaddition in the presence of a Ni catalyst.[2900] Eight-membered rings are produced by a Rh-catalyzed [4 + 2 + 2] cycloaddition.[2901] A Co catalyst is used for a [4 + 2 + 2] cycloaddition of buta-1,3-diene and bicyclo[2.2.2]octa-2,5-diene.[2902]

Allenes and vinylcyclopropanes undergo [5 + 2] and [5 + 2 + 1][2903] cycloadditions in the presence of a Rh catalyst.[2904] A reductive elimination step determines the selectivity for various substrates in Rh-catalyzed [5 + 2] cycloadditions.[2905]

Ene diynes undergo [2 + 2 + 2 + 1] cycloaddition to form seven-membered ring ketones, in the presence of CO and a Rh catalyst.[2906] Nickel-catalyzed [2 + 2 + 2 + 2] cycloadditions of alkynes leads to eight-membered rings.[2907]

OS **VI**, 512; **VII**, 485; **X**, 1, 336.

[2899] Evans, P.A.; Inglesby, P.A. *J. Am. Chem. Soc.* ***2008***, *130*, 12838.

[2900] Ni, Y.; Montgomery, J. *J. Am. Chem. Soc.* ***2006***, *128*, 2609.

[2901] Gilbertson, S.R.; DeBoef, B. *J. Am. Chem. Soc.* ***2002***, *124*, 8784; Wender, P.A.; Christy, J.P. *J. Am. Chem. Soc.* ***2006***, *128*, 5354. For a computational study, see Baik, M.-H.; Baum, E.W.; Burland, M.C.; Evans, P.A. *J. Am. Chem. Soc.* ***2005***, *127*, 1602.

[2902] Kiattansakul, R.; Snyder, J.K. *Tetrahedron Lett.* ***1999***, *40*, 1079.

[2903] Wang, Y.; Yu, Z.-X. *Acc. Chem. Res.* ***2015***, *48*, 2286.

[2904] See Wang, Y.; Wang, J.; Su, J.; Huang, F.; Jiao, L.; Liang, Y.; Yang, D.; Zhang, S.; Wender, P.A.; Yu, Z.-X. *J. Am. Chem. Soc.* ***2007***, *129*, 10060.

[2905] Yu, Z.X.; Cheong, P.H.-Y.; Liu, P.; Legault, C.Y.; Wender, P.A.; Houk, K.N. *J. Am. Chem. Soc.* ***2008***, *130*, 2378.

[2906] Bennacer, B.; Fujiwara, M.; Lee, S.-Y.; Ojima, I. *J. Am. Chem. Soc.* ***2005***, *127*, 17756.

[2907] Wender, P.A.; Christy, J.P. *J. Am. Chem. Soc.* ***2007***, *129*, 13402.

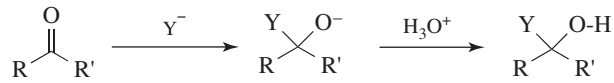
CHAPTER 16

Addition to Carbon–Heteroatom Multiple Bonds

16.A. MECHANISM AND REACTIVITY

The reactions considered in this chapter involve addition to the carbon–oxygen, carbon–nitrogen, and carbon–sulfur double bonds, and to the carbon–nitrogen triple bond. The mechanistic study of these reactions is much simpler than that of the additions to carbon–carbon multiple bonds considered in Chapter 15;[1] this is because C═O, C═N, and C≡N bonds are strongly polar, with the carbon always being the positive end (except for isocyanides, Sec. 16.B.iv). The carbonyl carbon is polarized δ+, so an attacking nucleophilic species always goes to the carbon.[2] Additions to C═S bonds are much less common,[3] but in a few cases the addition is in the other direction (reaction at sulfur is called *thiophilic addition* and addition to the carbon is called *carbophilic addition*).[4] For example, the reaction of phenyllithium with thiobenzophenone $Ph_2C{=}S$ gives, after hydrolysis, benzhydryl phenyl sulfide (Ph_2CHSPh).[5]

The normal acyl addition of a nucleophile, represented by Y^-, to a ketone forms a new C—Y bond and generates an alkoxide, and hydrolysis gives an alcohol.



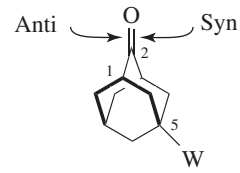
Note that the product has a stereogenic carbon, but unless there is chirality in R or R′ or the nucleophile is optically active, the product must be a racemic mixture because there is no facial bias for addition to the carbonyl. The same holds true for acyl-type addition to C═N and C═S bonds. The addition of a single nucleophile to the carbon–nitrogen triple

[1] See Jencks, W.P. *Prog. Phys. Org. Chem.* ***1964***, *2*, 63.
[2] Nigst, T.A.; Mayr, H. *Eur. J. Org. Chem.* ***2013***, 2155.
[3] See Schaumann, E. in Patai, S. *The Chemistry of Double-Bonded Functional Groups*, *Supplement A*, Vol. 2, pt. 2, Wiley, NY, ***1989***, pp. 1269–1367; Ohno, A. in Oae, S. *Organic Chemistry of Sulfur*, Plenum, NY, ***1977***, pp. 189–229; Mayer, R. in Janssen, M.J. *Organosulfur Chemistry*, Wiley, NY, ***1967***, pp. 219–240; Campaigne, E. in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, ***1966***, pp. 917–959.
[4] See Wardell, J.L.; Paterson, E.S. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 219–338 (pp. 261–267).
[5] See Metzner, P.; Vialle, J.; Vibet, A. *Tetrahedron* ***1978***, *34*, 2289.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

bond gives an imine, which can exist in (*E*) and (*Z*) forms (Sec. 4.K.i), but the imine is generally so reactive that further reactions ensue. Of course, if R or R′ *is* chiral, a mixture of diastereomers will result, and the stereochemistry of addition can be studied in such cases. *Cram's rule* or the *Felkin-Anh model* (Sec. 4.H) allows the direction of nucleophilic attack to be predicted in many cases.[6] However, the relative orientation of the substrate molecule must be considered.

In Sec. 15.B.iii, electronic effects were shown to play a part in determining which face of a carbon–carbon double bond is attacked. The same applies to additions to carbonyl groups. For example, in 5-substituted adamantan-2-ones (shown) electron-withdrawing (−*I*) groups W cause the attack to come from the *syn* face, while electron-donating groups cause it to come from the *anti* face.[7]



In 5,6-disubstituted norborn-2-en-7-one systems, the carbonyl appears to tilt away from the π bond, with reduction occurring from the more hindered face.[8] An *ab initio* study of nucleophilic addition to 4-*tert*-butylcyclohexanones attempted to predict π-facial selectivity.[9]

The mechanistic picture is further simplified by the fact that free-radical additions to carbon–heteroatom double bonds are not as prevalent (but see **16-31**).[10] In most cases, the nucleophile forms the first new bond to carbon, and these reactions are regarded as *nucleophilic additions*, which is usually followed by a protonation step to give the alcohol product. In almost all the reactions considered in this chapter the electrophilic atom is either hydrogen or carbon.[11] After the initial acyl addition, the alkoxide intermediate looks a little like the tetrahedral intermediate in Sec. 16.A.i, but carbon groups are poor leaving groups so subsequent substitution is not possible, allowing protonation to give the alcohol. When a conjugating C═C unit is present, it is noted that electrophilic attack at the double bond is often observed to be *anti* to the most electron-donating σ bond at the α position (referred to as the *extended anomeric effect*).[12]

Both acids and bases can catalyze many of these reactions.[13] Bases catalyze the reaction by converting a reagent Y—H to the more powerful nucleophile Y^- (Sec. 10.G.ii). Acids

[6] See Eliel, E.L. *The Stereochemistry of Carbon Compounds*, McGraw-Hill, NY, ***1962***, pp. 68–74. Also see Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2, 22; Ashby, E.C.; Laemmle, J.T. *Chem. Rev.* ***1975***, *75*, 521.

[7] See Laube, T.; Stilz, H.U. *J. Am. Chem. Soc.* ***1987***, *109*, 5876.

[8] Kumar, V.A.; Venkatesan, K.; Ganguly, B.; Chandrasekhar, J.; Khan, F.A.; Mehta, G. *Tetrahedron Lett.* ***1992***, *33*, 3069.

[9] Yadav, V.K.; Jeyaraj, D.A. *J. Org. Chem.* ***1998***, *63*, 3474. For a discussion of models, see Priyakumar, U.D.; Sastry, G.N.; Mehta, G. *Tetrahedron* ***2004***, *60*, 3465.

[10] See Beckwith, A.L.J.; Hay, B.P. *J. Am. Chem. Soc.* ***1989***, *111*, 2674; Clerici, A.; Porta, O. *J. Org. Chem.* ***1989***, *54*, 3872; Cossy, J.; Pete, J.P.; Portella, C. *Tetrahedron Lett.* ***1989***, *30*, 7361.

[11] Appel, R.; Mayr, H. *J. Am. Chem. Soc.* ***2011***, *133*, 8240.

[12] Naruse, Y.; Hasegawa, Y.; Ikemoto, K. *Tetrahedron Lett.* ***2016***, *57*, 2029.

[13] See Jencks, W.P.; Gilbert, H.F. *Pure Appl. Chem.* ***1977***, *49*, 1021.

catalyze reactions by converting the substrate to an heteroatom-stabilized cation (a resonance stabilized[14] *oxocarbenium ion* $^{+}C{-}O{-}H \leftrightarrow C{=}O^{+}{-}H$; Sec. 5.A.ii), making it more attractive to nucleophilic attack and making the reverse reaction somewhat less favorable. Similar catalysis can also be achieved with metallic ions (e.g., Ag^{+}), which act as Lewis acids.[15] The oxocarbenium ion quickly reacts with the nucleophile to give the acyl addition product. The rate-determining step is usually the one involving nucleophilic attack. If one heteroatom such as oxygen stabilizes an adjacent carbocation, a second heteroatom (X) will stabilize an oxocarbenium ion ($-X-C^{+}-X-$) to a greater extent.[16]

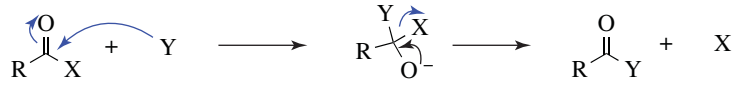
Reactivity factors for carbon–heteroatom multiple bonds are similar to those for the tetrahedral mechanism of nucleophilic substitution (Sec. 16.A.i).[17] If electron-donating groups such as alkyl groups are present, rates are decreased, and conversely the presence of electron-attracting substituents increase rates. This means that aldehydes are more reactive than ketones. Aryl groups are somewhat deactivating compared to alkyl, because of resonance that stabilizes the substrate molecule but is lost on going to the intermediate. Double bonds in conjugation with the carbon–heteroatom multiple bond also lower addition rates, for similar reasons but, more important, may provide competition from 1,4-addition (Sec. 15.A.ii). Steric factors are also quite important and contribute to the decreased reactivity of ketones compared with aldehydes. Highly hindered ketones such as hexamethylacetone and dineopentyl ketone either do not undergo many of these reactions or require extreme conditions.

16.A.i. Nucleophilic Substitution at an Aliphatic Trigonal Carbon: The Tetrahedral Mechanism

All the mechanisms discussed in previous chapters for substitution take place at a saturated carbon atom. Nucleophilic substitution is also important at trigonal carbons, especially when the carbon is double bonded to an oxygen, a sulfur, or a nitrogen. Substitution at a carbonyl group (or the corresponding nitrogen and sulfur analogs) most often proceeds by a second-order mechanism, which in this book is called the *tetrahedral*[18] *mechanism*.[19] The IUPAC designation is $A_N + D_N$. The S_N1 mechanisms, involving carbocations, are sometimes found with these substrates, especially with essentially ionic substrates such as $RCO^{+}\ BF_4^{-}$; there is evidence that in certain cases simple S_N2 mechanisms can take place, especially with a very good leaving group such as Cl^{-},[20] and an SET mechanism has also been reported.[21] However, the tetrahedral mechanism is by far the most prevalent. Although this mechanism displays second-order kinetics, it is not the same as the S_N2

[14] See Brada, B.; Bundhoo, D.; Engels, B.; Hiberty, P.C. *Org. Lett.* ***2008***, *10*, 1951.
[15] Toromanoff, E. *Bull. Soc. Chim. Fr.* ***1962***, 1190.
[16] Chamberland, S.; Ziller, J.W.; Woerpel, K.A. *J. Am. Chem. Soc.* ***2005***, *127*, 5322.
[17] For a review of the reactivity of nitriles, see Schaefer, F.C. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 239–305.
[18] This mechanism has also been called the "addition-elimination mechanism."
[19] See Talbot, R.J.E. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 10, Elsevier, NY, ***1972***, pp. 209–223; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, ***1969***, pp. 463–554; Satchell, D.P.N.; Satchell, R.S. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 375–452; Johnson, S.L. *Adv. Phys. Org. Chem.* ***1967***, *5*, 237.
[20] Williams, A. *Acc. Chem. Res.* ***1989***, *22*, 387. See Bentley, T.W.; Koo, I.S. *J. Chem. Soc., Perkin Trans. 2* ***1989***, 1385. See, however, Buncel, E.; Um, I.H.; Hoz, S. *J. Am. Chem. Soc.* ***1989***, *111*, 971.
[21] Bacaloglu, R.; Blaskó, A.; Bunton, C.A.; Ortega, F. *J. Am. Chem. Soc.* ***1990***, *112*, 9336.

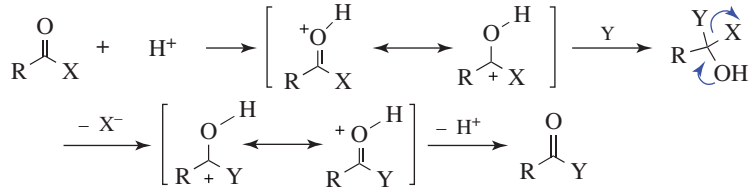
mechanism discussed in Sec. 10.A.i. In the tetrahedral mechanism, the nucleophile (Y) attacks to give an intermediate containing both X and Y (**1**). Since X is such reactions is a good leaving group, the electron pair on oxygen "kicks out" the X group, regenerating the carbonyl to give the new acyl derivative.



1

This sequence is impossible at a saturated carbon since there is no leaving group after the nucleophile reacts.

When reactions are carried out in acid solution the carbonyl reacts as a base with H^+ to give an oxocarbenium ion. An electron pair on oxygen allows formation of a carbonyl as an oxocarbenium ion, with concomitant expulsion of the X leaving group to give the new acyl product.



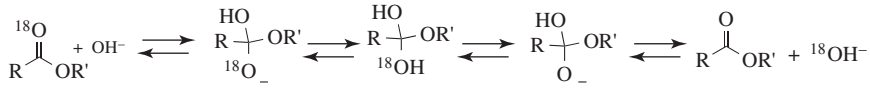
The reaction rate is increased because it is easier for the nucleophile to attack the carbon when the electron density of the latter has been decreased.[22]

Evidence for the existence of the tetrahedral mechanism is as follows:[23]

1. The kinetics are first order in both the substrate and the nucleophile, as predicted by the mechanism.
2. There is other kinetic evidence in accord with a tetrahedral intermediate. For example, the rate "constant" for the reaction between acetamide and hydroxylamine is not constant, but decreases with increasing hydroxylamine concentration.[24] This is not a smooth decrease; there is a break in the curve. A straight line is followed at low hydroxylamine concentration and another straight line at high concentration. This means that the identity of the rate-determining step is changing. Obviously, *this result cannot happen if there is only one step: so, there must be two steps, and hence an intermediate.* Similar kinetic behavior has been found in other cases as well;[25] in particular, plots of rate against pH are often bell shaped.
3. Basic hydrolysis has been carried out on carboxylic esters labeled with ^{18}O in the carbonyl group.[26] If this reaction proceeded by the normal S_N2 mechanism, all the ^{18}O would remain in the carbonyl group, even if, in an equilibrium process, some of

[22] See Jencks, W.P. *Acc. Chem. Res.* ***1976***, *9*, 425; *Chem. Rev.* ***1972***, *72*, 705.
[23] Also see Guthrie, J.P. *J. Am. Chem. Soc.* ***1978***, *100*, 5892; Kluger, R.; Chin, J. *J. Am. Chem. Soc.* ***1978***, *100*, 7382; O'Leary, M.H.; Marlier, J.F. *J. Am. Chem. Soc.* ***1979***, *101*, 3300.
[24] Jencks, W.P.; Gilchrist, M. *J. Am. Chem. Soc.* ***1964***, *86*, 5616.
[25] Kevill, D.N.; Johnson, S.L. *J. Am. Chem. Soc.* ***1965***, *87*, 928; Leinhard, G.E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1965***, *87*, 3855; Schowen, R.L.; Jayaraman, H.; Kershner, L.D. *J. Am. Chem. Soc.* ***1966***, *88*, 3373.
[26] Bender, M.L.; Thomas, R.J. *J. Am. Chem. Soc.* ***1961***, *83*, 4183, 4189.

the carboxylic acid formed went back to the starting material. On the other hand, if the tetrahedral mechanism operates then the tetrahedral intermediate would have the $^{18}O^{-}$, which will react with an acid such as water and be converted to the conjugate acid, symmetrical intermediate with the ^{18}OH moiety. In such an intermediate the OH and the ^{18}OH groups are equivalent with respect to reactivity, and (except for the small $^{18}O/^{16}O$ isotope effect) either one can lose a proton with equal facility to generate an alkoxide, which can lose an alkoxide with ^{-}OH or $H^{18}O^{-}$ and regenerate the ester.



Reversion back to the ester from one intermediate will give the labeled ester whereas loss from the other intermediate will give the unlabeled ester. A test of the two possible mechanisms is to stop the reaction before completion and to analyze the recovered ester for ^{18}O. Experiments by Bender and Thomas found that in alkaline hydrolysis of methyl, ethyl, and isopropyl benzoates, the esters had lost ^{18}O. A similar experiment carried out for acid-catalyzed hydrolysis of ethyl benzoate showed that the ester also lost ^{18}O. However, alkaline hydrolysis of substituted benzyl benzoates showed *no* ^{18}O loss.[27] This result does not necessarily mean that no tetrahedral intermediate is involved in this case. If either the labeled or unlabeled intermediate do not revert to ester, but go entirely to acid, no ^{18}O loss will be found even with a tetrahedral intermediate. In the case of benzyl benzoates this situation may very well be happening, because formation of the acid relieves steric strain. Another possibility is that the labeled intermediate loses OR′ before it can become protonated to give the unlabeled intermediate.[28] Even the experiments that *do* show ^{18}O loss do not *prove* the existence of the tetrahedral intermediate, since it is possible that ^{18}O is lost by some independent process not leading to ester hydrolysis. To deal with this possibility, Bender and Heck[29] measured the rate of ^{18}O loss in the hydrolysis of ethyl trifluorothioloacetate-^{18}O, $F_3CC^{18}OSEt$. This reaction had previously been shown[30] to involve an intermediate by the kinetic methods mentioned above. Bender and Heck showed that the rate of ^{18}O loss and the value of the partitioning ratio k_2/k_3 as determined by the oxygen exchange technique were exactly in accord with these values as previously determined by kinetic methods. Thus the original ^{18}O-exchange measurements showed that there is a tetrahedral species present, but not necessarily on the reaction path, while the kinetic experiments showed that there is some intermediate present, but not necessarily tetrahedral. Bender and Heck's results demonstrate that there is a tetrahedral intermediate and that it lies on the reaction pathway.

4. In some cases, tetrahedral intermediates have been isolated[31] or detected spectrally.[32]

[27] Bender, M.L.; Matsui, H.; Thomas, R.J.; Tobey, S.W. *J. Am. Chem. Soc.* ***1961***, *83*, 4193. See also, Shain, S.A.; Kirsch, J.F. *J. Am. Chem. Soc.* ***1968***, *90*, 5848.

[28] For evidence for this possibility, see McClelland, R.A. *J. Am. Chem. Soc.* ***1984***, *106*, 7579.

[29] Bender, M.L.; Heck, H. d'A. *J. Am. Chem. Soc.* ***1967***, *89*, 1211.

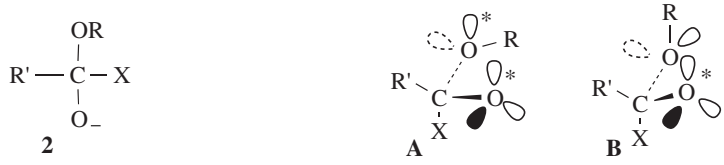
[30] Fedor, L.R.; Bruice, T.C. *J. Am. Chem. Soc.* ***1965***, *87*, 4138.

[31] See Khouri, F.F.; Kaloustian, M.K. *J. Am. Chem. Soc.* ***1986***, *108*, 6683.

[32] See Capon, B.; Dosunmu, M.I.; Sanchez, M.de N. *Adv. Phys. Org. Chem.* ***1985***, *21*, 37; McClelland, R.A.; Santry, L.J. *Acc. Chem. Res.* ***1983***, *16*, 394; Capon, B.; Ghosh, A.K.; Grieve, D.M.A. *Acc. Chem. Res.* ***1981***, *14*, 306. See also, van der Wel, H.; Nibbering, N.M.M. *Recl. Trav. Chim. Pays-Bas* ***1988***, *107*, 479, 491.

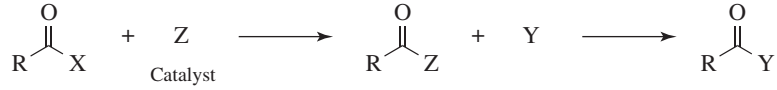
Several studies have been made of the directionality of approach by the nucleophile.[33] Menger has proposed for reactions in general, and specifically for those that proceed by the tetrahedral mechanism, that there is no single definable preferred transition state, but rather a "cone" of trajectories. All approaches within this cone lead to reaction at comparable rates; it is only when the approach comes outside of the cone that the rate falls.

Directionality has also been studied for the second step. Once the tetrahedral intermediate (**1**) is formed, it loses Y (giving the product) or X (reverting to the starting compound). Deslongchamps[34] has proposed that one of the factors affecting this choice is the conformation of the intermediate; more specifically, the positions of the lone pairs. In this view, a leaving group X or Y can depart only if the other two atoms on the carbon both have an orbital antiperiplanar to the C—X or C—Y bond. For example, consider an intermediate **2** formed by attack of $^-$OR on a substrate R′COX. Cleavage of the C—X bond with loss of X can take place from conformation **A**, because the two lone-pair orbitals marked * are antiperiplanar to the C—X bond, but not from **B** because only the O^- has such an orbital.



If the intermediate is in conformation **B**, the OR may leave (if X has a lone-pair orbital in the proper position) rather than X. This factor is called *stereoelectronic control*.[35] Free rotation in acyclic intermediates leads to many conformations, but some are preferred, and cleavage reactions may take place faster than rotation, so stereoelectronic control can be a factor in some situations. Much evidence has been presented for this concept.[34] More generally, the term *stereoelectronic effects* refers to any case in which orbital position requirements affect the course of a reaction. The back-side attack in the S_N2 mechanism is an example of a stereoelectronic effect.

Some nucleophilic substitutions at a carbonyl carbon are *catalyzed* by nucleophiles.[36] There occur, in effect, two tetrahedral mechanisms. The first is:



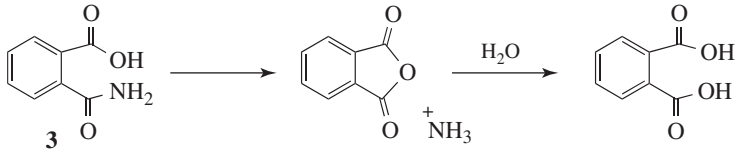
[33] See Menger, F.M. *Tetrahedron* ***1983***, *39*, 1013; Liotta, C.L.; Burgess, E.M.; Eberhardt, W.H. *J. Am. Chem. Soc.* ***1984***, *106*, 4849.

[34] Kirby, A.J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer, NY, ***1983***; Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, NY, ***1983***. See Sinnott, M.L. *Adv. Phys. Org. Chem.* ***1988***, *24*, 113; Gorenstein, D.G. *Chem. Rev.* ***1987***, *87*, 1047. Also see Ndibwami, A.; Deslongchamps, P. *Can. J. Chem.* ***1986***, *64*, 1788; Hegarty, A.F.; Mullane, M. *J. Chem. Soc., Perkin Trans. 2* ***1986***, 995. For evidence against the theory, see Perrin, C.L.; Nuñez, O. *J. Am. Chem. Soc.* ***1986***, *108*, 5997; ***1987***, *109*, 522.

[35] It has also been called the "antiperiplanar lone pair hypothesis (ALPH)." For a reinterpretation of this factor in terms of the principle of least nuclear motion (see **15-10**), see Hosie, L.; Marshall, P.J.; Sinnott, M.L. *J. Chem. Soc., Perkin Trans. 2* ***1984***, 1121; Sinnott, M.L. *Adv. Phys. Org. Chem.* ***1988***, *24*, 113.

[36] See Bender, M.L. *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, Wiley, NY, ***1971***, pp. 147–179; Johnson, S.L. *Adv. Phys. Org. Chem.* ***1967***, *5*, 271. For a review where Z = a tertiary amine, see Cherkasova, E.M.; Bogatkov, S.V.; Golovina, Z.P. *Russ. Chem. Rev.* ***1977***, *46*, 246.

and an example is shown in **16-57**. When this type if reaction occurs internally, it is a neighboring-group mechanism at a carbonyl carbon.[37] For example, the hydrolysis of phthalamic acid (**3**) takes place as follows via formation of phthalic anhydride, which is hydrolyzed to phthalic acid.



Evidence comes from comparative rate studies.[38] It was found that **3** was hydrolyzed $\sim 10^5$ times faster than benzamide ($PhCONH_2$) at about the same concentration of hydrogen ions. That this enhancement of rate was not caused by the resonance or field effects of COOH (an electron-withdrawing group) was shown by the fact both *o*-nitrobenzamide and terephthalamic acid (the *para* isomer of **3**) were hydrolyzed more slowly than benzamide. Other examples of neighboring-group participation at a carbonyl carbon have been reported.[39] It is likely that nucleophilic catalysis is involved in enzyme-catalyzed ester hydrolysis.

The attack of a nucleophile on a carbonyl group can result in substitution or addition, depending on the substituents, but the first step of each mechanism is the same. The main factor that determines the product is the identity of the group X in RCOX. When X is alkyl or hydrogen, addition usually takes place and an alcohol is the product. When X is halogen, OCOR, NH_2, and so on, the usual reaction is substitution and an acyl derivative is the product. When X = OH, protonation to generate $^+OH_2$ is usually required before the group can be lost.

In both the S_N1 and S_N2 mechanisms the leaving group departs during the rate-determining step and so directly affects the rate. In the tetrahedral mechanism at a carbonyl carbon, the bond between the substrate and leaving group is still intact during the slow step. Nevertheless, the nature of the leaving group still affects the reactivity in two ways:

1. By altering the electron density at the carbonyl carbon, the rate of the reaction is affected. The greater the electron-withdrawing character of X, the greater the partial positive charge on C and the more rapid the attack by a nucleophile.
2. The nature of the leaving group affects the *position of equilibrium*. In the intermediate **1** above, there is competition between X and Y as to which group leaves. If X is a poorer leaving group than Y, then Y will preferentially leave and **4** will revert to the starting compounds. Thus there is a partitioning factor between **4** going on to product (loss of X) or back to starting compound (loss of Y).

The sum of these two factors causes the sequence of reactivity to be $RCOCl > RCOOCOR' > RCOOAr > RCOOR' > RCONH_2 > RCONR'_2 > RCOO^-$.[40] Note that this

[37] Kirby, A.J.; Fersht, A.R. *Prog. Bioorg. Chem.* ***1971***, *1*, 1; Capon, B. *Essays Chem.* ***1972***, *3*, 127.
[38] Bender, M.L.; Chow, Y.; Chloupek, F.J. *J. Am. Chem. Soc.* ***1958***, *80*, 5380.
[39] See Page, M.I.; Render, D.; Bernáth, G. *J. Chem. Soc., Perkin Trans. 2* ***1986***, 867.
[40] RCOOH would belong in this sequence just after RCOOAr, but it fails to undergo many reactions for a special reason. Many nucleophiles, instead of attacking the C=O group, are basic enough to take a proton from the acid, converting it to the unreactive $RCOO^-$.

TABLE 16.1 The more important synthetic reactions that take place by the tetrahedral mechanism[a]

Reaction No.	Reaction
16-56	$RCOX + H_2O \longrightarrow RCOOH$
16-57	$RCOOCOR' + H_2O \longrightarrow RCOOH + R'COOH$
16-58	$RCO_2R' + H_2O \longrightarrow RCOOH + R'OH$
16-58	$RCONR''_2 + H_2O \longrightarrow RCOOH + R'_2NH$ (R′ = H, alkyl, aryl)
16-60	$RCOX + R'OH \longrightarrow RCO_2R'$
16-61	$RCOOCOR + R'OH \longrightarrow RCO_2R'$
16-62	$RCOOH + R'OH \longrightarrow RCO_2R'$
16-63	$RCO_2R' + R''OH \longrightarrow RCO_2R'' + R'OH$
16-65	$RCOX + R'COO^- \longrightarrow RCOOCOR'$
10-21	$RCOX + H_2O_2 \longrightarrow RCO_3H$
16-68	$RCOX + R'SH \longrightarrow RCOSR'$
16-71	$RCOX + NHR'_2 \longrightarrow RCONR'_2$ (R′ = H, alkyl, aryl)
16-72	$RCOOCOR + NHR'_2 \longrightarrow RCONR'_2$ (R′ = H, alkyl, aryl)
16-73	$RCOOH + NHR'_2 \xrightarrow[\text{agent}]{\text{Coupling}} RCONR'_2$ (R′ = H, alkyl, aryl)
16-74	$RCO_2R' + NHR_2 \longrightarrow RCONR_2$ (R_2 = H, alkyl, aryl)
16-78	$RCOOH + SOCl_2 \longrightarrow RCOCl$
19-43	$RCOX + LiAlH(O\text{-}t\text{-}Bu)_3 \longrightarrow RCHO$
19-45	$RCONR'_2 + LiAlH_4 \longrightarrow RCHO$
16-28	$RCOX + R'_2CuLi \longrightarrow RCOR'$
16-81	$2\,RCH_2CO_2R' \longrightarrow RCH_2COCHRCO_2R'$

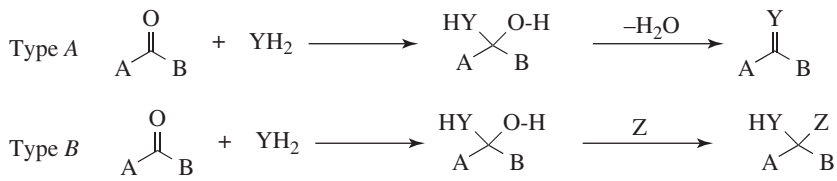
[a] Catalysts are not shown.

order is approximately the order of decreasing stability of the leaving-group anion. If the leaving group is bulky, it may exert a steric effect and retard the rate for this reason.

For a list of some of the more important reactions that operate by the tetrahedral mechanism, see Table 16.1.

16.B. REACTIONS

Many of the reactions in this chapter are simple additions to carbon–heteroatom multiple bonds, with the reaction ending when a new group has been added. But in many other cases subsequent reactions take place. There are generally two types, *A* and *B*:



In type *A*, the initially formed adduct loses water (or, in the case of addition to C═NH, ammonia, etc.), and the net result of the reaction is the substitution of C═Y for C═O (or C═NH, etc.). In type *B* there is a rapid substitution, and the OH (or NH_2, etc.) is replaced by another group Z, which is often another YH moiety. This substitution is nucleophilic in most cases: Y usually has an unshared electron pair and S_N1 reactions occur very well on

this type of compound (Sec. 10.G.i, category 2), even when the leaving group is as poor as OH or NH_2. In this chapter, reactions will be classified according to what is initially adding to the carbon–heteroatom multiple bond, even if subsequent reactions take place so rapidly that it is impossible to isolate the initial adduct.

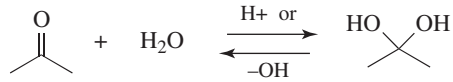
Most of the reactions considered in this chapter can be reversed. In many cases, the reverse reactions will be considered with the forward ones, in the same section. The reverse of some of the other reactions are considered in other chapters. In still other cases, one of the reactions in this chapter is the reverse of another from this chapter (e.g., **16-2** and **16-12**). For reactions that are reversible, the principle of microscopic reversibility applies (see Sec. 6.H).

First, reactions in which hydrogen or a metallic ion (or in one case phosphorus or sulfur) adds to the heteroatom will be discussed. Secondly, reactions in which carbon adds to the heteroatom will be discussed. Within each group, the reactions are classified by the nature of the nucleophile. Additions to isocyanides, which are different in character, follow. Acyl substitution reactions that proceed by the tetrahedral mechanism, which mostly involve derivatives of carboxylic acids, are treated at the end.

16.B.i. Reactions in Which Hydrogen or a Metallic Ion Adds to the Heteroatom

A. Attack by OH (Addition of H_2O)

16-1 The Addition of Water to Aldehydes and Ketones: Formation of Hydrates



The adduct formed upon addition of water to an aldehyde or ketone is called a hydrate or *gem*-diol.[41] These compounds are usually stable only in water solution and decompose on distillation; i.e., the equilibrium shifts back toward the carbonyl compound, usually via formation of an enol and tautomerization to the carbonyl. The position of the equilibrium is greatly dependent on the structure of the hydrate. Thus, formaldehyde in water at 20 °C exists 99.99% in the hydrated form, while for acetaldehyde this figure is 58%, and for acetone the hydrate concentration is negligible.[42] Aldehyde hydrates are highly unstable, transient intermediates but *N*-oxides are capable of stabilizing such compounds based on the formation of hydrogen bonds.[43]

It has been found, by exchange with ^{18}O, that the reaction with acetone is quite rapid when catalyzed by acid or base, but the equilibrium lies on the side of acetone and water.[44] Since methyl, a *+I* group, inhibits hydrate formation, it may be expected that electron-attracting groups would have the opposite effect, and this is indeed the case. The hydrate of chloral (trichloroacetaldehyde)[45] is a stable crystalline substance. In order

[41] See Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***, pp. 183–187. See Wang, B.; Cao, Z. *Angew. Chem. Int. Ed.* ***2011***, *50*, 3266.

[42] Bell, R.P.; Clunie, J.C. *Trans. Faraday Soc.* ***1952***, *48*, 439. See also, Bell, R.P.; McDougall, A.O. *Trans. Faraday Soc.* ***1960***, *56*, 1281.

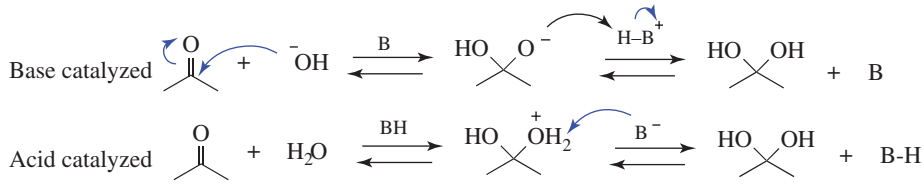
[43] Roth, A.J.K.; Tretbar, M.; Stark, C.B.W. *Chem. Commun.* ***2015***, *51*, 14175.

[44] Cohn, M.; Urey, H.C. *J. Am. Chem. Soc.* ***1938***, *60*, 679.

[45] For a review of chloral, see Luknitskii, F.I. *Chem. Rev.* ***1975***, *75*, 259.

for it to revert to chloral, ^{-}OH or H_2O must leave; this is made difficult by the electron-withdrawing character of the Cl_3C group and by the absence of a proton on the α carbon, which is required for loss of water to form an enol. Some other[46] polychlorinated and polyfluorinated aldehydes and ketones[47] and α-keto aldehydes also form stable hydrates, as do cyclopropanones.[48] In the last case,[49] formation of the hydrate relieves some of the *I* strain (Sec. 9.B) of the parent ketone.

The reaction is subject to both general-acid and general-base catalysis. The following mechanisms can be written for basic (B) and acidic (BH) catalysis, respectively:[50]



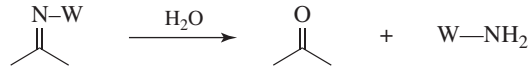
As the hydroxide attacks in the base-catalyzed mechanism, the base pulls off a proton to give an alkoxide, which reacts with an endogenous acid (usually water, H—O—H) to give the hydrate. In the acid-catalyzed mechanism, the carbonyl oxygen reacts with an acid to give an oxocarbenium ion which reacts with water to form an oxonium ion. Removal of the acidic hydrogen with an endogenous base, usually water, gives the hydrate.

Reactions in which the catalyst donates a proton to the electrophilic reagent in one direction and removes it in the other have been called *class e reactions*, and those reactions in which the catalyst does the same to the nucleophilic reagent are called *class n reactions*.[51] Thus the acid-catalyzed process here is a class e reaction, while the base-catalyzed process is a class n reaction.

For the reaction between ketones and H_2O_2, see **17-35**.

There are no OS references, but see OS **VIII**, 597, for the reverse reaction.

16-2 Hydrolysis of the Carbon–Nitrogen Double Bond[52]



Compounds containing C—N double bonds can be hydrolyzed to the corresponding aldehydes or ketones.[53] For imines (W = R or H) the hydrolysis is easy and can be carried out with

[46] Schulman, E.M.; Bonner, O.D.; Schulman, D.R.; Laskovics, F.M. *J. Am. Chem. Soc.* ***1976***, *98*, 3793.

[47] For a review of addition to fluorinated ketones, see Gambaryan, N.P.; Rokhlin, E.M.; Zeifman, Yu.V.; Ching-Yun, C.; Knunyants, I.L. *Angew. Chem. Int. Ed.* ***1966***, *5*, 947.

[48] See Krois, D.; Lehner, H. *Monatsh. Chem.* ***1982***, *113*, 1019.

[49] Turro, N.J.; Hammond, W.B. *J. Am. Chem. Soc.* ***1967***, *89*, 1028. For a review of cyclopropanone chemistry, see Wasserman, H.H.; Clark, G.M.; Turley, P.C. *Top. Curr. Chem.* ***1974***, *47*, 73.

[50] Sørensen, P.E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1987***, *109*, 4675; Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row, NY, ***1987***, pp. 662–680. A theoretical treatment is in Wolfe, S.; Kim, C.-K.; Yang, K.; Weinberg, N.; Shi, Z. *J. Am. Chem. Soc.* ***1995***, *117*, 4240.

[51] Jencks, W.P. *Acc. Chem. Res.* ***1976***, *9*, 425.

[52] For a review, see Khoee, S.; Ruoho, A.E. *Org. Prep. Proceed. Int.* ***2003***, *35*, 527.

[53] For proton affinities of imines, see Hammerum, S.; Sølling, T.I. *J. Am. Chem. Soc.* ***1999***, *121*, 6002.

water in some cases. When W = H, the imine is seldom stable enough for isolation, and in aqueous media hydrolysis usually occurs *in situ*, without isolation. The hydrolysis of *Schiff bases* (W = Ar) is more difficult and requires acid or base catalysis. Oximes (W = OH), arylhydrazones (W = NHAr), and, most easily, semicarbazones ($W = NHCONH_2$) can also be hydrolyzed. Often a reactive aldehyde (e.g., formaldehyde) is added to combine with the liberated amine. A number of reagents[54] have been used to cleave C=N bonds, especially those not easily hydrolyzable with acidic or basic catalysts or those that contain other functional groups that are attacked under these conditions.

Oximes have been converted to the corresponding aldehyde or ketone[55] by treatment with NBS in water,[56] Chloramine-T,[57] HCO_2H on SiO_2 with microwave irradiation,[58] O_2/a nitrite-containing resin (FPA53-NO_2)/Amberlyst-15,[59] anhydrous $Ce(SO_4)_2$ in chloroform,[60] or in an ionic liquid on SiO_2.[61] Transition metal compounds have been used, including those of Sb,[62] Co,[63] Hg,[64] Bi,[65] Cu,[66] or Zn.[67] Oxidizing agents can be quite effective, including tetraalkylammonium permanganates,[68] and quinolinium dichromate[69] has also been used.

Phenylhydrazones can be converted to a ketone using Oxone® and $KHCO_3$,[70] or polymer-bound iodonium salts.[71] Dimethylhydrazones have been converted to ketones with $FeSO_4 \bullet 7\ H_2O$ in chloroform,[72] or Me_3SiCl/NaI in acetonitrile with 1% water.[73] Hydrazones, such as RAMP or SAMP (**10-68**, category 4), can be hydrolyzed with aq. $CuCl_2$.[74] Tosylhydrazones can be hydrolyzed to the corresponding ketones with aqueous acetone and BF_3-etherate,[75] as well as with other reagents.[76] Semicarbazones have been cleaved with ammonium chlorochromates on alumina,[77] ($Mg(HSO_4)_2$ on wet silica,[78] or by $SbCl_3$ with microwave irradiation.[79]

[54] For a list of reagents, with references, see Ranu, B.C.; Sarkar, D.C. *J. Org. Chem.* ***1988***, *53*, 878.
[55] For a review, see Corsaro, A.; Chiacchio, U.; Pistarà, V. *Synthesis* ***2001***, 1903.
[56] Bandgar, B.P.; Makone, S.S. *Org. Prep. Proceed. Int.* ***2000***, *32*, 391.
[57] Padmavathi, V.; Reddy, K.V.; Padmaja, A.; Venugopalan, P. *J. Org. Chem.* ***2003***, *68*, 1567.
[58] A solvent-free reaction. See Zhou, J.-F.; Tu, S.-J.; Feng, J.-C. *Synth. Commun.* ***2002***, *32*, 959.
[59] Guo, S.; Zeng, R.; Li, C. *Synth. Commun.* ***2016***, *46*, 1446.
[60] Asutay, O.; Hamarat, N.; Uludag, N.; Coşkun, N. *Tetrahedron Lett.* ***2015***, *56*, 3902.
[61] See Li, D.; Shi, F.; Deng, Y. *Tetrahedron Lett.* ***2004***, *45*, 6791.
[62] Narsaiah, A.V.; Nagaiah, K. *Synthesis* ***2003***, 1881.
[63] Mukai, C.; Nomura, I.; Kataoka, O.; Hanaoka, M. *Synthesis* ***1999***, 1872.
[64] De, S.K. *Synth. Commun.* ***2004***, *34*, 2289.
[65] See Arnold, J.N.; Hayes, P.D.; Kohaus, R.L.; Mohan, R.S. *Tetrahedron Lett.* ***2003***, *44*, 9173.
[66] See Hashemi, M.M.; Beni, Y.A. *Synth. Commun.* ***2001***, *31*, 295.
[67] Tamami, B.; Kiasat, A.R. *Synth. Commun.* ***2000***, *30*, 4129.
[68] Hajipour, A.R.; Mallakpour, S.E.; Khoee, E. *Synth. Commun.* ***2002***, *32*, 9.
[69] Sadeghi, M.M.; Mohammadpoor-Baltork, I.; Azarm, M.; Mazidi, M.R. *Synth. Commun.* ***2001***, *31*, 435. See also, Zhang, G.-S.; Yang, D.-H.; Chen, M.-F. *Org. Prep. Proceed. Int.* ***1998***, *30*, 713.
[70] Hajipour, A.R.; Mahboubghah, N. *Org. Prep. Proceed. Int.* ***1999***, *31*, 112.
[71] Chen, D.-J.; Cheng, D.-P.; Chen, Z.-C. *Synth. Commun.* ***2001***, *31*, 3847.
[72] Nasreen, A.; Adapa, S.R. *Org. Prep. Proceed. Int.* ***1999***, *31*, 573.
[73] Kamal, A.; Ramana, K.V.; Arifuddin, M. *Chem. Lett.* ***1999***, 827.
[74] Enders, D.; Hundertmark, T.; Lazny, R. *Synth. Commun.* ***1999***, *29*, 27.
[75] Sacks, C.E.; Fuchs, P.L. *Synthesis* ***1976***, 456.
[76] See Chandrasekhar, S.; Reddy, Ch.R.; Reddy, M.V. *Chem. Lett.* ***2000***, 430; Jiricny, J.; Orere, D.M.; Reese, C.B. *Synthesis* ***1970***, 919.
[77] See Gong, H.; Zhang, G.-S. *Synth. Commun.* ***1999***, *29*, 2591.
[78] Shirini, F.; Zolfigol, J.-P.; Mallakpour, S.E.; Hajipour, A.R.; Baltork, I.M. *Tetrahedron Lett.* ***2002***, *43*, 1555.
[79] Mitra, S.K.; De, A.; Karchaudhuri, N. *Synth. Commun.* ***2000***, *30*, 1651.

The hydrolysis of C—N double bonds involves initial addition of water and elimination of a nitrogen moiety.[80] In specific cases there are variations in the sequence of the steps, depending on acid or basic catalysis or other conditions.[81] Which step is rate determining also depends on the acidity and on the nature of W (see above) and of the groups connected to the carbonyl.[82]

Iminium ions (**4**)[83] would be expected to undergo hydrolysis quite readily (note that there is a resonance contributor with a positive charge on the carbon).

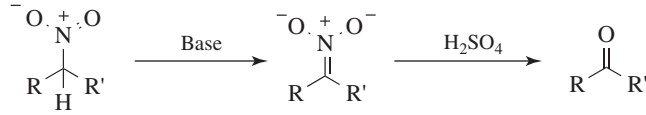
4

Indeed, iminium ions react with water at room temperature.[84] Acid-catalyzed hydrolysis of enamines to the corresponding carbonyl (the last step of the *Stork enamine reaction*, **10-69**), involves conversion to iminium ions that react with water. Loss of a proton gives the carbonyl.[85] The mechanism of enamine hydrolysis is similar to that of vinyl ether hydrolysis (**10-6**).

OS **I**, 217, 298, 318, 381; **II**, 49, 223, 234, 284, 310, 333, 395, 519, 522; **III**, 20, 172, 626, 818; **IV**, 120; **V**, 139, 277, 736, 758; **VI**, 1, 358, 640, 751, 901, 932; **VII**, 8; **65**, 108, 183; **67**, 33; **76**, 23.

OS **II**, 24; **IV**, 819; **V**, 273; **VI**, 910.

16-3 Hydrolysis of Aliphatic Nitro Compounds



Primary or secondary aliphatic nitro compounds can be hydrolyzed to aldehydes or ketones, respectively, by treatment of their conjugate bases with sulfuric acid. This is called the *Nef reaction*.[86] Tertiary aliphatic nitro compounds do not give the reaction because they cannot be converted to their conjugate bases. Like **16-2**, this reaction involves hydrolysis of a C═N

[80] For reviews of the mechanism, see Bruylants, A.; Feytmants-de Medicis, E. in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 465–504; Salomaa, P. in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, ***1966***, pp. 199–205.

[81] See Sayer, J.M.; Conlon, E.H. *J. Am. Chem. Soc.* ***1980***, *102*, 3592.

[82] Cordes, E.H.; Jencks, W.P. *J. Am. Chem. Soc.* ***1963***, *85*, 2843.

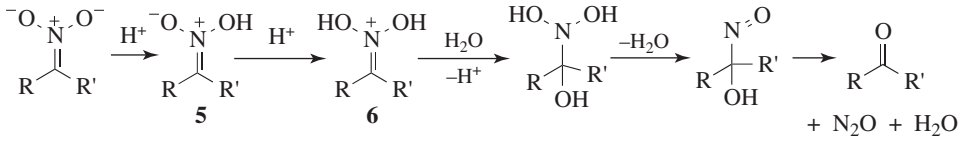
[83] For a review of iminium ions, see Böhme, H.; Haake, M. *Adv. Org. Chem.* ***1976***, *9*, pt. 1, 107.

[84] Hauser, C.R.; Lednicer, D. *J. Org. Chem.* ***1959***, *24*, 46. For a study of the mechanism, see Gopalakrishnan, G.; Hogg, J.L. *J. Org. Chem.* ***1989***, *54*, 768.

[85] Sollenberger, P.Y.; Martin, R.B. *J. Am. Chem. Soc.* ***1970***, *92*, 4261. For enamine hydrolysis, see Stamhuis, E.J.; Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, pp. 165–180.

[86] See Pinnick, H.W. *Org. React.* ***1990***, *38*, 655; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1988***, pp. 220–231, 416–419. See Umemiya, S.; Nishino, K.; Sato, I.; Hayashi, Y. *Chem. Eur. J.* ***2014***, *20*, 15753.

double bond. A possible mechanism involves initial formation of the *aci form* of the nitro compound (**5**).[87] Intermediates of type **6** have been isolated in some cases.[88]

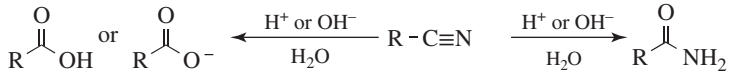


The conversion of nitro compounds to aldehydes or ketones has been carried out with better yields and fewer side reactions by several alternative methods.[89] Among these are treatment of the nitro compound with basic H_2O_2 in an ionic liquid,[90] with DBU in MeCN,[91] or with ceric ammonium nitrate (CAN).[92]

When *primary* nitro compounds are treated with sulfuric acid without previous conversion to the conjugate bases, they give carboxylic acids. Hydroxamic acids are intermediates and can be isolated, so that this is also a method for their preparation.[93] Both the Nef reaction and the hydroxamic acid process involve the *aci form*; the difference in products arises from higher acidity, for example, a difference in sulfuric acid concentration from 2 to 15.5 M changes the product from the aldehyde to the hydroxamic acid.[94] The mechanism of the hydroxamic acid reaction is not known with certainty, but if higher acidity is required, it may be that the protonated *aci form* of the nitro compound is further protonated.

OS **VI**, 648; **VII**, 414. See also, OS **IV**, 573.

16-4 Hydrolysis of Nitriles



Nitriles can be hydrolyzed to give either amides or carboxylic acids.[95] The amide is formed initially, but amides can be hydrolyzed using more vigorous acidic or basic conditions to give the carboxylic acid. When the acid is desired,[96] the reagent of choice is aqueous NaOH containing ~6 to 12% H_2O_2, but acid-catalyzed hydrolysis can also be used. The reaction of nitriles with TFA/acetic acid/sulfuric acid, followed by treatment with water, gives the corresponding amide.[97] A Rh-catalyzed hydrolysis with aqueous isopropyl alcohol leads

[87] Hawthorne, M.F. *J. Am. Chem. Soc.* ***1957***, *79*, 2510. Also see van Tamelen, E.E.; Thiede, R.J. *J. Am. Chem. Soc.* ***1952***, *74*, 2615; Sun, S.F.; Folliard, J.T. *Tetrahedron* ***1971***, *27*, 323.
[88] Feuer, H.; Spinicelli, L.F. *J. Org. Chem.* ***1977***, *42*, 2091.
[89] For a review, see Ballini, R.; Petrini, M. *Tetrahedron* ***2004***, *60*, 1017.
[90] Bortolini, O.; De Nino, A.; Garofalo, A.; Maiuolo, L.; Russo, B. *Synth. Commun.* ***2010***, *40*, 2483.
[91] Ballini, R.; Bosica, G.; Fiorini, D.; Petrini, M. *Tetrahedron Lett.* ***2002***, *43*, 5233.
[92] Olah, G.A.; Gupta, B.G.B. *Synthesis* ***1980***, 44.
[93] See Sosnovsky, G.; Krogh, J.A. *Synthesis* ***1980***, 654.
[94] Kornblum, N.; Brown, R.A. *J. Am. Chem. Soc.* ***1965***, *87*, 1742. See also, Edward, J.T.; Tremaine, P.H. *Can. J. Chem.* ***1971***, *49*, 3483, 3489, 3493.
[95] Zil'berman, E.N. *Russ. Chem. Rev.* ***1984***, *53*, 900. See Guthrie, J.P.; Yim, J.C.-H.; Wang, Q. *J. Phys. Org. Chem.* ***2014***, *27*, 27.
[96] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1986–1987.
[97] Moorthy, J.N.; Singhal, N. *J. Org. Chem.* ***2005***, *70*, 1926.

to the amide.[98] A "dry" hydrolysis of nitriles has been reported.[99] Enzymatic hydrolysis to give the amide was reported with nitrilase ZmNIT2.[100] Nitriles can be hydrolyzed to the carboxylic acids without disturbing carboxylic ester functions also present by the use of tetrachloro- or tetrafluorophthalic acid.[101]

Nitriles were hydrolyzed to the corresponding carboxylic acid using a recyclable ionic liquid, [bmim]HSO_4.[102] The bioreduction of nitriles to carboxylic acids used *Rhodococcus erythropolis* SET1, a novel nitrile-hydrolyzing bacterial isolate, with a phosphate buffer.[103] Nitrilases converted nitriles to the corresponding carboxylic acid, and a chromogenic reagent has been developed to screen for nitrilase activity.[104] Cobalt-centered nitrile hydratases gave enantioselective hydrolysis.[105]

There are a number of procedures for stopping at the amide stage,[106] among them the use of concentrated H_2SO_4 and of aqueous NaOH with PEG-400 and microwave irradiation.[107] The same result can also be obtained by use of water and certain metal ions or complexes[108] including In,[109] Au,[110] a Ru catalyst.[111] or MnO_2/SiO_2 with microwave irradiation.[112] A bimetallic catalyst composed of Pd and a Lewis acid was used to convert nitriles to the amide.[113] Nitriles were hydrolyzed to amides using a Mo catalyst in water.[114] Hydrolysis of benzonitrile derivatives with 3 equivalents of KO-*t*-Bu in *t*-BuOH gave the benzamide derivative under anhydrous conditions.[115] A flow chemistry process (Sec. 7.D) for the hydration of nitriles gave the corresponding amide by passage of an aqueous solution of the nitrile through a column containing commercially available amorphous manganese dioxide.[116] The hydration of nitriles used amorphous manganese oxide with a reduced amount of water.[117] The mild hydration of nitriles to amides used a Cu catalyst.[118] The selective hydration of nitriles was catalyzed by a Pd catalyst in aqueous solution.[119]

[98] Goto, A.; Endo, K.; Saito, S. *Angew. Chem. Int. Ed.* ***2008***, *47*, 3607.
[99] Chemat, F.; Poux, M.; Berlan, J. *J. Chem. Soc., Perkin Trans. 2* ***1994***, 2597; ***1996***, 1781.
[100] Mukherjee, C.; Zhu, D.; Biehl, E.R.; Parmar, R.R.; Hua, L. *Tetrahedron* ***2006***, *62*, 6150. Also see Black, G.W.; Gregson, T.; McPake, C.B.; Perry, J.J.; Zhang, M. *Tetrahedron Lett.* ***2010***, *51*, 1639.
[101] Rounds, W.D.; Eaton, J.T.; Urbanowicz, J.H.; Gribble, G.W. *Tetrahedron Lett.* ***1988***, *29*, 6557.
[102] Kumar, S.; Dixit, S.K.; Awasthi, S.K. *Tetrahedron Lett.* ***2014***, *55*, 3802.
[103] Coady, T.M.; Coffey, L.V.; O'Reilly, C.; Lennon, C.M. *Eur. J. Org. Chem.* ***2015***, 1108.
[104] Black, G.W.; Brown, N.L.; Perry, J.J.B.; Randall, P.D.; Turnbull, G.; Zhang, M. *Chem. Commun.* ***2015***, *51*, 2660.
[105] van Pelt, S.; Zhang, M.; Otten, L.G.; Holt, J.; Sorokin, Y.; van Rantwijk, F.; Black, G.W.; Perr, J.J.; Sheldon, R.A. *Org. Biomol. Chem.* ***2011***, *9*, 3011.
[106] See Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 119–125. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1988–1990.
[107] Bendale, P.M.; Khadilkar, B.M. *Synth. Commun.* ***2000***, *30*, 1713.
[108] See McKenzie, C.J.; Robson, R. *J. Chem. Soc., Chem. Commun.* ***1988***, 112.
[109] Kim, E.S.; Lee, H.S.; Kim, S.H.; Kim, J.N. *Tetrahedron Lett.* ***2010***, *51*, 1589.
[110] Ramón, R.S.; Marion, N.; Nolan, S.P. *Chem. Eur. J.* ***2009***, *15*, 8695.
[111] See Polshettiwar, V.; Varma, R.S. *Chem. Eur. J.* ***2009***, *15*, 1582.
[112] For a solvent-free reaction. See Khadilkar, B.M.; Madyar, V.R. *Synth. Commun.* ***2002***, *32*, 1731.
[113] Zhang, S.; Xu, H.; Lou, C.; Senan, A.M.; Chen, Z.; Yin, G. *Eur. J. Org. Chem.* ***2017***, 1870.
[114] Ma, X.; He, Y.; Lu, M. *Synth. Commun.* ***2014***, *44*, 474.
[115] Midya, G.C.; Kapat, A.; Maiti, S.; Dash, J. *J. Org. Chem.* ***2015***, *80*, 4148.
[116] Battilocchio, C.; Hawkins, J.M.; Ley, S.V. *Org. Lett.* ***2014***, *16*, 1060.
[117] Yamaguchi, K.; Wang, Y.; Kobayashi, H.; Mizuno, N. *Chem. Lett.* ***2012***, *41*, 574.
[118] Marcé, P.; Lynch, J.; Blacker, A.J.; Williams, J.M.J. *Chem. Commun.* ***2016***, *52*, 1436.
[119] Sharley, D.D.S.; Williams, J.M.J. *Tetrahedron. Lett.* ***2017***, *58*, 4090.

Nitriles are converted to thioamides $ArC(=S)NH_2$ with ammonium sulfide $(NH_4)_2S$ in methanol, with microwave irradiation.[120] Thioamides are also prepared using phosphorus pentasulfide.[121] Thiocyanates are converted to thiocarbamates in a similar reaction:[122]

$$R—S—C\equiv N + H_2O \rightarrow R—S—CO—NH_2$$

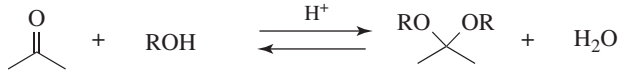
Hydrolysis of cyanamides gives amines, produced by the breakdown of the unstable carbamic acid intermediates:

$$R_2NCN \rightarrow [R_2NCOOH] \rightarrow R_2NH$$

OS **I**, 21, 131, 201, 289, 298, 321, 336, 406, 436, 451; **II**, 29, 44, 292, 376, 512, 586 (see, however, **V**, 1054), 588; **III**, 34, 66, 84, 88, 114, 221, 557, 560, 615, 851; **IV**, 58, 93, 496, 506, 664, 760, 790; **V**, 239; **VI**, 932; **76**, 169. Also see, OS **III**, 609; **IV**, 359, 502; **66**, 142.

B. Attack by OR (Addition of ROH or RCO_2H)

16-5 The Addition of Alcohols to Aldehydes and Ketones

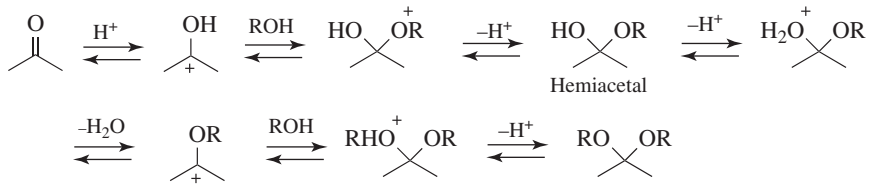


Acetals and ketals are formed by treatment of aldehydes and ketones, respectively, with alcohols in the presence of acid catalysts.[123] Lewis acid derivatives of Ti,[124] Cu,[125] In,[126] Ru,[127] or Co[128] can be used in conjunction with alcohols. Organocatalysts have been used for this conversion under acid-free conditions.[129] This reaction is reversible, and acetals and ketals can be hydrolyzed by treatment with acid.[130] With small unbranched aldehydes the equilibrium lies to the right. If ketals or acetals of larger molecules are to be prepared the equilibrium must be shifted, usually by removal of water. Removal of water can be done by azeotropic distillation, ordinary distillation, or the use of a drying agent such as Al_2O_3 or a molecular sieve.[131] The reaction is not catalyzed in either direction by bases, so most acetals and ketals are quite stable to bases, though they are easily hydrolyzed by acids. This reaction is therefore a useful method of protection of aldehyde or ketone functions from attack by bases. The reaction is of wide scope.

[120] Bagley, M.C.; Chapaneri, K.; Glover, C.; Merritt, E.A. *Synlett* ***2004*** 2615.
[121] Kaboudin, B.; Elhamifar, D. *Synthesis* ***2006***, 224.
[122] Zil'berman, E.N.; Lazaris, A.Ya. *J. Gen. Chem. USSR* ***1963***, *33*, 1012.
[123] For reviews, see Meskens, F.A.J. *Synthesis* ***1981***, 501; Schmitz, E.; Eichhorn, I. in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 309–351.
[124] Clerici, A.; Pastori, N.; Porta, O. *Tetrahedron* ***2001***, *57*, 217.
[125] Kumar, R.; Chakraborti, A.K. *Tetrahedron Lett.* ***2005***, *46*, 8319.
[126] Gregg, B.T.; Golden, K.C.; Quin, J.F. *Tetrahedron* ***2008***, *64*, 3287.
[127] De, S.K.; Gibbs, R.A. *Tetrahedron Lett.* ***2004***, *45*, 8141.
[128] Velusamy, S.; Punniyamurthy, T. *Tetrahedron Lett.* ***2004***, *45*, 4917.
[129] Kotke, M.; Schreiner, P.R. *Tetrahedron* ***2006***, *62*, 434.
[130] See Heravi, M.M.; Tajbakhsh, M.; Habibzadeh, S.; Ghassemzadeh, M. *Monat. Chem.* ***2001***, *132*, 985.
[131] For many examples, see Meskens, F.A.J. *Synthesis* ***1981***, 501 (pp. 502–505).

Most aldehydes are easily converted to acetals,[132] but the reaction with ketones is more difficult, presumably for steric reasons. The reaction of aldehydes with alcohols using a photochemical reaction under low-energy visible light irradiation in the presence of a catalytic amount of Eosin Y and green LEDs gave the corresponding acetal.[133] While the reaction with ketones often fails, many ketals, especially from cyclic ketones, have been made in this manner.[134] Many functional groups may be present without being affected. 1,2-Diols and 1,3-diols form cyclic acetals and ketals (1,3-dioxolanes[135] and 1,3-dioxanes,[136] respectively), and these are often used to protect aldehydes and ketones. Chiral dioxolanes have been prepared from chiral diols.[137] Dioxolanes have been prepared from ketones in ionic liquids.[138] Ketones are converted to dimethyl ketals by electrolysis with NaBr in methanol.[139] Intramolecular reactions are possible in which a keto diol or an aldehyde diol generates a bicyclic ketal or acetal. The Ru-catalyzed synthesis of mixed alkyl alkyl acetals occurred via addition of primary alcohols to allyl ethers.[140]

The mechanism for acid-catalyzed acetal/ketal formation involves initial formation of a *hemiacetal*,[141] and this reaction is the reverse of that given for acetal hydrolysis. In a study of the acid-catalyzed formation of hemiacetals, Grunwald showed[142] that the data best fit a mechanism in which the reaction is simultaneously catalyzed by acid and base, with water acting as the base.[143]



Hemiacetals themselves are no more stable than the corresponding hydrates (**16-1**). If the original aldehyde or ketone has an α hydrogen, it is possible to lose water from the hemiacetal, and enol ethers can be prepared. Similarly, treatment with an anhydride and a catalyst can give an enol ester (see **16-5**).[144] As with hydrates, it is noted that hemiacetals of

[132] See Ott, J.; Tombo, G.M.R.; Schmid, B.; Venanzi, L.M.; Wang, G.; Ward, T.R. *Tetrahedron Lett.* ***1989***, *30*, 6151; Liao, Y.; Huang, Y.; Zhu, F. *J. Chem. Soc., Chem. Commun.* ***1990***, 493.

[133] Yi, H.; Niu, L.; Wang, S.; Liu, T.; Singh, A.K.; Lei, A. *Org. Lett.* ***2017***, *19*, 122.

[134] High pressure has been used to improve the results with ketones: Dauben, W.G.; Gerdes, J.M.; Look, G.C. *J. Org. Chem.* ***1986***, *51*, 4964. For other methods, see Otera, J.; Mizutani, T.; Nozaki, H. *Organometallics* ***1989***, *8*, 2063; Thurkauf, A.; Jacobson, A.E.; Rice, K.C. *Synthesis* ***1988***, 233.

[135] See Gopinath, R.; Haque, Sk.J.; Patel, B.K. *J. Org. Chem.* ***2002***, *67*, 5842.

[136] See Wu, H.-H.; Yang, F.; Cui, P.; Tang, J.; He, M.-Y. *Tetrahedron Lett.* ***2004***, *45*, 4963.

[137] Kurihara, M.; Hakamata, W. *J. Org. Chem.* ***2003***, *68*, 3413.

[138] See Li, D.; Shi, F.; Peng, J.; Guo, S.; Deng, Y. *J. Org. Chem.* ***2004***, *69*, 3582.

[139] Elinson, M.N.; Feducovich, S.K.; Dmitriev, D.E.; Dorofeev, A.S.; Vereshchagin, A.N.; Nikishin, G.I. *Tetrahedron Lett.* ***2001***, *42*, 5557.

[140] Krompiec, S.; Penkala, M.; Kowalska, E.; Penczek, R.; Bujak, P.; Danikiewicz, W.; Spólnik, G.; Kita, A.; Grudzka, I. *Monatsh. Chem.* ***2011***, *142*, 1241.

[141] For a review of hemiacetals, see Hurd, C.D. *J. Chem. Educ.* ***1966***, *43*, 527.

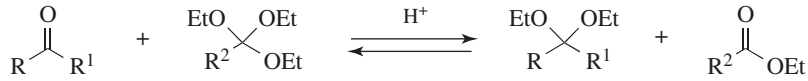
[142] Grunwald, E. *J. Am. Chem. Soc.* ***1985***, *107*, 4715.

[143] Grunwald, E. *J. Am. Chem. Soc.* ***1985***, *107*, 4710; Leussing, D.L. *J. Org. Chem.* ***1990***, *55*, 666.

[144] For a list of catalysts, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1484–1485.

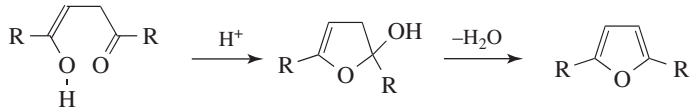
cyclopropanones[145] and of polychloro and polyfluoro aldehydes and ketones may be quite stable.

The conversion of acetals back to aldehydes or ketones is accomplished by many reagents, including aqueous acid. Heating with water under microwave irradiation converts acetals to the corresponding carbonyl compound.[146] Transition metal compounds of Bi[147] catalyze this conversion as well. When acetals or ketals are treated with an alcohol of higher molecular weight than the one already there, *transacetalation* is possible (see **10-13**). In another type of transacetalation, aldehydes or ketones can be converted to acetals or ketals by treatment with another acetal or ketal or with an ortho ester,[148] in the presence of an acid catalyst. This is shown here for an ortho ester.



This method is useful for the conversion of ketones to ketals, since the direct reaction of a ketone with an alcohol often gives poor results. Alternatively, the substrate is treated with an alkoxysilane ($ROSiMe_3$) in the presence of trimethylsilyl trifluoromethanesulfonate.[149] An In catalyst converted acyclic acetals and ketals in the presence of diols or triols under solvent-free conditions to give the corresponding new cyclic acetal or ketal.[150]

1,4-Diketones give furans when treated with acids. This is actually an example of an intramolecular addition of an alcohol to a ketone, since it is the enol form that adds.



Similarly, 1,5-diketones give pyrans.

1,4-Diphenylbut-2-en-1,4-dione, a conjugated 1,4-diketone, is converted to 2,5-diphenylfuran with formic acid, 5% Pd/C, PEG-200, and a sulfuric acid catalyst with microwave irradiation.[151]

OS **I**, 1, 298, 364, 381; **II**, 137; **III**, 123, 387, 502, 536, 644, 731, 800; **IV**, 21, 479, 679; **V**, 5, 292, 303, 450, 539; **VI**, 567, 666, 954; **VII**, 59, 149, 168, 177, 241, 271, 297; **VIII**, 357. Also see, OS **IV**, 558, 588; **V**, 25; **VIII**, 415.

[145] See Salaun, J. *Chem. Rev.* ***1983***, *83*, 619.

[146] Procopio, A.; Gaspari, M.; Nardi, M.; Oliverio, M.; Tagarelli, A.; Sindona, G. *Tetrahedron Lett.* ***2007***, *48*, 8623.

[147] Bailey, A.D.; Baru, A.R.; Tasche, K.K.; Mohan, R.S. *Tetrahedron Lett.* ***2008***, *49*, 691.

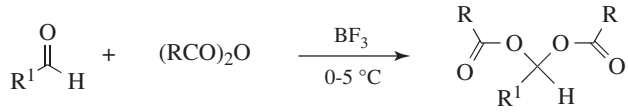
[148] See DeWolfe, R.H. *Carboxylic Ortho Ester Derivatives*, Academic Press, NY, ***1970***, pp. 154–164. See Leonard, N.M.; Oswald, M.C.; Freiberg, D.A.; Nattier, B.A.; Smith, R.C.; Mohan, R.S. *J. Org. Chem.* ***2002***, *67*, 5202.

[149] Kato, J.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* ***1985***, 743. See also, Torii, S.; Takagishi, S.; Inokuchi, T.; Okumoto, H. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 775.

[150] Smith, B.M.; Kubczyk, T.M.; Graham, A.E. *Tetrahedron* ***2012***, *68*, 7775.

[151] Rao, H.S.P.; Jothilingam, S. *J. Org. Chem.* ***2003***, *68*, 5392.

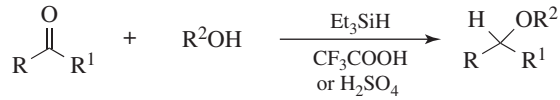
Aldehydes can be converted to *acylals* by treatment with an anhydride in the presence of proton acids,[152] BF_3, $LiBF_4$,[153] and Lewis acid compounds of Fe,[154] In,[155] Cu,[156] Bi,[157] W,[158] or Zr.[159] *N*-Chlorosuccinimide (NCS) with thiourea is a highly efficient catalyst.[160] Silica-supported perchloric acid is useful for the preparation of acylals.[161]



Formic acid reacts with alcohols to give orthoformates. The Co-catalyzed intramolecular ketone hydroacylation reactions of 2-acylbenzaldehydes and 2-alkenylbenzaldehydes gave phthalide and indanone derivatives, respectively.[162]

OS **IV**, 489.

16-6 Reductive Alkylation of Alcohols



Aldehydes and ketones can be converted to ethers by treatment with an alcohol and triethylsilane in the presence of a strong acid[163] or by hydrogenation in alcoholic acid in the presence of a Pt catalyst.[164] The process can formally be regarded as addition of ROH to give a hemiacetal RR′C(OH)OR^2, followed by reduction of the OH. In this respect, it is similar to **16-15**. Homoallylic ethers are formed by the Fe-catalyzed reaction of acetals and aldehydes,[165] and by reactions in ionic liquids.[166] The In-catalyzed reaction of aldehydes with allyltriethoxysilane leads to the corresponding ether.[167]

[152] See Olah, G.A.; Mehrotra, A.K. *Synthesis* ***1982***, 962.
[153] Yadav, J.S.; Reddy, B.V.S.; Venugapal, C.; Ramalingam, V.T. *Synlett* ***2002***, 604.
[154] Trost, B.M.; Lee, C.B. *J. Am. Chem. Soc.* ***2001***, *123*, 3671; Wang, C.; Li, M. *Synth. Commun.* ***2002***, *32*, 3469.
[155] Smith, B.M.; Graham, A.E. *Tetrahedron Lett.* ***2006***, *47*, 9317.
[156] Chandra, K.L.; Saravanan, P.; Singh, V.K. *Synlett* ***2000***, 359.
[157] Aggen, D.H.; Arnold, J.N.; Hayes, P.D.; Smoter, N.J.; Mohan, R.S. *Tetrahedron* ***2004***, *60*, 3675.
[158] Solvent-free reaction: Karimi, B.; Ebrahimian, G.-R.; Seradj, H. *Synth. Commun.* ***2002***, *32*, 669.
[159] Smitha, G.; Reddy, Ch.S. *Tetrahedron* ***2003***, *59*, 9571.
[160] Mei, Y.; Bentley, P.A.; Du, J. *Tetrahedron Lett.* ***2009***, *50*, 4199.
[161] Kamble, V.T.; Jamode, V.S.; Joshi, N.S.; Biradar, A.V.; Deshmukh, R.Y. *Tetrahedron Lett.* ***2006***, *47*, 5573.
[162] Yang, J.; Yoshikai, N. *J. Am. Chem. Soc.* ***2014***, *136*, 16748.
[163] Doyle, M.P.; DeBruyn, D.J.; Kooistra, D.A. *J. Am. Chem. Soc.* ***1972***, *94*, 3659.
[164] Gooßen, L.J.; Linder, C. *Synlett* ***2006***, 3489. For another method, see Loim, L.M.; Parnes, Z.N.; Vasil'eva, S.P.; Kursanov, D.N. *J. Org. Chem. USSR* ***1972***, *8*, 902.
[165] Spafford, M.J.; Anderson, E.D.; Lacey, J.R.; Palma, A.C.; Mohan, R.S. *Tetrahedron Lett.* ***2007***, *48*, 8665.
[166] Anzalone, P.W.; Mohan, R.S. *Synthesis* ***2005***, 2661.
[167] Yang, M.-S.; Xu, L.-W.; Qiu, H.-Y.; Lai, G.-Q.; Jiang, J.-X. *Tetrahedron Lett.* ***2008***, *49*, 253.

The Ni-catalyzed, silane-mediated reductive cyclization of ynals gave 2-triethylsilyloxy alkylidene cyclopentanes in the presence of Et_3SiH.[168] The In-catalyzed reductive coupling of an aldehyde to give its symmetrical ether used Et_3SiH.[169]

16-7 The Addition of Alcohols to Isocyanates

The reaction of an isocyanate with alcohols gives a carbamate (a substituted urethane),[170] is of wide scope, and gives good yields. Isocyanic acid HNCO gives unsubstituted carbamates. Addition of a second equivalent of HNCO gives an *allophanate*: $NH(CO_2R')CON_2$.

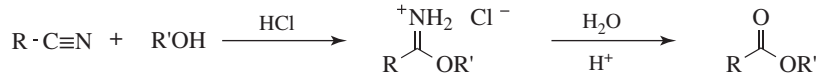
The isocyanate can be generated *in situ* by the reaction of an amine and oxalyl chloride, and subsequent reaction with HCl and then an alcohol gives the carbamate.[171] Combining compounds with two NCO groups with compounds containing two OH groups makes polyurethanes. Cyclic carbamates, such as 1,3-oxazine-2-ones, are generated by the reaction of an isocyanate with an oxetane, in the presence of a Pd catalyst.[172] Isothiocyanates similarly give thiocarbamates[173] RNHCSOR′, but they react slower than the corresponding isocyanates. Isocyanates react with LiAlHSeH and then iodomethane to give the corresponding selenocarbonate (RNHCOSeMe).[174] The reaction of CS_2, amines, and boronic acids gave the corresponding dithiocarbamate using a Cu catalyst.[175]

The details of the mechanism are poorly understood,[176] but the oxygen of the alcohol certainly attacks the carbon of the isocyanate. Hydrogen bonding complicates the kinetic picture.[177] Metallic compounds can also catalyze the addition of ROH to isocyanates,[178] as can light,[179] and, for tertiary ROH, so can lithium alkoxides[180] or *n*-butyllithium.[181]

OS **I**, 140; **V**, 162; **VI**, 95, 226, 788, 795.

[168] Baxter, R.D.; Montgomery, J. *J. Am. Chem. Soc.* ***2011***, *133*, 5728.
[169] Mineno, T.; Tsukagoshi, R.; Iijima, T.; Watanabe, K.; Miyashita, H.; Yoshimitsu, H. *Tetrahedron Lett.* ***2014***, *55*, 3765.
[170] Chaturvedi, D. *Tetrahedron* ***2012***, *68*, 15.
[171] Oh, L.M.; Spoors, P.G.; Goodman, R.M. *Tetrahedron Lett.* ***2004***, *45*, 4769.
[172] Larksarp, C.; Alper, H. *J. Org. Chem.* ***1999***, *64*, 4152.
[173] See Walter, W.; Bode, K. *Angew. Chem. Int. Ed.* ***1967***, *6*, 281. See also, Wynne, J.H.; Jensen, S.D.; Snow, A.W. *J. Org. Chem.* ***2003***, *68*, 3733.
[174] Koketsu, M.; Ishida, M.; Takakura, N.; Ishihara, H. *J. Org. Chem.* ***2002***, *67*, 486.
[175] Qi, C.; Guo, T.; Xiong, W. *Synlett* ***2016***, *27*, 2626.
[176] See Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975***, *4*, 231.
[177] See Donohoe, G.; Satchell, D.P.N.; Satchell, R.S. *J. Chem. Soc., Perkin Trans. 2* ***1990***, 1671 and references cited therein. See also, Sivakamasundari, S.; Ganesan, R. *J. Org. Chem.* ***1984***, *49*, 720.
[178] See Kim, Y.H.; Park, H.S. *Synlett* ***1998***, 261; Duggan, M.E.; Imagire, J.S. *Synthesis* ***1989***, 131.
[179] McManus, S.P.; Bruner, H.S.; Coble, H.D.; Ortiz, M. *J. Org. Chem.* ***1977***, *42*, 1428.
[180] Bailey, W.J.; Griffith, J.R. *J. Org. Chem.* ***1978***, *43*, 2690.
[181] Nikoforov, A.; Jirovetz, L.; Buchbauer, G. *Liebigs Ann. Chem.* ***1989***, 489.

16-8 Alcoholysis of Nitriles

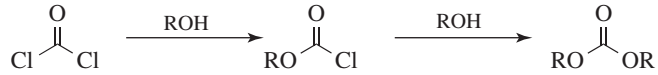


The addition of dry HCl to a mixture of a nitrile and an alcohol in the absence of water leads to the hydrochloride salt of an imino ester. (Note that imino esters are also called imidates and imino ethers.) This reaction is called the *Pinner synthesis*.[182] The salt can be converted to the free imino ester by treatment with a weak base such as sodium bicarbonate, or it can be hydrolyzed with water and an acid catalyst to the corresponding carboxylic ester. If the latter is desired, water may be present from the beginning, in which case aqueous HCl can be used and the need for gaseous HCl is eliminated. Imino esters can also be prepared from nitriles with basic catalysts.[183] Amides were prepared by the Ru-catalyzed reaction of alcohols and nitriles.[184]

This reaction is of broad scope and is good for aliphatic, aromatic, and heterocyclic R and for nitriles with oxygen-containing functional groups. The application of the reaction to nitriles containing a carboxyl group constitutes a good method for the synthesis of mono esters of dicarboxylic acids with the desired group esterified and with no diester or diacid present.

OS **I**, 5, 270; **II**, 284, 310; **IV**, 645; **VI**, 507; **VIII**, 415.

16-9 The Formation of Carbonates and Xanthates



The reaction of phosgene with an alcohol generates a haloformic ester (XCO_2R), and reaction with a second equivalent of alcohol gives a carbonate. This reaction is related to the acyl addition reactions of acyl chlorides in reaction **16-92**. An important example is the preparation of carbobenzoxy chloride ($PhCH_2OCOCl$; CbzCl) from phosgene and benzyl alcohol. When CbzCl reacts with an amine, the product is the benzyl carbamate, *N*-Cbz, which is widely used for the protection of amino groups during peptide synthesis. When an alcohol reacts with certain alkyl halides (e.g., benzyl chloride) and CO_2, in the presence of Cs_2CO_3 and tetrabutylammonium iodide, a mixed carbonate is formed.[185]

[182] See Compagnon, P.L.; Miocque, M. *Ann. Chim. (Paris)* ***1970***, *[14] 5*, 23 (see pp. 24–26). Imino esters: see Neilson, D.G. in Patai, S. *The Chemistry of Amidines and Imidates*, Wiley, NY, ***1975***, pp. 385–489.

[183] Schaefer, F.C.; Peters, G.A. *J. Org. Chem.* ***1961***, *26*, 412.

[184] Kang, B.; Fu, Z.; Hong, S.-H. *J. Am. Chem. Soc.* ***2013***, *135*, 11704.

[185] Kim, S.i.; Chu, F.; Dueno, E.E.; Jung, K.W. *J. Org. Chem.* ***1999***, *64*, 4578.

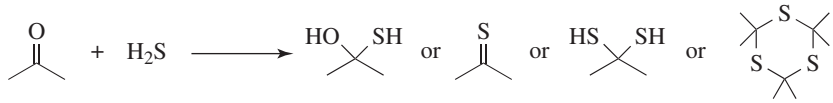
Epoxides reacted with CO_2 in the presence of an Al complex to give a carbonate.[186] An aluminum(salen) catalyst,[187] choline iodide,[188] cellulose/KI,[189] triethanolamine/KI,[190] 3-hydroxypridine/Bu_4NI,[191] and phosphonium iodides in alcoholic solvents[192] have been used for this carbonate-forming reaction. Electrosynthesis has also been used.[193] A bromine-catalyzed reaction of CO_2 and epoxides to give cyclic carbonates has ben reported using flow conditions (Sec. 7.D).[194] The *N*-heterocyclic carbene-catalyzed preparation of cyclic carbonates from diols and CO_2 has been reported.[195] Unsymmetrical carbonates were prepared from alcohols and dimethylcarbonate.[196]

The addition of alcohols to carbon disulfide (S═C═S) in the presence of a base produces xanthates.[197] The base is often HO^-, but in some cases better results can be obtained by using methylsulfinyl carbanion $MeSOCH_2^-$.[198] If an alkyl halide RX is present, the xanthate ester ROCSSR′ can be produced directly. In a similar manner, alkoxide ions add to CO_2 to give carbonate ester salts ($ROCO_2^-$).

OS **V**, 439; **VI**, 207, 418; **VII**, 139.

C. Sulfur Nucleophiles

16-10 The Addition of H_2S and Thiols to Carbonyl Compounds



7 **8** **9** **10**

The addition of H_2S to an aldehyde or ketone can result in a variety of products. α-Hydroxy thiols (**7**) can be prepared from polychloro and polyfluoro aldehydes and ketones,[199] although hydroxy thiols appear to be stable only when prepared from these compounds. The most usual product is the trithiane **10**.[200] A much more useful application is the addition of thiols to aldehydes and ketones to give hemi-mercaptals (CH(OH)SR) and dithioacetals, $CH(SR)_2$ (**16-5**). The reaction of aldehydes or ketones with hydrogen sulfide is generally

[186] Whiteoak, C.J.; Kielland, N.; Laserna, V.; Escudero-Adán, E.C.; Martin, E.; Kleij, A.W. *J. Am. Chem. Soc.* ***2013***, *135*, 1228. See Kumar, S.; Jain, S.L.; Sain, B. *Tetrahedron Lett.* ***2011***, *52*, 6957.

[187] North, M.; Villuendas, P.; Young, C. *Tetrahedron Lett.* ***2012***, *53*, 2736. See Whiteoak, C.J.; Kielland, N.; Laserna, V.; Castro-Gómez, F.; Martin, E.; Escudero-Adán, E.C.; Bo, C.; Kleij, A.W. *Chem. Eur. J.* ***2014***, *20*, 2264; Castro-Osma, J.A.; North, M.; Wu, X. *Chem. Eur. J.* ***2014***, *20*, 15005.

[188] Amaral, A.J.R.; Coelho, J.F.J.; Serra, A.C. *Tetrahedron Lett.* ***2013***, *54*, 5518.

[189] Liang, S.; Li, H.; Jiang, T.; Song, J.; Yang, G.; Han, B. *Chem. Commun.* ***2011***, *47*, 2131.

[190] Xiao, B.; Sun, J.; Wang, J.; Liu, C.; Cheng, W. *Synth. Commun.* ***2013***, *43*, 2885.

[191] Wang, X.; Wang, L.; Zhao, Y.; Kodama, K.; Hirose, T. *Tetrahedron* ***2017***, *73*, 1190.

[192] Aoyagi, N.; Furusho, Y.; Endo, T. *Tetrahedron Lett.* ***2013***, *54*, 7031.

[193] Buckley, B.R.; Patel, A.P.; Wijayantha, K.G.U. *Chem. Commun.* ***2011***, *47*, 11888.

[194] Kozak, J.A.; Wu, J.; Su, X.; Simeon, F.; Hatton, T.A.; Jamison, T.F. *J. Am. Chem. Soc.* ***2013***, *135*, 18497.

[195] Bobbink, F.D.; Gruszka, W.; Hulla, M.; Das, S.; Dyson, P.J. *Chem. Commun.* ***2016***, *52*, 10787.

[196] Kunar, S.; Jain, S.L. *Monatsh. Chem.* ***2014***, *145*, 791.

[197] See Dunn, A.D.; Rudorf, W. *Carbon Disulphide in Organic Chemistry*, Ellis Horwood, Chichester, ***1989***, pp. 316–367.

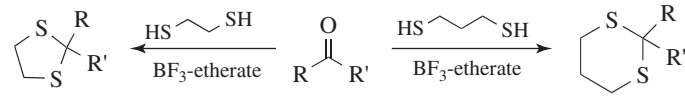
[198] Meurling, P.; Sjöberg, B.; Sjöberg, K. *Acta Chem. Scand.* ***1972***, *26*, 279.

[199] Harris Jr., J.F. *J. Org. Chem.* ***1960***, *25*, 2259.

[200] Campaigne, E.; Edwards, B.E. *J. Org. Chem.* ***1962***, *27*, 3760.

not a good route to thioketones (**8**). *gem*-Dithiols (**9**) are much more stable than the corresponding hydrates or α-hydroxy thiols.[201] *gem*-Dithiols have been prepared by the treatment of ketones with H_2S under pressure[202] and under mild conditions with HCl as a catalyst.[203]

Thiols add to aldehydes and ketones to initially give hemi-mercaptals (RS—C—OH) and dithioacetals (RS—C—SR). Hemi-mercaptals are ordinarily unstable,[204] but they are usually more stable than the corresponding hemiacetals and can be isolated in certain cases.[205] The isolated product of this reaction is most often the dithioacetal, which, like the acetals obtained by reaction with an alcohol, are stable in the presence of base. The reaction of aldehydes or ketones with thiols most commonly uses a Lewis acid catalyst such as boron trifluoride etherate (BF_3•OEt_2).[206] to give the dithioacetal[207] or dithioketal. Dithioacetals can also be prepared from aldehydes or ketones by treatment with thiols in the presence of a Lewis acid or of tosic acid on silica gel in dichloromethane,[208] while oxalic acid promotes the reaction.[209] Similarly, reactions that use 1,2-ethanedithiol or 1,3-propanedithiol lead to 1,3-dithiolanes (**11**)[210] or 1,3-dithianes (**12**).[211]

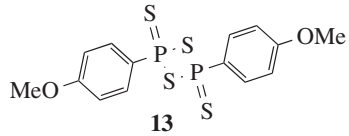


11 **12**

Dithioacetals and dithioketals are used as protecting groups for aldehydes and ketones, and after subsequent reactions involving the R or R′ group, deprotection regenerates the carbonyl.[212] Simple hydrolysis is the most common method for converting thiocarbonyls to carbonyls, and there are a variety of reagents for this conversion.[213] Lewis acids such as aluminum chloride ($AlCl_3$) and mercuric salts are common reagents (the *Corey-Seebach procedure*).[214] Other reagents, which include BF_3•OEt_2 in aqueous THF containing mercuric oxide (HgO)[215] or ceric ammonium nitrate [$Ce(NH_4)_2(NO_3)_6$],[216] have been used.[217] When aldehydes and ketones react with mercapto alcohols, mixed acetals or ketals are formed. Aldehydes and ketones were converted to dithianes and dithiolanes via reaction with dithiolanylium and dithianylium derivatives on resin solid supports.[218]

[201] See Mayer, R.; Hiller, G.; Nitzschke, M.; Jentzsch, J. *Angew. Chem. Int. Ed.* ***1963***, *2*, 370.
[202] Cairns, T.L.; Evans, G.L.; Larchar, A.W.; McKusick, B.C. *J. Am. Chem. Soc.* ***1952***, *74*, 3982.
[203] See Demuynck, M.; Vialle, J. *Bull. Soc. Chim. Fr.* ***1967***, 1213.
[204] See, for example, Fournier, L.; Lamaty, G.; Nata, A.; Roque, J.P. *Tetrahedron* ***1975***, *31*, 809.
[205] For example, see Field, L.; Sweetman, B.J. *J. Org. Chem.* ***1969***, *34*, 1799.
[206] Fujita, E.; Nagao, Y.; Kaneko, K. *Chem. Pharm. Bull.* ***1978***, *26*, 3743; Corey, E.J.; Bock, M.G. *Tetrahedron Lett.* ***1975***, 2643.
[207] See Samajdar, S.; Basu, M.K.; Becker, F.F.; Banik, N.K. *Tetrahedron Lett.* ***2001***, *42*, 4425.
[208] Ali, M.H.; Goretti Gomes, M. *Synthesis* ***2005***, 1326.
[209] Miyake, H.; Nakao, Y.; Sasaki, M. *Chem. Lett.* ***2007***, *36*, 104.
[210] See Kamal, A.; Chouhan, G. *Synlett* ***2002***, 474. For a review, see Olsen, R.K.; Currie Jr., J.O. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 521–532.
[211] See Laskar, D.D.; De, S.K. *Tetrahedron Lett.* ***2004***, *45*, 1035, 2339.
[212] See Ganguly, N.C.; Datta, M. *Synlett* ***2004***, 659.
[213] Corsaro, A.; Pistarà, V. *Tetrahedron* ***1998***, *54*, 15027.
[214] Seebach, D.; Corey, E.J. *J. Org. Chem.* ***1975***, *40*, 231; Seebach, D. *Synthesis* ***1969***, 17.
[215] Vedejs, E.; Fuchs, P.L. *J. Org. Chem.* ***1971***, *36*, 366.
[216] Ho, T.-L.; Ho, H.C.; Wong, C.M. *J. Chem. Soc., Chem. Commun.* ***1972***, 791a.
[217] Myles, L.; Gathergood, N.; Connon, S.J. *Eur. J. Org. Chem.* ***2015***, 188.
[218] Jung, N.; Grässle, S.; Lütjohann, D.S.; Bräse, S. *Org. Lett.* ***2014***, *16*, 1036.

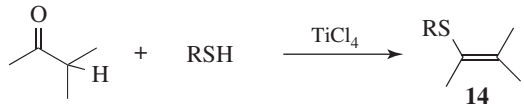
Thioketones (**8**) can be prepared from certain ketones, such as diaryl ketones, by treatment with H_2S and an acid catalyst, usually HCl. They are often unstable and usually trimerize (to **10**) or react with air. Thioaldehydes[219] are even less stable and simple ones[220] apparently have never been isolated, although *tert*-BuCHS has been prepared in solution, where it exists for several hours at 20 °C.[221] A high-yield synthesis of thioketones involves treatment of acyclic[222] ketones with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide[223] (**13**, known as *Lawesson's reagent*)[224]. Thioketones can also be prepared by treatment of ketones with P_4S_{10},[225] or P_4S_{10} on alumina.[226] Reagent **13** converts the C═O groups of amides and carboxylic esters[227] to C═S groups.[228] Lactones react with **13** in the presence of hexamethyldisiloxane an microwave irradiation to give the thiolactone.[229]



13

Other reagents that may be used for this transformation include $POCl_3$ followed by $S(TMS)_2$, which converts lactams to thiolactams.[230] Treatment with aqueous $S(NH_4)_2$[231] converts amides to thioamides, as does the microwave-assisted reaction with $PSCl_2/H_2O/Et_3N$, without solvent.[232]

If an aldehyde or ketone possesses an α hydrogen, it can be converted to the corresponding enol thioether (**14**) by treatment with a thiol in the presence of $TiCl_4$.[233]



14

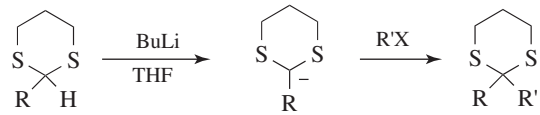
[219] See Usov, V.A.; Timokhina, L.V.; Voronkov, M.G. *Russ. Chem. Rev.* ***1990***, *59*, 378.
[220] See Muraoka, M.; Yamamoto, T.; Enomoto, K.; Takeshima, T. *J. Chem. Soc., Perkin Trans. 1* ***1989***, 1241, and references cited therein.
[221] Vedejs, E.; Perry, D.A. *J. Am. Chem. Soc.* ***1983***, *105*, 1683. See also, Baldwin, J.E.; Lopez, R.C.G. *J. Chem. Soc., Chem. Commun.* ***1982***, 1029.
[222] Cyclopentanone and cyclohexanone gave different products: Scheibye, S.; Shabana, R.; Lawesson, S.; Rømming, C. *Tetrahedron* ***1982***, *38*, 993.
[223] See Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S. *Org. Synth.* VII, 372.
[224] See Jesberger, M.; Davis, T.P.; Barner, L. *Synthesis* ***2003***, 1929. For a study of the mechanism, see Rauchfuss, T.B.; Zank, G.A. *Tetrahedron Lett.* ***1986***, *27*, 3445. See Ozturk, T.; Ertas, E.; Mert, O. *Chem. Rev.* ***2007***, *107*, 5210.
[225] See Scheeren, J.W.; Ooms, P.H.J.; Nivard, R.J.F. *Synthesis* ***1973***, 149.
[226] Polshettiwar, V.; Kaushik, M.P. *Tetrahedron Lett.* ***2004***, *45*, 6255.
[227] For a review of thiono esters RC(=S)OR', see Jones, B.A.; Bradshaw, J.S. *Chem. Rev.* ***1984***, *84*, 17.
[228] Yde, B.; Yousif, N.M.; Pedersen, U.S.; Thomsen, I.; Lawesson, S.-O. *Tetrahedron* ***1984***, *40*, 2047; Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S. *Org. Synth.* VII, 372.
[229] Filippi, J.-J.; Fernandez, X.; Lizzani-Cuvelier, L.; Loiseau, A.-M. *Tetrahedron Lett.* ***2003***, *44*, 6647.
[230] Smith, D.C.; Lee, S.W.; Fuchs, P.L. *J. Org. Chem.* ***1994***, *59*, 348.
[231] Charette, A.B.; Grenon, M. *J. Org. Chem.* ***2003***, *68*, 5792.
[232] Pathak, U.; Pandey, L.K.; Tank, R. *J. Org. Chem.* ***2008***, *73*, 2890.
[233] Mukaiyama, T.; Saigo, K. *Chem. Lett.* ***1973***, 479.

Aldehydes and ketones have been converted to sulfides by treatment with thiols and pyridine/borane[234] in a reductive alkylation reaction, analogous to **16-6**.

$$RCOR' + R^2SH \rightarrow RR'CHSR^2$$

OS **II**, 610; **IV**, 927; **VI**, 109; **VII**, 124, 372. Also see, OS **III**, 332; **IV**, 967; **V**, 780; **VI**, 556; **VIII**, 302.

The presence of a sulfur atom on a carbon enhances the acidity of a proton on that carbon, and in dithioacetals and dithioketals that proton ($RSCH_2SR$) is even more acidic. The pK_a of such protons is typically 31–37,[235] so removal requires a strong base, and deprotonation[236] to form the corresponding carbanion is often quite slow. The reaction of 1,3-sithianes with a strong base such as butyllithium in THF[237] followed by reaction with an alkyl halide gave the 2-alkylated dithiane.[238]



Since 1,3-dithianes can be prepared by treatment of an aldehyde or its acetal (see OS **VI**, 556) with 1,3-propanedithiol and can be hydrolyzed (**10-7**), this is a method for the conversion of an aldehyde to a ketone[239] (see also, **10-68** and **18-9**). A catalytic dithioacetalization process to give the corresponding 1,3-dithianes used aldehydes and 2-chloro-1,3-dithiane with an Fe catalyst.[240]

The alkylation reaction just described is another example of Umpolung (see **10-68**);[241] the normally electrophilic carbon of the aldehyde is made to behave as a nucleophile. The reaction can be applied to the unsubstituted dithiane (R = H) and one or two alkyl groups can be introduced, so a wide variety of aldehydes and ketones can be made starting with formaldehyde.[242] The R′ group may be primary alkyl, secondary alkyl, or benzylic. Carbanions generated from 1,3-dithianes also react with epoxides[243] to give the expected products. Reaction with epoxides leads to intermediates that undergo the *Brook rearrangement* (**18-44**), which is synthetically useful in what is known as *anion relay chemistry*.

A useful application of this reaction stems from the fact that dithianes can be desulfurated with *Raney nickel* (**14-22**). Aldehydes can therefore be converted first to the dithiane

[234] Kikugawa, Y. *Chem. Lett.* ***1981***, 1157.

[235] Streitwieser Jr., A.; Maskornick, M.J.; Ziegler, G.R. *Tetrahedron Lett.* ***1971***, 3927; Ward, H.R.; Lawler, R.G. *J. Am. Chem. Soc.* ***1967***, *89*, 5517.

[236] Truce, W.E.; Roberts, F.E. *J. Org. Chem.* ***1963***, *28*, 961.

[237] See Lipshutz, B.H.; Garcia, E. *Tetrahedron Lett.* ***1990***, *31*, 7261.

[238] Seebach, D.; Corey, E.J. *J. Org. Chem.* ***1975***, *40*, 231. See Page, P.C.B.; van Niel, M.B.; Prodger, J.C. *Tetrahedron* ***1989***, *45*, 7643; Ager, D.J. in Hase, T.A. *Umpoled Synthons*, Wiley, NY, ***1987***, pp. 19–37; Seebach, D. *Synthesis* ***1969***, 17, especially pp. 24–27; Olsen, R.K.; Curriev Jr., Y.O. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 536–547.

[239] Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1451–1454.

[240] Lai, J.; Du, W.; Tian, L.; Zhao, C.; She, X.; Tang, S. *Org. Lett.* ***2014***, *16*, 4396.

[241] See Hünig, S. *Chimia,* ***1982***, *36*, 1.

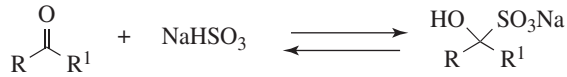
[242] For a direct conversion of RX to RCHO, see **10-77**.

[243] See Corey, E.J.; Seebach, D. *J. Org. Chem.* ***1975***, *40*, 231.

and desulfurization gives the chain-extended hydrocarbons.[244] Similar reactions have been carried out with other thioacetals, as well as with compounds containing three thioether groups on a carbon.[245]

Thioamides are converted to amides with *Caro's acid* (H_2SO_5) on SiO_2.[246] The use of 2-mercaptoethanol ($HSCH_2CH_2OH$), for example, leads to an oxathiolane[247] and 3-mercaptopropanol ($HSCH_2CH_2CH_2OH$) leads to an oxathiane.

16-11 Formation of Bisulfite Addition Products

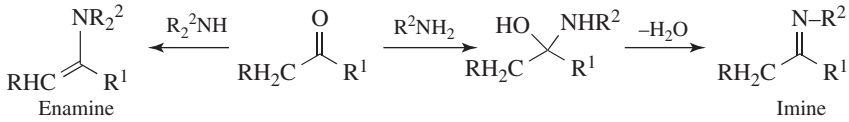


Bisulfite addition products are formed from aldehydes, methyl ketones, cyclic ketones (generally seven-membered and smaller rings), α-keto esters, and isocyanates, upon treatment with sodium bisulfite ($NaHSO_3$). Most other ketones do not undergo the reaction, probably for steric reasons. The reaction is reversible (by treatment of the addition product with either acid or base)[248] and is useful for the purification of the starting compounds, since the addition products are soluble in water and many of the impurities are not.[249] The effect of the counterion has been discussed.[250]

OS **I**, 241, 336; **III**, 438; **IV**, 903; **V**, 437.

D. Attack by NH_2, NHR, or NR_2 (Addition of NH_3, RNH_2, R_2NH)

16-12 The Addition of Amines to Aldehydes and Ketones



The addition of ammonia[251] to aldehydes or ketones does not generally give useful products. According to the pattern followed by analogous nucleophiles, the initial products would be

[244] See Hylton, T.; Boekelheide, V. *J. Am. Chem. Soc.* ***1968***, *90*, 6887; Jones, J.B.; Grayshan, R. *Chem. Commun.* ***1970***, 141, 741.

[245] See Lissel, M. *Liebigs Ann. Chem.* ***1982***, 1589.

[246] Movassagh, B.; Lakouraj, M.M.; Ghodrati, K. *Synth. Commun.* ***2000***, *30*, 2353.

[247] See Ballini, R.; Bosica, G.; Maggi, R.; Mazzacani, A.; Righi, P.; Sartori, G. *Synthesis* ***2001***, 1826; Mondal, E.; Sahu, P.R.; Khan, A.T. *Synlett* ***2002***, 463.

[248] For cleavage with ion-exchange resins, see Khusid, A.Kh.; Chizhova, N.V. *J. Org. Chem. USSR* ***1985***, *21*, 37. For a discussion of the mechanism, see Young, P.R.; Jencks, W.P. *J. Am. Chem. Soc.* ***1978***, *100*, 1228.

[249] The reaction has also been used to protect an aldehyde group in the presence of a keto group: Chihara, T.; Wakabayashi, T.; Taya, K. *Chem. Lett.* ***1981***, 1657.

[250] Kissane, M.G.; Frank, S.A.; Rener, G.A.; Ley, C.P.; Alt, C.A.; Stroud, P.A.; Vaid, R.K.; Boini, S.K.; McKee, L.A.; Vicenzi, J.T.; Stephenson G.A. *Tetrahedron Lett.* ***2013***, *54*, 6587.

[251] For a review of this reagent in organic synthesis, see Jeyaraman, R. in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 9–83.

expected to be *hemi-aminals*,[252] but these compounds are generally unstable. In addition, many imines with a hydrogen on the nitrogen spontaneously polymerize.[253]

In contrast to ammonia, primary, secondary, and tertiary amines can add to aldehydes[254] and ketones to give different kinds of products. Primary amines give imines[255] and secondary amines give enamines (for reactions, see **10-69**).[256] Such imines are stable enough for isolation, but, in some cases, especially with simple R groups, they rapidly decompose or polymerize unless there is at least one aryl group on the nitrogen or the carbon. When there is an aryl group, the compounds are quite stable, they are usually called *Schiff bases*, and this reaction is the best way to prepare them.[257] Even sterically hindered imines can be prepared.[258] The initial *N*-substituted hemi-aminals[259] lose water to give the stable Schiff bases.

In general, ketones react more slowly than aldehydes, and higher temperatures and longer reaction times are often required.[260] In addition, the equilibrium must often be shifted, usually by removal of the water. This can be done either azeotropically by distillation or with a drying agent, such as a molecular sieve.[261] Imines have been formed from aldehydes and amines in an ionic liquid.[262]

Heating a primary alcohol and a primary amine with a Mn catalyst led to dehydrogenative coupling to form aldimines.[263] The Co-catalyzed[264] and an Fe-catalyzed[265] coupling of alcohols and amines to give imines has been reported. *N*-Acyl enamides[266] were prepared from ketones by reaction with *N*,*N*,*N*′,*N*′-tetrakis(2-hydroxyethyl)ethylenediamine using a Ti catalyst, NEt_3/Ac_2O, and workup with ammonium hydroxide.[267]

[252] These compounds have been detected by 13C NMR: Chudek, J.A.; Foster, R.; Young, D. *J. Chem. Soc., Perkin Trans. 2* ***1985***, 1285.

[253] Methanimine CH2=NH is stable in solution for several hours at −95 °C, but rapidly decomposes at −80 °C: Braillon, B.; Lasne, M.C.; Ripoll, J.L.; Denis, J.M. *Nouv. J. Chim.* ***1982***, *6*, 121. See also, Bock, H.; Dammel, R. *Chem. Ber.* ***1987***, *120*, 1961.

[254] For a review of the reactions between amines and formaldehyde, see Farrar, W.V. *Rec. Chem. Prog.* ***1968***, *29*, 85. For a synthesis of imines, see Kwon, M.S.; Kim, S.; Park, S.; Bosco, W.; Chidrala, R.K.; Park, J. *J. Org. Chem.* ***2009***, *74*, 2877.

[255] See Dayagi, S.; Degani, Y. in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 64–83; Reeves, R.L. in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, ***1966***, pp. 600–614. Also see Guzen, K.P.; Guarezemini, A.S.; Órfão, A.T.G.; Cella, R.; Pereira, C.M.P.; Stefani, H.A. *Tetrahedron Lett.* ***2007***, *48*, 1845.

[256] See Davis, L.O.; Putri, M.A.; Meyer, C.I.; Durant, C.P. *Tetrahedron Lett.* ***2014***, *55*, 3100.

[257] See Lai, J.T. *Tetrahedron Lett.* ***2002***, *43*, 1965.

[258] Love, B.E.; Ren, J. *J. Org. Chem.* ***1993***, *58*, 5556.

[259] See Forlani, L.; Marianucci, E.; Todesco, P.E. *J. Chem. Res. (S)* ***1984***, 126.

[260] See Eisch, J.J.; Sanchez, R. *J. Org. Chem.* ***1986***, *51*, 1848.

[261] See Roelofsen, D.P.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* ***1972***, *91*, 605.

[262] Andrade, C.K.Z.; Takada, S.C.S.; Alves, L.M.; Rodrigues, J.P.; Suarez, P.A.Z.; Branda, R.F.; Soares, V.C.D. *Synlett* ***2004***, 2135.

[263] Mukherjee, A.; Nerush, A.; Leitus, G.; Shimon, L.J.W.; David, Y.B.; Jalapa, N.A.E.; Milstein, D. *J. Am. Chem. Soc.* ***2016***, *138*, 4298.

[264] Zhang, G.; Hanson, S.K. *Org. Lett.* ***2013***, *15*, 650.

[265] Zhang, E.; Tian, H.; Xu, S.; Yu, X.; Xu, Q. *Org. Lett.* ***2013***, *15*, 2704.

[266] For a discussion of nucleophilicity parameters, see Maji, B.; Lakhdar, S.; Mayr, H. *Chem. Eur. J.* ***2012***, *18*, 5732.

[267] Reeves, J.T.; Tan, Z.; Han, Z.S.; Li, G.; Zhang, Y.; Xu, Y.; Reeves, D.C.; Gonnella, N.C.; Ma, S.; Lee, H.; Lu, B.Z.; Senanayake, C.H. *Angew. Chem. Int. Ed.* ***2012***, *51*, 1400.

The reaction of secondary amines with ketones leads to enamines (see **10-69** for the *Stork enamine reaction*).[268] When secondary amines are added to aldehydes or ketones, the initially formed *N*,*N*-disubstituted hemi-aminals cannot lose water since *the iminium ion intermediate does not have a proton on nitrogen*, and in some cases it is possible to isolate them.[269] However, they are generally highly reactive, and under the reaction conditions usually react further. If no α hydrogen is present, a hemi-aminal is converted to the more stable *aminal*.[270] However, if an α hydrogen is present, water or RNH_2 can be lost in that direction to give an enamine.[271] This is the most common method for the preparation of enamines[272] and usually takes place when an aldehyde or ketone containing an α hydrogen is treated with a secondary amine.[273] The water is usually removed azeotropically or with a drying agent,[274] and molecular sieves can also be used.[275] Stable primary enamines have also been prepared.[276] Enamino ketones have been prepared from diketones and secondary amines using low molecular weight amines in water,[277] or using microwave irradiation on silica gel.[278] Enamines have been prepared by the reaction of an aldehyde, using AgI in an ionic liquid,[279] CuI with microwave irradiation,[280] or a Au catalyst.[281] Tertiary amines can only give salts.

The reaction is often used to effect ring closure[282] and in the formation of heterocycles.[283] The *Friedländer quinoline synthesis*[284] is an example where *ortho* alkenyl aniline derivatives give the quinoline.[285] 3-Haloquinolines have been prepared from α-halo ketones.[286] Pyrylium ions react with ammonia or primary amines to give pyridinium ions[287] (see **10-57**). Primary amines react with 1,4-diketones, with microwave

[268] See Hodgson, D.M.; Bray, C.D.; Kindon, N.D.; Reynolds, N.J.; Coote, S.J.; Um, J.M.; Houk, K.N. *J. Org. Chem.* ***2009***, *74*, 1019.
[269] See Duhamel, P.; Cantacuzène, J. *Bull. Soc. Chim. Fr.* ***1962***, 1843.
[270] Duhamel, P. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 849–907.
[271] See Haynes, L.W.; Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, pp. 103–163; Pitacco, G.; Valentin, E. in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 623–714.
[272] See Katritzky, A.R.; Long, Q.; Lue, P.; Jozwiak, A. *Tetrahedron* ***1990***, *46*, 8153.
[273] Bélanger, G.; Doré, M.; Ménard, F.; Darsigny, V. *J. Org. Chem.* ***2006***, *71*, 7481.
[274] See Nilsson, A.; Carlson, R. *Acta Chem. Scand. Ser. B* ***1984***, *38*, 523.
[275] See Carlson, R.; Nilsson, A.; Strömqvist, M. *Acta Chem. Scand. Ser. B* ***1983***, *37*, 7.
[276] Erker, G.; Riedel, M.; Koch, S.; Jödicke, T.; Würthwein, E.-U. *J. Org. Chem.* ***1995***, *60*, 5284.
[277] Stefani, H.A.; Costa, I.M.; Silva, D. de O. *Synthesis* ***2000***, 1526.
[278] Rechsteiner, B.; Texier-Boullet, F.; Hamelin, J. *Tetrahedron Lett.* ***1993***, *34*, 5071.
[279] Li, Z.; Wei, C.; Chen, L.; Varma, R.S.; Li, C.-J. *Tetrahedron Lett.* ***2004***, *45*, 2443.
[280] Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A. *Org. Lett.* ***2004***, *6*, 1001.
[281] Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* ***2003***, *125*, 9584.
[282] For a review, see Katritzky, A.R.; Ostercamp, D.L.; Yousaf, T.I. *Tetrahedron* ***1987***, *43*, 5171.
[283] Majumdar, K.C.; De, N.; Ghosh, T.; Roy, B. *Tetrahedron* ***2014***, *70*, 4827.
[284] Cheng, C.; Yan, S. *Org. React.* ***1982***, *28*, 37. See Reddy, B.V.S.; Venkateswarlu, A.; Reddy, G.N.; Reddy, Y.V.R. *Tetrahedron Lett.* ***2013***, *54*, 5767; Luo, L.; Zhou, Z.; Zhu, J.; Lu, X.; Wang, H. *Tetrahedron Lett.* ***2016***, *57*, 4987; Shen, Q.; Wang, L.; Yu, J.; Liu, M.; Qiu, J.; Fang, L.; Guo, F.; Tang, J. *Synthesis* ***2012***, *44*, 389; Ma, F.-P.; Cheng, G.-T.; He, Z.-G.; Zhang, Z.-H. *Aust. J. Chem.* ***2012***, *65*, 409.
[285] See Yadav, J.S.; Reddy, B.V.S.; Premalatha, K. *Synlett* ***2004***, 963.
[286] Ryabukhin, S.V.; Naumchik, V.S.; Plaskon, A.S.; Grygorenko, O.O.; Tolmachev, A.A. *J. Org. Chem.* ***2011***, *76*, 5774.
[287] See Zvezdina, E.A.; Zhadonva, M.P.; Dorofeenko, G.N. *Russ. Chem. Rev.* ***1982***, *51*, 469.

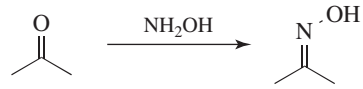
irradiation, to give *N*-substituted pyrroles.[288] Similar reactions in the presence of Montmorillonite KSF[289] or by simply heating the components with tosic acid[290] have been reported. Pyrroles were formed by the iodine-catalyzed reaction of α-amino carbonyl compounds and aldehydes.[291] Heating cyclic amines such as 1,2,3,4-tetrahydroisoquinoline with acetic acid or with 2-ethylhexanoic acid led to regiodivergent annulation reactions with 4-nitrobutyraldehydes.[292] The intramolecular addition of the nitrogen of an amide moiety to a distal carbonyl led to a lactam via reaction with $Al(OTf)_3$ and Et_3SiH.[293] The reaction of an aldehyde and an amine with poly(2-methoxyaniline-5-sulfonic acid)/gold nanoparticles gave the imine in aqueous media.[294] The reaction of aldehydes with RNH_2 used tris(2,2,2-trifluoroethyl)borate [$B(OCH_2CF_3)_3$ to prepare the corresponding imines, including *N*-sulfinyl,[295] *N*-toluenesulfonyl, *N*-(dimethylamino)sulfamoyl, *N*-diphenylphosphinoyl, *N*-(α-methylbenzyl), and *N*-(4-methoxyphenyl) aldimines.[296] *N*-Sulfonyl imines have bee prepared using chloramine-T and an organocatalyst in aqueous media.[297]

The condensation of a 1,4-dicarbonyl compound with an excess of a primary amine or ammonia to give a pyrrole is known as the *Paal-Knorr pyrrole synthesis*.[298] The mechanism involves formation of an imine *in situ*.[299] Furans and thiophenes are produced by reaction with alcohols and an acid catalyst[300] or P_4S_{10}[301] to give the furan in the *Paal-Knorr furan synthesis* or the thiophene in the *Paal-Knorr thiophene synthesis*. The Paal-Knorr reaction has been done in deep eutectic solvents.[302] The reaction has been shown to be catalyzed by MgI_2-etherate, chemoselectively.[303] The Paal-Knorr pyrrole synthesis has been done under flow conditions (Sec. 7.D).[304]

OS **I**, 80, 355, 381; **II**, 31, 49, 65, 202, 231, 422; **III**, 95, 328, 329, 332, 358, 374, 513, 753, 827; **IV**, 210, 605, 638, 824; **V**, 191, 277, 533, 567, 627, 703, 716, 736, 758, 808, 941, 1070; **VI**, 5, 448, 474, 496, 520, 526, 592, 601, 818, 901, 1014; **VII**, 8, 135, 144, 473; **VIII**, 31, 132, 403, 451, 456, 493, 586, 597. Also see, OS **IV**, 283, 464; **VII**, 197; **VIII**, 104, 112, 241.

[288] Danks, T.N. *Tetrahedron Lett.* ***1999***, *40*, 3957.
[289] Banik, B.K.; Samajdar, S.; Banik, I. *J. Org. Chem.* ***2004***, *69*, 213.
[290] Klappa, J.J.; Rich, A.E.; McNeill, K. *Org. Lett.* ***2002***, *4*, 435.
[291] Yan, R.; Kang, X.; Zhou, X.; Li, X.; Liu, X.; Xiang, L.; Li, Y.; Huang, G. *J. Org. Chem.* ***2014***, *79*, 465.
[292] Kang, Y.K.; Chen, W.; Breugst, M.; Seidel, D. *J. Org. Chem.* ***2015***, *80*, 9628.
[293] Qi, J.; Sun, C.; Tian, Y.; Wang, X.; Li, G.; Xiao, Q.; Yin, D. *Org. Lett.* ***2014***, *16*, 190.
[294] Amaya, T.; Ito, T.; Hiraom T. *Tetrahedron Lett.* ***2013***, *54*, 2409.
[295] See Visco, M.D.; Reeves, J.T.; Marsini, M.A.; Volchkov, I.; Busacca, C.A.; Mattson, A.E.; Senanayake, C.H. *Tetrahedron Lett.* ***2016***, *57*, 1903; Sanaboina, C.; Jana, S.; Eppakayala, L. *Synlett* ***2014***, *25*, 1006.
[296] Reeves, J.T.; Visco, M.D.; Marsini, M.A.; Grinberg, N.; Busacca, C.A.; Mattson, A.E.; Senanayake, C.H. *Org. Lett.* ***2015***, *17*, 2442.
[297] Chawla, R.; Singh, A.K.; Yadav, L.D.S. *Tetrahedron Lett.* ***2014***, *55*, 3553. See Ortiz, P.; Collados, J.F.; Harutyunyan, S.R. *Eur. J. Org. Chem.* ***2016***, 1247.
[298] Paal, C. *Ber. Deutsch. Chemisch Gesell.* ***1884***, *17*, 2756; Knorr, L. *Ber. Deutsch. Chemisch Gesell.* ***1884***, *17*, 2863.
[299] Amarnath, V.; Anthony, D.C.; Amarnath, K.; Valentine, W.M.; Wetterau, L.A.; Graham, D.G. *J. Org. Chem.* ***1991***, *56*, 6924.
[300] Gilchrist, T.L. *Heterocyclic Chemistry*, Harlow: Longman Scientific, ***1987***.
[301] Campaigne, E.; Foye, W.O. *J. Org. Chem.* ***1952***, *17*, 1405.
[302] Handy, S.; Lavender, K. *Tetrahedron Lett.* ***2013***, *54*, 4377.
[303] Zhang, X.; Weng, G.; Zhang, Y.; Li, P. *Tetrahedron* ***2015***, *71*, 2595.
[304] Cranwell, P.B.; O'Brien, M.; Browne, D.L.; Koos, P.; Polyzos, A.; Peña-López, M.; Ley, S.V. *Org. Biomol. Chem.* ***2012***, *10*, 5774.

16-13 The Addition of Hydrazine Derivatives to Carbonyl Compounds



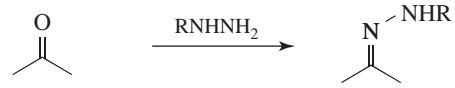
This section can be categorized as the preparation of functionalized imines, $R_2C{=}N{-}X$. When X = OH, the compound is an oxime, and when $X = NR_2$, the compound is a hydrazone. Oximes can be prepared by the addition of hydroxylamine (NH_2OH) to aldehydes or ketones. Derivatives of hydroxylamine [e.g., H_2NOSO_3H and $HON(SO_3Na)_2$] have also been used. For hindered ketones, such as 2,2,4,4-tetramethylpentan-3-one, high pressures (as high as 10 000 atm) may be necessary.[305] The reaction of hydroxylamine with unsymmetrical ketones or with aldehydes leads to a mixture of (*E*) and (*Z*) isomers. For aromatic aldehydes, heating with K_2CO_3 led to the (*E*) isomer whereas heating with $CuSO_4$ gave the (*Z*)-hydroxylamine.[306] Hydroxylamines react with ketones in ionic liquids.[307] Metal-mediated and metal-catalyzed synthesis of oximes are known.[308]

It has been shown[309] that the maximum rate of oxime formation is at a pH that depends on the substrate but is usually ~4. The rate decreases as the pH is either raised or lowered from this point (a bell-shaped curve). In Sec. 16.A.i, bell-shaped curves like this were shown to be caused by changes in the rate-determining step in many cases. In this case, at low pH values, loss of water to form the C=N moiety is rapid (because it is acid catalyzed), and the initial acyl addition of hydroxylamine to the carbonyl carbon is slow (and rate determining), because under these acidic conditions most of the NH_2OH molecules have been converted to the conjugate $^+NH_3OH$ ions, which cannot attack the substrate. As the pH is slowly increased, the fraction of free NH_2OH molecules increases and, consequently, so does the reaction rate, until the maximum rate is reached at around pH 4. As the rising pH causes an increase in the rate of acyl addition, it also causes a *decrease* in the rate of the acid-catalyzed loss of water. This latter process has not yet affected the overall rate since loss of water is much faster than the acyl addition. However, when the pH goes above ~4, loss of water *does* become rate determining although the rate of acyl addition is still increasing, as it will until essentially all the NH_2OH is unprotonated. Since loss of water now determines the rate, and is slowed by the decrease in acid concentration, the overall rate decreases as the pH rises beyond ~4. It is likely that similar considerations apply to the reaction of aldehydes and ketones with amines, hydrazines, and other nitrogen nucleophiles.[310] It is noted that the intermediate, HO—C—NHOH,[311] has been detected by NMR in the reaction between NH_2OH and acetaldehyde.[312] *O*-Methyl oximes were prepared from the reaction of ketones with *N*,*O*-*bis*-trimethylsilyl-*N*-methoxy carbamate, giving a mixture of *syn* and

[305] Jones, W.H.; Tristram, E.W.; Benning, W.F. *J. Am. Chem. Soc.* ***1959***, *81*, 2151.
[306] Sharghi, H.; Sarvari, M.H. *Synlett* ***2001***, 99.
[307] Ren, R.X.; Ou, W. *Tetrahedron Lett.* ***2001***, *42*, 8445.
[308] Bolotin, D.S.; Bokach, N.A.; Demakova, M.Ya.; Kukushkin, V.Yu. *Chem. Rev.* ***2017***, *117*, 13039.
[309] Jencks, W.P. *J. Am. Chem. Soc.* ***1959***, *81*, 475; *Prog. Phys. Org. Chem.* ***1964***, *2*, 63.
[310] See Cockerill, A.F.; Harrison, R.G.in Patai, S. *The Chemistry of Functional Groups, Supplement A*, pt. 1, Wiley, NY, ***1977***, pp. 288–299. For isotope effect studies, see Rossi, M.H.; Stachissini, A.S.; do Amaral, L. *J. Org. Chem.* ***1990***, *55*, 1300.
[311] See Sayer, J.M.; Edman, C. *J. Am. Chem. Soc.* ***1979***, *101*, 3010.
[312] Cocivera, M.; Effio, A. *J. Am. Chem. Soc.* ***1976***, *98*, 7371.

anti isomers.[313] Aldehydes are reported to react with hydroxylamine using NaOH under solvent-free mechanochemical conditions.[314]

OS **I**, 318, 327; **II**, 70, 204, 313, 622; **III**, 690, **IV**, 229; **V**, 139, 1031; **VII**, 149. See also, OS **VI**, 670.



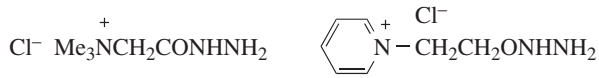
The product of condensation of a hydrazine and an aldehyde or ketone is called a *hydrazone*. Hydrazine itself gives hydrazones only with aryl ketones. With other aldehydes and ketones, either no useful product can be isolated, or the remaining NH_2 group condenses with a second equivalent of carbonyl compound to give an *azine*, ArCH═N─N═CHAr. This type of product is especially important for aromatic aldehydes. However, in some cases azines can be converted to hydrazones by treatment with excess hydrazine and NaOH.[315] Arylhydrazines, especially phenyl, *p*-nitrophenyl, and 2,4-dinitrophenyl,[316] are used much more often and give the corresponding hydrazones with most aldehydes and ketones.[317] Since these are usually solids, they make excellent derivatives to assist compound identification, and were commonly employed for this purpose in the past before the advent of modern spectroscopy methods. Cyclic hydrazones are known,[318] as are conjugated hydrazones.[319] Alkenes react with CO/H_2, phenylhydrazine, and a diphosphine catalyst to give a regioisomeric mixture of phenylhydrazones that favored "anti-Markovnikov" addition.[320] Oximes are converted to hydrazones with water and hydrazine in refluxing ethanol.[321]

The preparation of Boc-, Bz-, Ts-, and Fmoc-protected hydrazones from carbonyl compounds and the corresponding hydrazine used a ball-mill.[322] Anthranilic acids and aminobenzoic acids act as superior catalysts for oxime or hydrazone formation by the reaction of aldehydes and oxime esters or hydrazine derivatives.[323] The reaction of pyrrolidine and aldehydes generated an iminium salt that reacted with hydroxylamine to give the oxime, and hydrazones were also prepared.[324]

α-Hydroxy aldehydes and ketones and α-dicarbonyl compounds give *osazones*, in which two adjacent carbons have carbon–nitrogen double bonds: RNH─N═C─C═N─NHR. Osazones are particularly important in carbohydrate chemistry. The *osazone test*[325] with phenylhydrazine is used to test for the presence of sugars with an adjacent stereogenic carbon. In contrast to this behavior, β-diketones and β-keto esters give *pyrazoles* and *pyrazolones*, respectively. No azines are formed under these conditions. Other hydrazine derivatives frequently used to prepare the corresponding hydrazone are semicarbazide

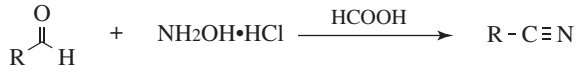
[313] Kardon, F.; Mörtl, M.; Csámpai, A.; Újsászy, K.; Knausz, D. *Synth. Commun.* ***2010–2011***, *41*, 914.
[314] Aakeröy, C.B.; Sinha, A.S.; Epa, K.N.; Spartz, C.L.; Desper, J. *Chem. Commun.* ***2012***, *48*, 11289.
[315] See Day, A.C.; Whiting, M.C. *Org. Synth.* VI, 10.
[316] See Behforouz, M.; Bolan, J.L.; Flynt, M.S. *J. Org. Chem.* ***1985***, *50*, 1186.
[317] For a review of arylhydrazones, see Buckingham, J. *Q. Rev. Chem. Soc.* ***1969***, *23*, 37.
[318] Nakamura, E.; Sakata, G.; Kubota, K. *Tetrahedron Lett.* ***1998***, *39*, 2157.
[319] Palacios, F.; Aparicio, D.; de los Santos, J.M. *Tetrahedron Lett.* ***1993***, *34*, 3481.
[320] Ahmed, M.; Jackstell, R.; Seayad, A.M.; Klein, H.; Beller, M. *Tetrahedron Lett.* ***2004***, *45*, 869.
[321] Pasha, M.A.; Nanjundaswamy, H.M. *Synth. Commun.* ***2004***, *34*, 3827.
[322] Nun, P.; Martin, C.; Martinez, J.; Lamaty, F. *Tetrahedron* ***2011***, *67*, 8187.
[323] Crisalli, P.; Kool, E.T. *J. Org. Chem.* ***2013***, *78*, 1184.
[324] Morales, S.; Aceña, J.L.; Ruano, J.L.G.; Cid, M.B. *J. Org. Chem.* ***2016***, *81*, 10016.
[325] See Mester, L.; El Khadem, H.; Horton, D. *J. Chem. Soc. C* ***1970***, 2567.

($NH_2NHCONH_2$), in which case the hydrazone product is called a semicarbazone: *Girard's reagents T* and *P* are hydrazones that are water soluble because of the ionic group. Girard's reagents are often used for the purification of carbonyl compounds.[326]



OS **II**, 395; **III**, 96, 351; **IV**, 351, 377, 536, 884; **V**, 27, 258, 747, 929; **VI**, 10, 12, 62, 242, 293, 679, 791; **VII**, 77, 438. Also see, OS **III**, 708; **VI**, 161; **VIII**, 597.

16-14 The Conversion of Aldehydes to Nitriles



Aldehydes can be converted to nitriles in one step by treatment with hydroxylamine hydrochloride and either formic acid,[327] $KF\text{-}Al_2O_3$,[328] or $NaHSO_4 \bullet SiO_2$ with microwave irradiation.[329] Heating in *N*-methylpyrrolidinone (NMP) is also effective with aryl aldehydes[330] and so is heating on dry alumina with an aliphatic aldehyde.[331] The reaction is a combination of **16-13** and **17-27**. Direct nitrile formation has also been accomplished with certain derivatives of NH_2OH, notably, NH_2OSO_2OH.[332] Treatment with hydroxylamine and NaI[333] or certain carbonates[334] also converts aldehydes to the nitrile. Another method involves treatment with hydrazoic acid, although the *Schmidt reaction* (**18-16**) may compete.[335] Microwave irradiation has been used with $NH_2OH \bullet HCl$ and another reagent, which includes phthalic anhydride[336] or H-Y zeolite.[337] The reaction of an aldehyde with hydroxylamine followed by diethyl cholorophosphate ($EtOPOCl_2$) gives the nitrile.[338] Heating with hydroxylamine in DMSO[339] and using hydroxylamine and oxalyl chloride[340] have been used. *tert*-Butanesulfinyl imines are also used for the conversion of aldehydes to nitriles.[341]

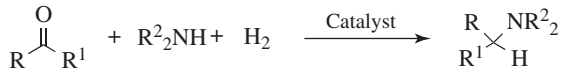
[326] See Stachissini, A.S.; Do Amaral, L. *J. Org. Chem.* ***1991***, *56*, 1419.
[327] Olah, G.A.; Keumi, T. *Synthesis* ***1979***, 112.
[328] Movassagh, B.; Shokri, S. *Tetrahedron Lett.* ***2005***, *46*, 6923.
[329] Das, B.; Ramesh, C.; Madhusudhan, P. *Synlett* ***2000***, 1599.
[330] Kumar, H.M.S.; Reddy, B.V.S.; Reddy, P.T.; Yadav, J.S. *Synthesis* ***1999***, 586; Chakraborti, A.K.; Kaur, G. *Tetrahedron* ***1999***, *55*, 13265.
[331] Sharghi, H.; Sarvari, M.H. *Tetrahedron* ***2002***, *58*, 10323.
[332] Streith, J.; Fizet, C.; Fritz, H. *Helv. Chim. Acta* ***1976***, *59*, 2786.
[333] Ballini, R.; Fiorini, D.; Palmieri, A. *Synlett* ***2003***, 1841.
[334] Bose, D.S.; Goud, P.R. *Synth. Commun.* ***2002***, *32*, 3621.
[335] See Neunhoeffer, H.; Diehl, W.; Karafiat, U. *Liebigs Ann. Chem.* ***1989***, 105.
[336] Veverková, E.; Toma, Š. *Synth. Commun.* ***2000***, *30*, 3109.
[337] Srinivas, K.V.N.S.; Reddy, E.B.; Das, B. *Synlett* ***2002***, 625.
[338] Zhu, J.-L.; Lee, F.-Y.; Wu, J.-D.; Kuo, C.-W.; Shia, K.-S. *Synlett* ***2007***, 1317.
[339] Chill, S.T.; Mebane, R.C. *Synth. Commun.* ***2009***, *39*, 3601.
[340] Movassagh, B.; Fazeli, A. *Synth. Commun.* ***2007***, *37*, 625.
[341] Tanuwidjaja, J.; Peltier, H.M.; Lewis, J.C.; Schenkel, L.B.; Ellman, J.A. *Synthesis* ***2007***, 3385.

The reaction of a conjugated aldehyde with ammonia, CuCl, and 50% H_2O_2 gave the conjugated nitrile.[342] Reaction of aldehydes with IBX (*o*-iodoxybenzoic acid) and liquid ammonia gives the nitrile.[343] Tetrabutylammonium tribromide in aqueous ammonia has also been used.[344]

Aldehydes were converted to nitriles by the reaction with *O*-(diphenylphosphinyl) hydroxylamine by heating in toluene.[345] Benzaldehydes reacted with ammonium acetate and a catalytic amount of 4-acetamido-2,2,6,6-tetramethylpiperidine-*N*-oxyl, $NaNO_2$, and HNO_3, and following aerobic oxidation under an O_2 balloon gave the nitrile.[346] Aldehydes were converted to the nitrile by reaction with *O*-(4-CF_3-benzoyl)-hydroxylamine with the assistance of a Brønsted acid.[347] Hydroxylamine *O*-sulfonic acid in acidic water has also been used.[348] The conversion of aldehydes to nitriles in DMSO has been reported,[349] and so has heating in glycerol.[350] Aldehydes reacted with $K_4Fe(CN)_6$ in water, with *Aloe vera*-mediated Ag nanoparticles as a catalyst, to give the nitrile.[351] Nitriles were prepared from aldehydes by reaction with an oxoammonium salt (4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate) and hexamethyldisilazane (HMDS).[352]

OS **V**, 656.

16-15 Reductive Alkylation of Ammonia or Amines: Reductive Amination or Reductive Amidation

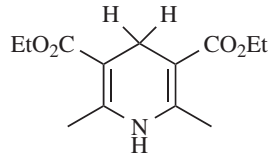


When an aldehyde or a ketone is treated with ammonia or a primary or secondary amine in the presence of hydrogen gas and an appropriate catalyst such as Rh or Ir (heterogeneous or homogeneous),[353] *reductive alkylation* of ammonia or the amine (or *reductive amination* of the carbonyl compound) takes place.[354] The reaction can formally be regarded as occurring by addition of the amine to the carbonyl to give an iminium salt (**16-31**), followed by reduction of the C═N unit (**19-46**) in the intermediate to give the amine product:[355] The reagents

[342] Erman, M.B.; Snow, J.W.; Williams, M.J. *Tetrahedron Lett.* ***2000***, *41*, 6749.
[343] Arote, N.D.; Bhalerao, D.S.; Akamanchi, K.G. *Tetrahedron Lett.* ***2007***, *48*, 3651. Also see Zhu, C.; Ji, L.; Wei, Y. *Synthesis* ***2010***, 3121.
[344] Zhu, Y.-Z.; Cai, C. *Monat. Chem.* ***2010***, *141*, 637.
[345] Laulhé, S.; Gori, S.S.; Nantz, M.H. *J. Org. Chem.* ***2012***, *77*, 9334.
[346] Noh, J.-H.; Kim, J. *J. Org. Chem.* ***2015***, *80*, 11624.
[347] An, X.-D.; Yu, S. *Org. Lett.* ***2015***, *17*, 5064.
[348] Quinn, D.J.; Haun, G.J.; Moura-Letts, G. *Tetrahedron Lett.* ***2016***, *57*, 3844.
[349] Augustine, J.K.; Bombrun, A.; Atta, R.N. *Synlett* ***2011***, *22*, 2223.
[350] Ingale, A.P.; Patil, S.M.; Shinde, S.V. *Tetrahedron. Lett.* ***2017***, *58*, 4845.
[351] Das, V.K.; Harsh, S.N.; Karak, N. *Tetrahedron Lett.* ***2016***, *57*, 549.
[352] Kelly, C.B.; Lambert, K.M.; Mercadante, M.A.; Ovian, J.M.; Bailey, W.F.; Leadbeater, N.E. *Angew. Chem. Int. Ed.* ***2015***, *54*, 4241.
[353] See Kadyrov, R.; Riermeier, T.H.; Dingerdissen, U.; Tararov, V.; Börner, A. *J. Org. Chem.* ***2003***, *68*, 4067; Chi, Y.; Zhou, Y.-G.; Zhang, X. *J. Org. Chem.* ***2003***, *68*, 4120.
[354] See Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 82–93; Klyuev, M.V.; Khidekel, M.L. *Russ. Chem. Rev.* ***1980***, *49*, 14; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 291–303.
[355] Le Bris, A.; Lefebvre, G.; Coussemant, F. *Bull. Soc. Chim. Fr.* ***1964***, 1366, 1374, 1584, 1594.

used to reduce the C═N intermediate include other reducing agents.[356] Rather than hydrogen and a catalyst, reducing agents include boranes,[357] triethylsilane with an Ir[358] or an In catalyst,[359] zinc and HCl, or Zn (with formaldehyde for reductive methylation).[360] Several hydride reducing agents can be used, including $NaBH_4$,[361] $NaBH_4/H_3BO_4$,[362] borohydride-exchange resin (BER),[363] $LiBH_4$,[364] $ZrBH_4$,[365] $NaBH_3CN$,[366] or sodium triacetoxyborohydride.[367]

For ammonia and primary amines there are two possible pathways: (i) reduction of the imine intermediate or (ii) hydrogenolysis of a hydroxy amine intermediate. However, when secondary amines are involved, only the hydrogenolysis pathway (**19-59**) is possible; the OH unit is replaced by H to give the amine directly. The reaction is compatible with amino acids, giving the *N*-alkylated amino acid.[368] A *Hantzsch dihydropyridine* in conjunction with a Sc catalyst has been used,[369] and the use of a *Hantzsch ester* (**15**) in a reductive amination is sometimes called a hydrogen bond-catalyzed reaction.[370]



15

The reaction of an aldehyde and an amine in propan-2-ol, in the presence of Ni nanoparticles, involves reductive amination via hydrogen transfer.[371] Primary amines have been prepared from many aldehydes with at least five carbons and from many ketones by treatment with ammonia and a reducing agent. Smaller aldehydes are usually too reactive to permit isolation of the primary amine.

[356] For a list of many of these, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 835–840.

[357] Nugent, T.C.; El-Shazly, M.; Wakchaure, V.N. *J. Org. Chem.* ***2008***, *73*, 1297. For a reaction using ammonia-borane, see Ramachandran, P.V.; Gagare, P.D.; Sakavuyi, K.; Clark, P. *Tetrahedron Lett.* ***2010***, *51*, 3167.

[358] Lee, O.-Y.; Law, K.-L.; Ho, C.-Y; Yang, D. *J. Org. Chem.* ***2008***, *73*, 8829.

[359] Lee, O.-Y.; Law, K.-L.; Yang, D. *Org. Lett.* ***2009***, *11*, 3302.

[360] da Silva, R.A.; Estevam, I.H.S.; Bieber, L.W. *Tetrahedron Lett.* ***2007***, *48*, 7680.

[361] Gribble, G.W.; Nutaitis, C.F. *Synthesis* ***1987***, 709. For the use of an ionic liquid/water system, see Nagaiah, K.; Kumar, V.N.; Rao, R.S.; Reddy, B.V.S.; Narsaiah, A.V.; Yadav, J.S. *Synth. Commun.* ***2006***, *36*, 3345. With $NiCl_2$, see Saxena, I.; Borah, R.; Sarma, J.C. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 503.

[362] This is a solvent-free reaction: see Cho, B.T.; Kang, S.K. *Synlett* ***2004***, 1484.

[363] Yoon, N.M.; Kim, E.G.; Son, H.S.; Choi, J. *Synth. Commun.* ***1993***, *23*, 1595.

[364] Cabral, S.; Hulin, B.; Kawai, M. *Tetrahedron Lett.* ***2007***, *48*, 7134.

[365] Heydari, A.; Khaksar, S.; Esfandyari, M.; Tajbakhsh, M. *Tetrahedron* ***2007***, *63*, 3363.

[366] Mattson, R.J.; Pham, K.M.; Leuck, D.J.; Cowen, K.A. *J. Org. Chem.* ***1990***, *55*, 2552. See Barniol-Xicota, M.; Turcu, A.L.; Codony, S.; Escolano, C.; Vázquez, S. *Tetrahedron Lett.* ***2014***, *55*, 2548. See also, Grenga, P.N.; Sumbler, B.L.; Beland, F.; Priefer, R. *Tetrahedron Lett.* ***2009***, *50*, 6658.

[367] Abdel-Magid, A.F.; Carson, K.G.; Harris, B.D.; Maryanoff, C.A.; Shah, R.D. *J. Org. Chem.* ***1996***, *61*, 3849.

[368] Song, Y.; Sercel, A.D.; Johnson, D.R.; Colbry, N.L.; Sun, K.-L.; Roth, B.D. *Tetrahedron Lett.* ***2000***, *41*, 8225.

[369] Itoh, T.; Nagata, K.; Miyazaki, M.; Ishikawa, H.; Kurihara, A.; Ohsawa, A. *Tetrahedron* ***2004***, *60*, 6649.

[370] Menche, D.; Hassfeld, J.; Li, J.; Menche, G.; Ritter, A.; Rudolph, S. *Org. Lett.* ***2006***, *8*, 741.

[371] Alonso, F.; Riente, P.; Yus, M. *Synlett* ***2008***, 1289.

Aldehydes and primary amines react with allylic halides, in the presence of Zn dust, to give a homoallylic secondary amine.[372] Reductive monoalkylation of nitroarenes used aldehydes as alkylating agents, H_2 as a reducing agent, and PtO_2 as a catalyst in methanol.[373] The reductive amination of carbonyl compounds with aromatic amines using stannous chloride gave tertiary amines while using inexpensive polymethylhydrosiloxane as reducing agent in methanol.[374] The reaction of ketones and amines led to reductive amination when treated with CO and a Ru catalyst, to give the amine.[375] The reaction of an alkyl cyclopropyl ketone with an amine and CO with a Rh catalyst gave the reductive amination product, whereas a Ru catalyst gave a pyrrolidine via ring expansion.[376] The reductive amination of aldehydes used $NaBH_4$ in the presence of an Fe catalyst.[377] Reductive amination of ketones or aldehydes with amines using triethylsilane and a Bi catalyst gave the amine.[378]

Reductive amination of ketones has been reported using flow conditions (Sec. 7.D).[379] Propargylamines were prepared by the coupling reaction of alkynyl carboxylic acids with amines and paraformaldehyde in water at 140 °C, using a continuous flow reaction system (Sec. 7.D).[380] Amines were prepared from cyclic ketones by use of ω-transaminases.[381] Amines reacted with aldehydes or ketones using a Ru catalyst and CO to give the amine.[382] The Ru-catalyzed reductive amination reaction has been extensively studied.[383] The reductive amination of ketones with electron-deficient anilines gave the amine derivative, using BH_3·THF/AcOH/CH_2Cl_2, which required longer reaction times, or BH_2·THF/TMSCl/DMF or $NaBH_4$/TMSCl/DMF, when the reaction was complete in less than an hour.[384]

Reductive amination of amine with dimethyl carbonate using $PhSiH_3$ and a Pt catalyst gave the tertiary amine.[385] With a hydrogen source, reductive amination of carbonyl compounds used a Ni/Al alloy in water.[386] Tertiary amines were formed by the Ru-catalyzed reductive *N*-benzylation of imines by reaction with benzyl bromide derivatives using $PhSiH_3$.[387] The reaction of ketones with a new amine dehydrogenase gave chiral (*R*)-1,3-dimethylbutylamines.[388]

The reductive amination of aldehydes or ketones in the presence of ammonia catalyzed by unsupported ultra-thin Pt nanowires gave the secondary amine.[389] Two equivalents of

[372] Fan, R.; Pu, D.; Qin, L.; Wen, F.; Yao, G.; Wu, J. *J. Org. Chem.* ***2007***, *72*, 3149.
[373] Sreedhar, B.; Rawat, V.S. *Synth. Commun.* ***2012***, *42*, 2490.
[374] Nayal, O.S.; Bhatt, V.; Sharma, S.; Kumar, N. *J. Org. Chem.* ***2015***, *80*, 5912.
[375] Kolesnikov, P.N.; Yagafarov, N.Z.; Usanov, D.L.; Maleev, V.I.; Chusov, D. *Org. Lett.* ***2015***, *17*, 173.
[376] Afanasyev, O.I.; Tsygankov, A.A.; Usanov, D.L.; Chusov, D. *Org. Lett.* ***2016***, *18*, 5968.
[377] Kumar, N.U.; Reddy, B.S.; Reddy, V.P.; Bandichhor, R. *Tetrahedron Lett.* ***2012***, *53*, 4354.
[378] Matsumura, T.; Nakada, M. *Tetrahedron Lett.* ***2014***, *55*, 1829.
[379] Falus, P.; Boros, Z.; Hornyánszky, G.; Nagy, J.; Darvas, F.; Ürge, L.; Poppe, L. *Tetrahedron Lett.* ***2011***, *52*, 1310.
[380] Jung, B.; Park, K.; Song, K.H.; Lee, S. *Tetrahedron Lett.* ***2015***, *56*, 4697.
[381] Richter, N.; Simon, R.C.; Lechner, H.; Froutil, W.; Ward, J.M.; Hailes, H.C. *Org. Biomol. Chem.* ***2015***, *13*, 8843.
[382] Chusov, D.; List, B. *Angew. Chem. Int. Ed.* ***2014***, *53*, 5199.
[383] Strotman, N.A.; Baxter, C.A.; Brands, K.M.J.; Cleator, E.; Krska, S.W.; Reamer, R.A.; Wallace, D.J.; Wright, T.J. *J. Am. Chem. Soc.* ***2011***, *133*, 8362.
[384] Pletz, J.; Berg, B.; Breinbauer, R. *Synthesis* ***2016***, *48*, 1301.
[385] Li, Y.; Sorribes, I.; Vicent, C.; Junge, K.; Beller, M. *Chem. Eur. J.* ***2015***, *21*, 16759.
[386] Schäfer, C.; Nişanci, B.; Bere, M.P.; Daştan, A.; Török, B. *Synthesis* ***2016***, *48*, 3127.
[387] Li, B.; Yu, J.; Li, C.; Li, Y.; Luo, J.; Shao, Y. *Tetrahedron Lett.* ***2017***, *58*, 137.
[388] Abrahamson, M.J.; Vázquez-Figueroa, E.; Woodall, N.B.; Moore, J.C.; Bommarius, A.S. *Angew. Chem. Int. Ed.* ***2012***, *51*, 3969.
[389] Qi, F.; Hu, L.; Lu, S.; Cao, X.; Gu, H. *Chem. Commun.* ***2012***, *48*, 9631.

ketone and an amine gave the hindered tertiary amine when treated with 50 atm of CO, MS 4 Å, and a Rh catalyst.[390] Aldehydes reacted with primary amines using a Pd/NiO (nickel oxide) catalyst and H_2 to give the primary amine. The Ir-catalyzed reductive alkylation reaction of primary or secondary amines with carboxylic acids gave the amine product in the presence of a silane reductant.[391]

Formic acid is an effective reagent for reductive amination[392] in what is called the *Wallach reaction*. Secondary amines react with formaldehyde and NaH_2PO_3 to give the *N*-methylated tertiary amine[393] and microwave irradiation has also been used.[394] In the particular case where primary or secondary amines are reductively methylated with formaldehyde and formic acid, the method is called the *Eschweiler-Clarke procedure*. Heating with paraformaldehyde and oxalyl chloride has been used to give the same result.[395] It is possible to use ammonium (or amine) salts of formic acid,[396] or formamides, as a substitute for the *Wallach conditions*. This method is called the *Leuckart reaction*,[397] and in this case the products obtained are often the *N*-formyl derivatives of the amines instead of the free amines. A Rh-catalyzed variation has been reported.[398] Heating aldehydes and ketones with secondary amines and ammonium carbonate in a modified Leuckart reaction gave the tertiary amine.[399] The reductive amination of allylic alcohols via reaction with amines and formic acid, with a Ru catalyst, gave the saturated amine.[400] The Cu-catalyzed reductive methylation gave the methylamine product in the reaction of a secondary amine with formic acid; $PhSiH_3$ was the reductant.[401] Amines were prepared by the reaction of benzaldehyde and amines, catalyzed by Pd nanoparticles stabilized by a zwitterionic surfactant and using formate salts as hydrogen donors in aqueous isopropyl alcohol.[402]

Enantioselective reductive amination reactions are known, generating chiral amines. Ketones and anilines react in the presence of an organocatalyst and a catalytic amount of a chiral phosphoric acid to give the chiral amine.[403] The reaction of an aldehyde with a chiral amine initiated a reaction that gave a chiral primary amine.[404] An Yb-catalyzed reaction with a ketone gave a chiral secondary amine.[405] Aldehydes react with *N*-diphenylphosphinoylimines and Et_2Zn, in the presence of a chiral Cu precatalyst, to give

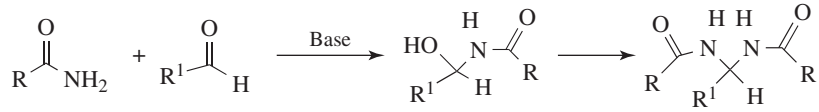
[390] Yagafarov, N.Z.; Kolesnikov, P.N.; Usanov, D.L.; Novikov, V.V.; Nelyubina, Y.V.; Chusov, D. *Chem. Commun.* ***2016***, *52*, 1397.
[391] Andrews, K.G.; Summers, D.M.; Donnelly, L.J.; Denton, R.M. *Chem. Commun.* ***2016***, *52*, 1855.
[392] For a microwave-induced reaction, see Torchy, S.; Barbry, D. *J. Chem. Res. (S)* ***2001***, 292.
[393] Davis, B.A.; Durden, D.A. *Synth. Commun.* ***2000***, *30*, 3353.
[394] Barbry, D.; Torchy, S. *Synth. Commun.* ***1996***, *26*, 3919.
[395] Rosenau, T.; Potthast, A.; Röhrling, J.; Hofinger, A.; Sixxa, H.; Kosma, P. *Synth. Commun.* ***2002***, *32*, 457.
[396] For a review of ammonium formate in organic synthesis, see Ram, S.; Ehrenkaufer, R.E. *Synthesis* ***1988***, 91. See Byun, E.; Hong, B.; De Castro, K.A.; Lim, M.; Rhee, H. *J. Org. Chem.* ***2007***, *72*, 9815.
[397] Leukart, R. *Ber.* ***1885***, 18, 2341; Moore, M.L. *Org. React.* ***1949***, *5*, 301; Pollard, C.B.; Young Jr., D.C. *J. Org. Chem.* ***1951***, *16*, 661. See Lejon, T.; Helland, I. *Acta Chem. Scand.* ***1999***, *53*, 76.
[398] Kitamura, M.; Lee, D.; Hayashi, S.; Tanaka, S.; Yoshimura, M. *J. Org. Chem.* ***2002***, *67*, 8685. See Riermeier, T.H.; Dingerdissen, U.; Börner, A. *Org. Prep. Proceed. Int.* ***2004***, *36*, 99.
[399] O'Connor, D.; Lauria, A.; Bondi, S.P.; Saba, S. *Tetrahedron Lett.* ***2011***, *52*, 129.
[400] Sahli, Z.; Sundararaju, B.; Achard, M.; Bruneau, C. *Org. Lett.* ***2011***, *13*, 3964.
[401] Qiao, C.; Liu, X.-F.; Liu, X.; He, L.-N. *Org. Lett.* ***2017***, *19*, 1490. See Guyon, C.; Duclos, M.-C.; Métay, E.; Lemaire, M. *Tetrahedron Lett.* ***2016***, *57*, 3002.
[402] Drinkel, E.E.; Campedelli, R.R.; Manfredi, A.M.; Fiedler, H.D.; Nome, F. *J. Org. Chem.* ***2014***, *79*, 2574.
[403] Storer, R.I.; Carrera, D.E.; Ni, Y.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2006***, *128*, 84. See Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* ***2006***, *128*, 13074.
[404] Sugiura, M.; Mori, C.; Kobayashi, S. *J. Am. Chem. Soc.* ***2006***, *128*, 11038.
[405] Nugent, T.C.; El-Shazly, M.; Wakchaure, V.N. *J. Org. Chem.* ***2008***, *73*, 1297.

a chiral amine.[406] Asymmetric biocatalytic reductive amination reactions are known.[407] Asymmetric reductive amination has been attempted using a *Hantzsch ester*-mediated reaction.[408]

Alkylation of an imine formed *in situ* is also possible.[409] Reductive alkylation has also been carried out on nitro, nitroso, azo, and other compounds that are reduced *in situ* to primary or secondary amines. Reductive amidation has been reported using a Ni catalyst for reaction of isocyanates with phenolic tosylates or benzylic pivalates to give the corresponding amide.[410]

OS **I**, 347, 528, 531; **II**, 503; **III**, 328, 501, 717, 723; **IV**, 603; **V**, 552; **VI**, 499; **VII**, 27.

16-16 The Addition of Amides to Aldehydes



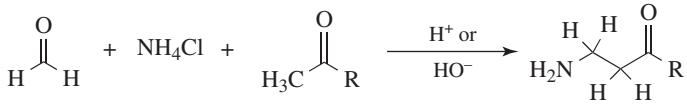
Amides can add to aldehydes in the presence of bases (so the nucleophile is actually $RCONH^-$) or acids to give acylated amino alcohols, which often react further to give alkylidene or arylidene bisamides.[411] If the R^1 group contains an α hydrogen, water may split out.

Sulfonamides add to aldehydes to give the *N*-sulfonyl imine. Benzaldehyde reacts with $TsNH_2$, for example, with trifluoroacetic anhydride (TFAA) in CH_2Cl_2 at reflux,[412] or with $TiCl_4$ in dichloroethane at reflux,[413] to give the *N*-tosylimine, Ts—N═CHPh. In a similar manner, the reaction of $TolSO_2Na$ and $PhSO_2Na$ with an aldehyde in aqueous formic acid gives the *N*-phenylsulfonyl imine.[414] The reaction of an aldehyde with Ph_3P═NTs and a Ru catalyst gives the *N*-tosyl imine.[415]

Primary and secondary amines add to ketenes to give, respectively, *N*-substituted and *N*,*N*-disubstituted amides[416] and add to ketenimines to give amidines, R_2N—C(R)═N—R.[417]

[406] Côté, A.; Charette, A.B. *J. Org. Chem.* ***2005***, *70*, 10864.
[407] Koszelewski, D.; Lavandera, I.; Clay, D.; Guebitz, G.M.; Rozzell, D.; Kroutil, W. *Angew. Chem. Int. Ed.* ***2008***, *47*, 9337.
[408] Wakchaure, V.N.; Nicoletti, M.; Ratjen, L.; List, B. *Synlett* ***2010***, 2708. See Nguyen, Q.P.B.; Kim, T.H. *Tetrahedron* ***2013***, *69*, 4938; Zhao, P.P.; Zhou, X.-F.; Dai, J.J.; Xu, H.J. *Org. Biomol. Chem.* ***2014***, *12*, 9092.
[409] See Yadav, J.S.; Reddy, B.V.S.; Raju, A.K. *Synthesis* ***2003***, 883.
[410] Correa, A.; Martin, R. *J. Am. Chem. Soc.* ***2014***, *136*, 7253.
[411] Challis, B.C.; Challis, J.A. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 754–759; Zaugg, H.E.; Martin, W.B. *Org. React.* ***1965***, *14*, 52 (pp. 91–95, 104–112); Gilbert, E.E. *Synthesis* ***1972***, 30.
[412] Lee, K.Y.; Lee, C.G.; Kim, J.N. *Tetrahedron Lett.* ***2003***, *44*, 1231.
[413] Ram, R.N.; Khan, A.A. *Synth. Commun.* ***2001***, *31*, 841.
[414] Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* ***2000***, 75.
[415] Jain, S.L.; Sharma, V.B.; Sain, B. *Tetrahedron Lett.* ***2004***, *45*, 4341.
[416] Tidwell, T.T. *Acc. Chem. Res.* ***1990***, *23*, 273; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975***, *4*, 231. For an enantioselective reaction, see Hodous, B.L.; Fu, G.C. *J. Am. Chem. Soc.* ***2002***, *124*, 10006.
[417] Stevens, C.L.; Freeman, R.C.; Noll, K. J. *Org. Chem.* ***1965***, *30*, 3718.

16-17 The Mannich Reaction



In the *Mannich reaction*, formaldehyde (or sometimes another aldehyde) is condensed with ammonia, in the form of its salt, and a compound containing an active hydrogen.[418] This can formally be considered as an addition of ammonia to give H_2NCH_2OH, followed by a nucleophilic substitution. The reaction can be carried out with salts of primary or secondary amines[419] or with amides,[420] rather than ammonia, in which cases the product is substituted on the nitrogen. The product is referred to as a *Mannich base*. The imine can be generated *in situ*. The reaction of a ketone, formaldehyde, and diethylamine with microwave irradiation gave the Mannich product, a β-amino ketone.[421] Arylamines do not normally give the reaction, but hydrazines can be used.[422] Vinylogous Mannich reactions are known[423] (see Sec. 6.B for vinylogy).

The Mannich base product can react further in three ways. If it is a primary or secondary amine, it may condense with one or two additional molecules of aldehyde and an active compound, to give $HN(CH_2CH_2COR)_2$ or $N(CH_2CH_2COR)_3$. If the active hydrogen compound has two or three active hydrogen atoms, the Mannich base may condense with one or two additional molecules of aldehyde and ammonia or amine. Another reaction consists of condensation of the Mannich base with excess formaldehyde to give an imine. Sometimes it is possible to obtain these products of further condensation as the main products of the reaction. At other times they are side products. When the Mannich base contains an amino group β to a carbonyl (and it usually does), ammonia is easily eliminated. This is a route to α,β-unsaturated aldehydes, ketones, esters, and so on.

Studies of the reaction kinetics have led to several proposals for the mechanism of the Mannich reaction.[424] The base-catalyzed reaction involves reaction with an enolate anion, whereas the acid-catalyzed reaction involves formation of an iminium ion, which reacts with an enol. There is kinetic evidence for the intermediacy of the iminium ion.[425]

When an unsymmetrical ketone is used as the active-hydrogen component, two products are possible. Regioselectivity has been obtained by treatment of the ketone with preformed iminium ions:[426] the use of $Me_2N^+{=}CH_2\ CF_3COO^-$ in CF_3COOH gives substitution at the more highly substituted position, while with $(i\text{-}Pr)_2N^+{=}CH_2\ ClO_4^-$ the reaction takes place at the less highly substituted position.[427] The preformed iminium compound

[418] Tramontini, M.; Angiolini, L. *Tetrahedron* ***1990***, *46*, 1791; Gevorgyan, G.A.; Tramontini, M. *Synthesis* ***1973***, 703; House, H.O. *Modern Synthetic Reactions*, 2nd ed.; W.A. Benjamin, NY, ***1972***, pp. 654–660; Gevorgyan, G.A.; Agababyan, A.G.; Mndzhoyan, O.L. *Russ. Chem. Rev.* ***1985***, *54*, 495.

[419] Agababyan, A.G.; Gevorgyan, G.A.; Mndzhoyan, O.L. *Russ. Chem. Rev.* ***1982***, *51*, 387.

[420] Hellmann, H. *Angew. Chem.* ***1957***, *69*, 463; *Newer Methods Prep. Org. Chem.* ***1963***, *2*, 277.

[421] Gadhwal, S.; Baruah, M.; Prajapati, D.; Sandhu, J.S. *Synlett* ***2000***, 341.

[422] El Kaim, L.; Grimaud, L.; Perroux, Y.; Tirla, C. *J. Org. Chem.* ***2003***, *68*, 8733.

[423] Bur, S.; Martin, S.F. *Tetrahedron* ***2001***, *57*, 3221; Martin, S.F. *Acc. Chem. Res.* ***2002***, *35*, 895.

[424] Cummings, T.F.; Shelton, J.R. *J. Org. Chem.* ***1960***, *25*, 419.

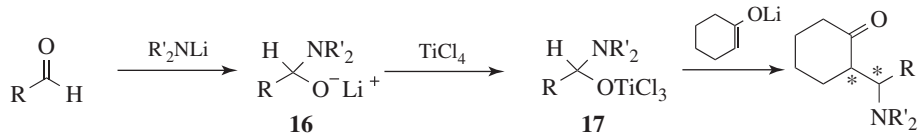
[425] Benkovic, S.J.; Benkovic, P.A.; Comfort, D.R. *J. Am. Chem. Soc.* ***1969***, *91*, 1860.

[426] Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem. Int. Ed.* ***1971***, *10*, 330.

[427] Jasor, Y.; Luche, M.; Gaudry, M.; Marquet, A. *J. Chem. Soc., Chem. Commun.* ***1974***, 253; Gaudry, M.; Jasor, Y.; Khac, T.B. *Org. Synth.* VI, 474.

dimethyl(methylene)ammonium iodide $CH_2{=}N^+Me_2\ I^-$, called *Eschenmoser's salt*,[428] has also been used in Mannich reactions.[429] The analogous chloride salt has been condensed with an imine to give a β,β′-dimethylamino ketone after acid hydrolysis.[430]

Another type of preformed reagent (**17**) has been used to carry out diastereoselective Mannich reactions. The lithium salts **16** are treated with $TiCl_4$ to give **17**, which is then treated with the enolate anion of a ketone.[431] The Pd-catalyzed Mannich reaction of enol ethers to imines is also known.[432] The reaction of silyl enol ethers and imines[433] is catalyzed by HBF_4 in aqueous methanol.[434] Similarly, silyl enol ethers react with aldehydes and aniline in the presence of $InCl_3$ to give the β-amino ketone.[435]



16 **17**

Enantioselective Mannich reactions are known.[436] Chiral catalysts are commonly used,[437] including proline,[438] proline derivatives or proline analogs,[439] other chiral amines,[440] a Pybox-La catalyst,[441] chiral aminosulfonamides,[442] or *Cinchona* alkaloids.[443] Other organocatalysts have been used.[444] Chiral Brønsted acids are also used as catalysts,[445] and also chiral ammonium salts.[446] Chiral diamine[447] or phosphine imine[448] ligands have

[428] Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem. Int. Ed.* ***1971***, *10*, 330.
[429] See Bryson, T.A.; Bonitz, G.H.; Reichel, C.J.; Dardis, R.E. *J. Org. Chem.* ***1980***, *45*, 524, and references cited therein.
[430] Arend, M.; Risch, N. *Tetrahedron Lett.* ***1999***, *40*, 6205.
[431] Seebach, D.; Schiess, M.; Schweizer, W.B. *Chimia* ***1985***, *39*, 272. See also, Katritzky, A.R.; Harris, P.A. *Tetrahedron* ***1990***, *46*, 987.
[432] See Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* ***1999***, *121*, 5450.
[433] See Fujisawa, H.; Takahashi, E.; Mukaiyama, T. *Chem. Eur. J.* ***2006***, *12*, 5082.
[434] Akiyama, T.; Takaya, J.; Kagoshima, H. *Tetrahedron Lett.* ***2001***, *42*, 4025.
[435] Loh, T.-P.; Wei, L.L. *Tetrahedron Lett.* ***1998***, *39*, 323.
[436] See Córdova, A. *Acc. Chem. Res.* ***2004***, *37*, 102; Marques, M.M.B. *Angew. Chem. Int. Ed.* ***2006***, *45*, 348; Amedjkouh, M.; Brandberg, M. *Chem. Commun.* ***2008***, 3043.
[437] See Karimi, B.; Enders, D.; Jafari, E. *Synthesis* ***2013***, *45*, 2769; Rachwalski, M.; Leenders, T.; Kaczmarczyk, S.; Kiełbasiński, P.; Lesniak, S.; Rutjes, F.P.J.T. *Org. Biomol. Chem.* ***2013***, *11*, 4207.
[438] See Yang, J.W.; Stadler, M.; List, B. *Angew. Chem. Int. Ed.* ***2007***, *46*, 609.
[439] Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas, III, C.F. *J. Am. Chem. Soc.* ***2006***, *128*, 9630. See also, Hayashi, Y.; Aratake, S.; Imai, Y.; Hibino, K.; Chen, Q.-Y.; Yamaguchi, J.; Uchimaru, T. *Chem. Asian J.* ***2008***, *3*, 225.
[440] Haurena, C.; LeGall, E.; Sengmany, S.; Martens, T. *Tetrahedron* ***2010***, *66*, 9902.
[441] Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2007***, *129*, 9588; Cutting, G.A.; Stainforth, N.E.; John, M.P.; Kociok-Köhn, G.; Willis, M.C. *J. Am. Chem. Soc.* ***2007***, *129*, 10632.
[442] See Kano, T.; Hato, Y.; Yamamoto, A.; Maruoka, K. *Tetrahedron* ***2008***, *64*, 1197.
[443] Wei, Y.; He, W.; Liu, Y.; Liu, P.; Zhang, S. *Org. Lett.* ***2012***, *14*, 704; Johnson, K.M.; Rattley, M.S.; Sladojevich, F.; Barber, D.M.; Nuñez, M.G.; Goldys, A.M.; Dixon, D.J. *Org. Lett.* ***2012***, *14*, 2492.
[444] Perera, S.; Sinha, D.; Rana, N.K.; Trieu-Do, V.; Zhao, J.C.-G. *J. Org. Chem.* ***2013***, *78*, 10947; Kano, T.; Yurino, T.; Maruoka, K. *Angew. Chem. Int. Ed.* ***2013***, *52*, 11509; Arai, T.; Matsumura, E. *Synlett* ***2014***, *25*, 1776.
[445] Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* ***2007***, *129*, 6756; Ávila, E.P.; Justo, R.M.S.; Gonçalves, V.P.; Pereira, A.A.; Diniz, R.; Amarante, G.W. *J. Org. Chem.* ***2015***, *80*, 590.
[446] Uraguchi, D.; Koshimoto, K.; Ooi, T. *J. Am. Chem. Soc.* ***2008***, *130*, 10878.
[447] Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* ***2002***, *124*, 5640; Trost, B.M.; Terrell, C.R. *J. Am. Chem. Soc.* ***2003***, *125*, 338.
[448] Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2007***, *129*, 500.

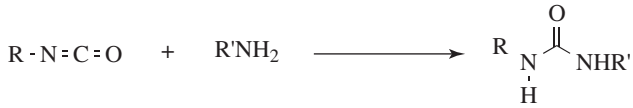
been used, as have chiral dinuclear zinc compounds[449] and chiral silver enolates.[450] Chiral auxiliaries on the carbonyl fragment can be used.[451] Chiral imines, in the form of chiral hydrazones, have been used with silyl enol ethers and a Sc catalyst.[452] Chiral amines react with silyl enol ethers, with an $InCl_3$ catalyst in ionic liquids, to give the Mannich product with good enantioselectivity.[453] A chiral thiourea catalyst has been used with a vinylogous Mannich reaction.[454]

The reaction of nitroalkanes and amines, usually in the presence of a metal catalyst such as CuBr,[455] has been called the nitro-Mannich reaction.[456] An asymmetric nitro-Mannich reaction used a Cu/Sm,[457] Cu,[458] Zn,[459] or a chiral thiourea catalyst.[460] An intramolecular nitro-Mannich gave tetrahydroquinolines.[461] Mannich-type reactions of nitrones, oximes, and hydrazones are known.[462] A β-coupling of cyclic ketones with imines used a synergistic combination of photoredox and organocatalysts that used DABCO as both a base and an electron-transfer agent to give coupling of transient β-enaminyl radicals with persistent α-amino radicals to give γ-amino ketones.[463]

Also see, **11-22**.

OS **III**, 305; **IV**, 281, 515, 816; **VI**, 474, 981, 987; **VII**, 34. See also, OS **VIII**, 358.

16-18 The Addition of Amines to Isocyanates



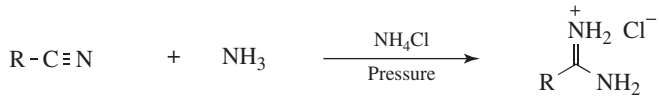
Ammonia and primary and secondary amines can be added to isocyanates[464] to give substituted ureas.[465] Isothiocyanates give thioureas.[466] This is an excellent method for the preparation of ureas and thioureas, and these compounds are often used as derivatives for primary and secondary amines. Isocyanic acid (HN═C═O) also gives the reaction; usually its salts

[449] Trost, B.M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* ***2006***, *128*, 2778.
[450] Yanagisawa, A.; Lin, Y.; Miyake, R.; Yoshida, K. *Org. Lett.* ***2014***, *16*, 86.
[451] Hata, S.; Iguchi, M.; Iwasawa, T.; Yamada, K.-i.; Tomioka, K. *Org. Lett.* ***2004***, *6*, 1721.
[452] Jacobsen, M.F.; Ionita, L.; Skrydstrup, T. *J. Org. Chem.* ***2004***, *69*, 4792.
[453] Sun, W.; Xia, C.-G.; Wang, H.-W. *Tetrahedron Lett.* ***2003***, *44*, 2409.
[454] Liu, T.-Y.; Cui, J.-L.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *J. Am. Chem. Soc.* ***2007***, *129*, 1878. See Roselló, M.S.; del Pozo, C.; Fustero, S. *Synthesis* ***2016***, *48*, 2553.
[455] Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* ***2005***, *127*, 3672.
[456] Noble, A.; Anderson, J.C. *Chem. Rev.* ***2013***, *113*, 2887. Lu, N.; Li, R.; Wei, Z.; Cao, J.; Liang, D.; Lin, Y.; Duan, H. *J. Org. Chem.* ***2017***, *82*, 4668.
[457] Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2007***, *129*, 4900.
[458] Anderson, J.C.; Howell, G.P.; Lawrence, R.M.; Wilson, C.S. *J. Org. Chem.* ***2005***, *70*, 5665.
[459] Anderson, J.C.; Blake, A.J.; Koovits, P.J.; Stepney, G.J. *J. Org. Chem.* ***2012***, *77*, 4711.
[460] Wang, C.-J.; Dong, X.-Q.; Zhang, Z.-H.; Xue, Z.-Y.; Teng, H.-L. *J. Am. Chem. Soc.* ***2008***, *130*, 8606. See Huang, W.; Peng, C.; Guo, L.; Hu, R.; Han, B. *Synlett* ***2011***, *22*, 2984.
[461] Anderson, J.C.; Noble, A.; Torres, P.R. *Tetrahedron Lett.* ***2012***, *53*, 5707.
[462] Merino, P.; Tejero, T. *Synlett* ***2011***, *22*, 1965.
[463] Jeffrey, J.L.; Petronijević, F.R.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2015***, *137*, 8404.
[464] For the mechanism, see Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975***, *4*, 231.
[465] See Vishnyakova, T.P.; Golubeva, I.A.; Glebova, E.V. *Russ. Chem. Rev.* ***1985***, *54*, 249.
[466] Herr, R.J.; Kuhler, J.L.; Meckler, H.; Opalka, C.J. *Synthesis* ***2000***, 1569.

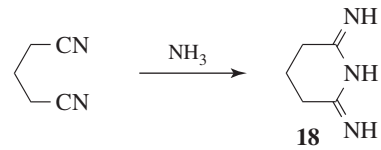
(e.g., NaNCO) are used. Wöhler's famous synthesis of urea involved the addition of ammonia to cyanic acid (HO—C═N).[467]

OS **II**, 79; **III**, 76, 617, 735; **IV**, 49, 180, 213, 515, 700; **V**, 555, 801, 802, 967; **VI**, 936, 951; **VIII**, 26.

16-19 The Addition of Ammonia or Amines to Nitriles



Unsubstituted amidines (in the form of their salts) can be prepared by addition of ammonia to nitriles.[468] Many amidines have been made in this way. Dinitriles of suitable chain length can give imidines such as **18**.[469]



18

Primary and secondary amines can be used instead of ammonia, to give substituted amidines, but only if the nitrile contains electron-withdrawing groups; for example, Cl_3CCN gives the reaction. Ordinary nitriles do not react, and, in fact, acetonitrile is often used as a solvent in this reaction.[470] The addition of ammonia to cyanamide (NH_2CN) gives guanidine, $(NH_2)_2C{=}NH$. Guanidines can also be formed from amines.[471] The Cu-catalyzed cross-coupling reaction of amidine salts and aryl iodides gave monoarylated amidines.[472] The *N*-arylation of amidines and *N*,*N*-disubstituted amidines was accomplished by reaction of *o*-silylaryl triflate with CsF.[473] If water is present, in the presence of a Ru[474] or a Pt catalyst,[475] the addition of a primary or secondary amine to a nitrile gives an amide.

OS **I**, 302 [but also see, OS **V**, 589]; **IV**, 245, 247, 515, 566, 769. See also, OS **V**, 39.

[467] See Shorter, J. *Chem. Soc. Rev.* ***1978***, *7*, 1. See also, Williams, A.; Jencks, W.P. *J. Chem. Soc., Perkin Trans. 2* ***1974***, 1753, 1760; Hall, K.J.; Watts, D.W. *Aust. J. Chem.* ***1977***, *30*, 781, 903.

[468] For reviews of amidines, see Granik, V.G. *Russ. Chem. Rev.* ***1983***, *52*, 377; Gautier, J.; Miocque, M.; Farnoux, C.C. in Patai, S. *The Chemistry of Amidines and Imidates*, Wiley, NY, ***1975***, pp. 283–348.

[469] Elvidge, J.A.; Linstead, R.P.; Salaman, A.M. *J. Chem. Soc.* ***1959***, 208.

[470] Grivas, J.C.; Taurins, A. *Can. J. Chem.* ***1961***, *39*, 761.

[471] Dräger, G.; Solodenko, W.; Messinger, J.; Schön, U.; Kirschning, A. *Tetrahedron Lett.* ***2002***, *43*, 1401.

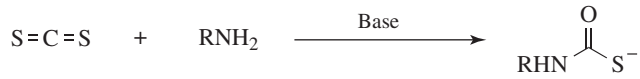
[472] Cortes-Salva, M.; Garvin, C.; Antilla, J.C. *J. Org. Chem.* ***2011***, *76*, 1456.

[473] Yao, T. *Tetrahedron Lett.* ***2015***, *56*, 4623.

[474] Murahashi, S.; Naota, T.; Saito, E. *J. Am. Chem. Soc.* ***1986***, *108*, 7846.

[475] Cobley, C.J.; van den Heuvel, M.; Abbadi, A.; de Vries, J.G. *Tetrahedron Lett.* ***2000***, *41*, 2467.

16-20 The Addition of Amines to Carbon Disulfide and Carbon Dioxide



Salts of dithiocarbamic acid can be prepared by the addition of primary or secondary amines to carbon disulfide.[476] This reaction is similar to **16-9**. Hydrogen sulfide can be eliminated from the product, directly or indirectly, to give isothiocyanates (RNCS). Isothiocyanates can be obtained directly by the reaction of primary amines and CS_2 in pyridine in the presence of dicyclohexylcarbodiimide.[477] A tosyl chloride-mediated preparation of isothiocyanates is also known.[478] Aniline derivatives react with CS_2 and NaOH, and then ethyl chloroformate, to give the aryl isothiocyanate.[479] In the presence of diphenyl phosphite and pyridine, primary amines add to CO_2 and to CS_2 to give, respectively, symmetrically substituted ureas and thioureas.[480] Isoselenoureas, $R_2NC(=NR^1)SeR^2$, can also be formed.[481]

OS **I**, 447; **III**, 360, 394, 599, 763; **V**, 223.

E. Halogen Nucleophiles

16-21 The Formation of *gem*-Dihalides from Aldehydes and Ketones

Aliphatic aldehydes and ketones can be converted to *gem*-dichlorides[482] by treatment with PCl_5. The reaction fails for perhalo ketones.[483] If the aldehyde or ketone has an α-hydrogen, elimination of HCl may follow. A vinylic chloride is a frequent side product,[484] or even the main product.[485] *gem*-Dichlorides can be prepared by reacting an aldehyde with $BiCl_3$.[486] Phosphorus pentabromide (PBr_5) does not give good yields of *gem*-dibromides,[487] but dibromides can be obtained from aldehydes by the use of Br_2 and triphenyl phosphite.[488]

[476] Dunn, A.D.; Rudorf, W. *Carbon Disuphide in Organic Chemistry*, Ellis Horwood, Chichester, ***1989***, pp. 226–315; Katritzky, A.R.; Faid-Allah, H.; Marson, C.M. *Heterocycles* ***1987***, *26*, 1657; Katritzky, A.R.; Marson, C.M.; Faid-Allah, H. *Heterocycles* ***1987***, *26*, 1333.

[477] See Molina, P.; Alajarin, M.; Arques, A. *Synthesis* ***1982***, 596.

[478] Wong, R.; Dolman, S.J. *J. Org. Chem.* ***2007***, *72*, 3969.

[479] Li, Z.; Qian, X.; Liu, Z.; Li, Z.; Song, G. *Org. Prep. Proceed. Int.* ***2000***, *32*, 571.

[480] Fournier, J.; Bruneau, C.; Dixneuf, P.H.; Lécolier, S. *J. Org. Chem.* ***1991***, *56*, 4456. See Chiarotto, I.; Feroci, M. *J. Org. Chem.* ***2003***, *68*, 7137; Lemoucheux, L.; Rouden, J.; Ibazizene, M.; Sobrio, F.; Lasne, M.-C. *J. Org. Chem.* ***2003***, *68*, 7289.

[481] Asanuma, Y.; Fujiwara, S.-i.; Shi-ike, T.; Kambe, N. *J. Org. Chem.* ***2004***, *69*, 4845.

[482] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 719–722.

[483] Farah, B.S.; Gilbert, E.E. *J. Org. Chem.* ***1965***, *30*, 1241.

[484] See Nikolenko, L.N.; Popov, S.I. *J. Gen. Chem. USSR* ***1962***, *32*, 29.

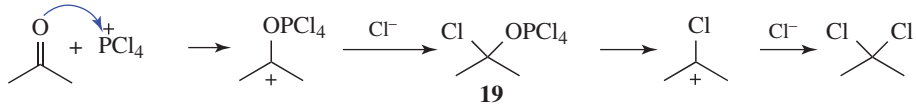
[485] See Newman, M.S.; Fraenkel, G.; Kirn, W.N. *J. Org. Chem.* ***1963***, *28*, 1851.

[486] Kabalka, G.W.; Wu, Z. *Tetrahedron Lett.* ***2000***, *41*, 579.

[487] See Napolitano, E.; Fiaschi, R.; Mastrorilli, E. *Synthesis* ***1986***, 122.

[488] Hoffmann, R.W.; Bovicelli, P. *Synthesis* ***1990***, 657. See also, Lansinger, J.M.; Ronald, R.C. *Synth. Commun.* ***1979***, *9*, 341.

The mechanism of *gem*-dichloride formation involves initial attack on PCl_4^+ (which is present in solid PCl_5) by the carbonyl oxygen, followed by addition of Cl^- to the carbon.[489] This chloride ion may come from PCl_6^- (which is also present in solid PCl_5). There follows a two-step S_N1 process. Alternatively, **19** can be converted to the product without going through the chlorocarbenium ion, by an S_Ni process.



19

Many aldehydes and ketones have been converted to *gem*-difluoro compounds with sulfur tetrafluoride SF_4.[490] Quinones give 1,1,4,4-tetrafluorocyclohexadiene derivatives. With ketones, yields can be raised and the reaction temperature lowered, by the addition of anhydrous HF.[491] Carboxylic acids, acyl chlorides, and amides react with SF_2 to give 1,1,1-trifluorides. In these cases the first product is the acyl fluoride, and *gem*-difluorination gave RCF_3. The acyl fluoride can be isolated. Carboxylic esters also give trifluorides, but more vigorous conditions are required. In this case the carbonyl group of the ester is attacked first, and RCF_2OR' can be isolated from RCO_2R'[492] and then converted to the trifluoride. Anhydrides can react in either manner. Both types of intermediate are isolable under the right conditions, and SF_4 even converts carbon dioxide to CF_4. A disadvantage of reactions with SF_4 is that they require a pressure vessel lined with stainless steel. Selenium tetrafluoride SeF_4 gives similar reactions, but atmospheric pressure and ordinary glassware can be used.[493] Another reagent that is often used to convert aldehydes and ketones to *gem*-difluorides is the commercially available diethylaminosulfur trifluoride (DAST, Et_2NSF_3), and CF_2Br_2 in the presence of zinc.[494] The mechanism with SF_4 is probably similar in general nature, if not in specific detail, to that with PCl_5. The α,α-difluorination of acid chlorides was reported.[495] The synthesis of α,α-difluorohalo esters has been reported via ynol ethers.[496]

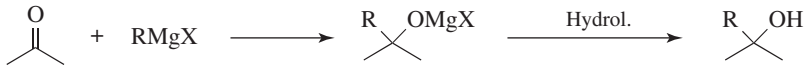
In a related process, α-halo ethers can be prepared by treatment of aldehydes and ketones with an alcohol and HX. The reaction is applicable to aliphatic aldehydes and ketones and to primary and secondary alcohols. The addition of HX to an aldehyde or ketone gives α-halo alcohols, which are usually unstable, although exceptions are known, especially with perfluoro and perchloro species.[497]

OS **II**, 549; **V**, 365, 396, 1082; **VI**, 505, 845; **VIII**, 247. Also see, OS **I**, 506. For α-halo ethers, see OS **I**, 377; **IV**, 101 (see, however, OS **V**, 218), 748; **VI**, 101.

[489] Newman, M.S. *J. Org. Chem.* ***1969***, *34*, 741.
[490] Wang, C.J. *Org. React.* ***1985***, *34*, 319; Boswell Jr., G.A.; Ripka, W.C.; Scribner, R.M.; Tullock, C.W. *Org. React.* ***1974***, *21*, 1.
[491] Muratov, N.N.; Mohamed, N.M.; Kunshenko, B.V.; Burmakov, A.I.; Alekseeva, L.A.; Yagupol'skii, L.M. *J. Org. Chem. USSR* ***1985***, *21*, 1292.
[492] See Bunnelle, W.H.; McKinnis, B.R.; Narayanan, B.A. *J. Org. Chem.* ***1990***, *55*, 768.
[493] Olah, G.A.; Nojima, M.; Kerekes, I. *J. Am. Chem. Soc.* ***1974***, *96*, 925.
[494] Hu, C.-M.; Qing, F.-L.; Shen, C.-X. *J. Chem. Soc., Perkin Trans. 1* ***1993***, 335.
[495] Bloom, S.; Scerba, M.T.; Erb, J.; Lectka, T. *Org. Lett.* ***2011***, *13*, 5068.
[496] Hu L.; Che, C.; Tan, Z.; Zhu, G. *Chem. Commun.* ***2015***, *51*, 16641.
[497] For example, see Clark, D.R.; Emsley, J.; Hibbert, F. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 1107.

F. Attack at Carbon by Organometallic Compounds[498]

16-22 The Addition of Grignard or Organolithium Reagents to Aldehydes and Ketones



Halo organomagnesium compounds, commonly known as *Grignard reagents* (RMgX), are formed by the reaction of alkyl, vinyl, or aryl halides with magnesium metal, usually in ether solvents such as diethyl ether or THF (**12-37**). Halogen/Mg exchange can generate a Grignard reagent by reaction of aryl halides with reactive aliphatic Grignard reagents.[499] Microwave irradiation has been used to facilitate the formation of Grignard reagents from aryl chlorides that are slow to react otherwise.[500] Grignard reactions have been done using ionic liquids.[501] When a Grignard reagent was formed in the "phase vanishing" solvent system of diethyl ether, magnesium, perfluoro polyether, and iodoalkane, subsequent addition to carbonyl compounds in the ether layer gave the alkylated alcohol.[502]

The addition of Grignard reagents to aldehydes and ketones[503] is known as the *Grignard reaction*.[504] The initial product of reaction with a carbonyl is a magnesium alkoxide, requiring a hydrolysis step to generate the final alcohol product. Formaldehyde gives primary alcohols, other aldehydes give secondary alcohols, and ketones give tertiary alcohols. The reaction is of very broad scope. In many cases, the hydrolysis step is carried out with dilute HCl or H_2SO_4, but such strong acids cannot be used for the preparation of tertiary alcohols in which at least one R group is alkyl because such alcohols are easily dehydrated under acidic conditions (**17-1**). In such cases (and often for other alcohols as well), an aqueous solution of ammonium chloride is used instead of a strong acid. Grignard reagents have been used in solid-phase synthesis.[505] Ionic liquids have been used for the Grignard reaction.[506]

Homoallylic alcohols were prepared by the reaction of allylic halides with carbonyl compounds, using magnesium powder as mediator under solvent-free conditions.[507] Cyclopropyl Grignard reagents reacted with aldehydes or ketones in the presence of diethyl phosphite to give homoallylic bromides.[508] The reactions and mechanism of reaction of allylmagnesium halides has been discussed.[509] Two different Grignard adducts were mixed and

[498] See Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vols. 2–4, Wiley, NY, ***1985–1987***.
[499] Song, J.J.; Yee, N.K.; Tan, Z.; Xu, J.; Kapadia, S.R.; Senanayake, C.H. *Org. Lett.* ***2004***, *6*, 4905.
[500] Gold, H.; Larhed, M.; Nilsson, P. *Synlett* ***2005***, 1596.
[501] Ford, L.; Atefi, F.; Singer, R.D.; Scammells, P.J. *Eur. J. Org. Chem.* ***2011***, 942.
[502] Matsubara, H.; Niwa, Y.; Matake, R. *Synlett* ***2015***, *26*, 1276.
[503] See Leung, S.S.-W.; Streitwieser, A. *J. Org. Chem.* ***1999***, *64*, 3390.
[504] See Eicher, T. in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, ***1966***, pp. 621–693; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 138–528; Stowell, J.C. *Chem. Rev.* ***1984***, *84*, 409. See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 555–558, 571–580, 561–573. For a computational study of this reaction, see Yamazaki, S.; Yamabe, S. *J. Org. Chem.* ***2002***, *67*, 9346.
[505] Franzén, R.G. *Tetrahedron* ***2000***, *56*, 685.
[506] Handy, S.T. *J. Org. Chem.* ***2006***, *71*, 4659.
[507] Li, S.; Wang, J.-X.; Wen, X.; Ma, X. *Tetrahedron* ***2011***, *67*, 849.
[508] Qi, W.; Wang, P.; Fan, L.; Zhang, S. *J. Org. Chem.* ***2013***, *78*, 5918.
[509] See Bartolo, N.D.; Read, J.A.; Valentín, E.M.; Woerpel, K.A. *Synthesis* ***2017***, *49*, 3237.

heated to 65 °C; allyl crossover was observed, indicating that the addition is reversible.[510] A retro-Grignard reaction is known.[511] Aryl iodides undergo halogen/magnesium exchange when pretreated with PhMgCl, and subsequent reaction with an aldehyde gives the alcohol.[512]

A deep eutectic solvent (1 equivalent of choline chloride in combination with 2 equivalents of glycerol) was used for the addition of organolithium reagents and Grignard reagents to ketones, in air.[513] Note that a deep eutectic solvent is formed from a eutectic mixture of Lewis or Brønsted acids and bases that usually contain a variety of anionic and/or cationic species,[514] where the eutectic has a melting point much lower than either of the individual components.

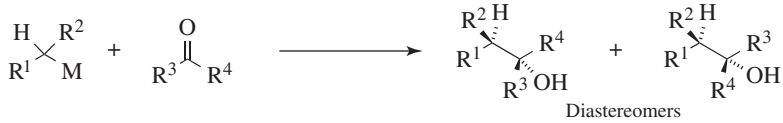
The reaction of aldehydes or ketones with alkyl and aryl Grignard reagents was done in the earliest work without preliminary formation of RMgX, by mixing RX, the carbonyl compound, and magnesium metal in an ether solvent. This approach preceded Grignard's work, and is now known as the *Barbier reaction*.[515] Yields were generally satisfactory. Carboxylic ester, nitrile, and imide groups in the R are not affected by the reaction conditions.[516] Modern versions of the Barbier reaction employ other metals and/or reaction conditions, and will be discussed in **16-23**. Magnesium Barbier reactions are catalyzed by metal complexes other than Mg, such as Cu compounds.[517] Some transition metal compounds are stable in water, so some Grignard-Barbier reactions can be done in water.[518] A retro-Barbier reaction has been reported in which a cyclic tertiary alcohol was treated to an excess of bromine and potassium carbonate to give 6-bromohexan-2-one from 1-methylcyclopentanol.[519]

Transition metal catalysts can promote 1,2-addition of Grignard reagents to ketones. The Zn-mediated Grignard reaction with ketones has been studied.[520] In the presence of a catalytic amount of $InCl_3$, Grignard reagents react to give a mixture of 1,2- and 1,4-addition products, with the 1,4-product predominating. However, there was an increase in 1,2-addition relative to the uncatalyzed reaction.[521] The Cu-catalyzed addition of Grignard reagents to aryl alkyl ketones gave the alcohol.[522] The Cu-catalyzed addition of arylmagnesium compounds to aryl heteroaryl ketones is also known.[523]

In a compound containing both an aldehyde and a ketone it is possible to add RMgX chemoselectively to the aldehyde without significantly disturbing the carbonyl of the ketone

[510] Benkeser, R.A.; Siklosi, M.P. *J. Org. Chem.* ***1976***, *41*, 3212.
[511] Christensen, S.H.; Holm, T.; Madsen, R. *Tetrahedron* ***2014***, *70*, 1478.
[512] Sapountzis, I.; Dube, H.; Lewis, R.; Gommermann, N.; Knochel, P. *J. Org. Chem.* ***2005***, *70*, 2445.
[513] Vidal, C.; García-Álvarez, J.; Hernán-Gómez, A.; Kennedy, A.R.; Hevia, E. *Angew. Chem. Int. Ed.* ***2014***, *53*, 5969.
[514] Smith, E.L.; Abbott, A.P.; Ryder, K.S. *Chem. Rev*. ***2014***, *114*, 11060.
[515] Barbier, P. *Compt. Rend.* ***1899***, *128*, 110. See Blomberg, C.; Hartog, F.A. *Synthesis* ***1977***, 18; Molle, G.; Bauer, P. *J. Am. Chem. Soc.* ***1982***, *104*, 3481. For a list of Barbier-type reactions, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1125–1134.
[516] Yeh, M.C.P.; Knochel, P.; Santa, L.E. *Tetrahedron Lett.* ***1988***, *29*, 3887.
[517] Erdik, E.; Koçoğlu, M. *Tetrahedron Lett.* ***2007***, *48*, 4211.
[518] Li, C.-J. *Tetrahedron* ***1996***, *52*, 5643.
[519] Zhang, W.-C.; Li, C.-J. *J. Org. Chem.* ***2000***, *65*, 5831.
[520] Armstrong, D.R.; Clegg, W.; García-Alvarez, P.; McCall, M.D.; Nuttall, L.; Kennedy, A.R.; Russo, L.; Hevia, E. *Chem. Eur. J.* ***2011***, *17*, 4470.
[521] Kelly, B.G.; Gilheany, D.G. *Tetrahedron Lett.* ***2002***, *43*, 887.
[522] Madduri, A.V.R.; Harutyunyan, S.R.; Minnaard, A.J. *Angew. Chem. Int. Ed.* ***2012***, *51*, 3164.
[523] Ortiz, P.; del Hoyo, A.M.; Harutyunyan, S.R. *Eur. J. Org. Chem.* ***2015***, 72.

group.[524] Diastereoselective addition[525] has been carried out with achiral reagents and chiral substrates.[526] The attacking atom in this reaction is carbon, so diastereoselective addition is possible with an achiral substrate and an optically active reagent.[527] Even if the organometallic compound is racemic, it still may be possible to get a diastereoselective reaction; that is, one pair of enantiomers is formed in greater amount than the other.[528]



Asymmetric Grignard reactions are possible under certain circumstances.[529] Chiral ligands with a chiral Cu[530] or a chiral Ti complex[531] gave alcohols with good enantioselectivity. Other chiral ligands have been developed.[532] An interesting method used an alkylmagnesium halide, dibutylmagnesium (Bu_2Mg), and a chiral diamine, and subsequent reaction with an aldehyde led to the alcohol derived from acyl addition of a butyl group with good enantioselectivity.[533] *N*-Heterocyclic carbenes have been used as organocatalysts for asymmetric Grignard reactions.[534]

The reaction of RMgX or RLi with α,β-unsaturated aldehydes or ketones can proceed via 1,4-addition (see organometallic conjugate addition in **15-21**) as well as normal 1,2-addition.[535] In general, alkyllithium reagents give less 1,4-addition than the corresponding Grignard reagents. Grignard reagents have been shown to add to some conjugated cyclic ketones with an α,β-OTf group via 1,2-addition, followed by cleavage to give an alkynyl ketone.[536]

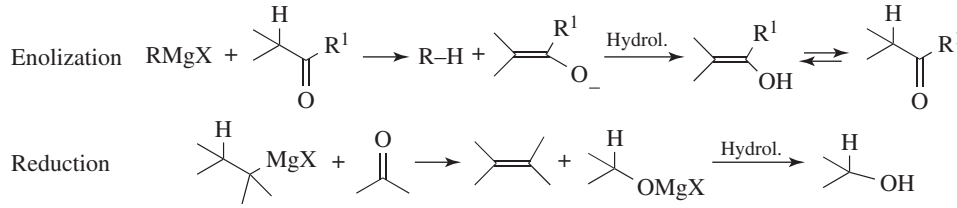
In some cases a Grignard reaction can be performed intramolecularly.[537] For example, treatment of 5-bromopentan-2-one with Mg and a small amount of mercuric chloride in THF produced 1-methyl-1-cyclobutanol in 60% yield.[538] Other four- and five-membered ring compounds were also prepared by this procedure. Similar closure of five- and

[524] Vaskan, R.N.; Kovalev, B.G. *J. Org. Chem. USSR* ***1973***, *9*, 501.
[525] Tomoda, S.; Senju, T. *Tetrahedron* ***1999***, *55*, 3871. See Schulze, V.; Nell, P.G.; Burton, A.; Hoffmann, R.W. *J. Org. Chem.* ***2003***, *68*, 4546.
[526] See Reetz, M.T. *Angew. Chem. Int. Ed.* ***1984***, *23*, 556. See also, Keck, G.E.; Castellino, S. *J. Am. Chem. Soc.* ***1986***, *108*, 3847.
[527] See Denmark, S.E.; Weber, E.J. *J. Am. Chem. Soc.* ***1984***, *106*, 7970. See Greeves, N.; Pease, J.E. *Tetrahedron Lett.* ***1996***, *37*, 5821; Zweifel, G.; Shoup, T.M. *J. Am. Chem. Soc.* ***1988***, *110*, 5578.
[528] See Masuyama, Y.; Takahara, J.P.; Kurusu, Y. *Tetrahedron Lett.* ***1989***, *30*, 3437.
[529] Luderer, M.R.; Bailey, W.F.; Luderer, M.R.; Fair, J.D.; Dancer, R.J.; Sommer, M.B. *Tetrahedron: Asymmetry* ***2009***, *20*, 981.
[530] Cotton, H.K.; Norinder, J.; Bäckvall, J.-E. *Tetrahedron* ***2006***, *62*, 5632; López, F.; van Zijl, A.W.; Minnaard, A.J.; Feringa, B.L. *Chem. Commun.* ***2006***, 409.
[531] See Fernández-Mateos, E.; Maciá, B.; Yus, M. *Eur. J. Org. Chem.* ***2014***, 6519.
[532] See Zhang, A.; Yang, N.; Yang, L.; Peng, D. *Chem. Lett.* ***2014***, *43*, 462; Bieszczad, B.; Gilheany, D.G. *Angew. Chem. Int. Ed.* ***2017***, *56*, 4272. See Osakama, K.; Nakajima, M. *Org. Lett.* ***2016***, *18*, 236.
[533] Yong, K.H.; Taylor, N.J.; Chong, J.M. *Org. Lett.* ***2002***, *4*, 3553.
[534] Xiao, K.-J.; Luo, J.-M.; Ye, K.-Y.; Wang, Y.; Huang, P.-Q. *Angew. Chem. Int. Ed.* ***2010***, *49*, 3037.
[535] For a discussion of the mechanism, see Holm, T. *Acta Chem. Scand.* ***1992***, *46*, 985.
[536] Kamijo, S.; Dudley, G.B. *J. Am. Chem. Soc.* ***2005***, *127*, 5028.
[537] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1134–1135.
[538] Leroux, Y. *Bull. Soc. Chim. Fr.* ***1968***, 359.

six-membered rings was achieved by treatment of a δ- or ε-halocarbonyl compound, not with a metal, but with a dianion derived from nickel tetraphenylporphine[539] (see **16-23**).

The *gem*-disubstituted Mg compounds formed from CH_2Br_2 or CH_2I_2 ($XMgCH_2MgX$) react with aldehydes or ketones to give alkenes in moderate to good yields.[540] *Wittig-type reactions* also produce alkenes and are discussed in **16-44**. The reaction could not be extended to other *gem*-dihalides.

Most aldehydes and ketones react smoothly with most Grignard reagents via acyl addition, but there are several potential side reactions that occur,[541] mostly with sterically hindered ketones and with bulky Grignard reagents. The two most important of these are *enolization* and *reduction*.



While enolization requires that the aldehyde or ketone have an α hydrogen, reduction requires that the Grignard reagent have a β hydrogen. There is general agreement that the mechanism leading to reduction[542] is usually a cyclic transition state with transfer to the β hydrogen from the Grignard reagent to the acyl carbon, and formation of the O—Mg bond and the Grignard substrate is converted to an alkene. There is evidence that the mechanism leading to enolization is also cyclic, but involves prior coordination with magnesium.[543]

Enolization is an acid–base reaction (**12-24**) in which a proton is removed from the α carbon by the Grignard reagent, which is a strong base. The carbonyl compound is converted to its enolate anion,[544] which, on hydrolysis, gives the original ketone or aldehyde. Enolization is important not only for hindered ketones but also for those that have a relatively high percentage of enol (e.g., β-keto esters). It is noted that the addition of NBu_4Cl as a catalyst and diglyme assisted the nucleophilic addition reactions of Grignard reagents to ketones to give the tertiary alcohol, and suppressed enolization and reduction.[545]

The carbonyl compound can be reduced to an alcohol (**19-40**) by the Grignard reagent, which itself undergoes elimination to give an alkene. The Grignard reagent must have a β carbon that bears a hydrogen atom. Highly hindered Grignard reagents show this reaction.

Two other side reactions are condensation (between enolate ion and excess ketone) and *Wurtz-type coupling* (**10-64**). Addition of Grignard reagents to ketones cannot be used to prepare highly hindered tertiary alcohols such as triisopropylcarbinol, tri-*tert*-butylcarbinol, and diisopropylneopentylcarbinol (or they can be prepared only in extremely low yields) because reduction and/or enolization become prominent.[546] However, these alcohols can

[539] Corey, E.J.; Kuwajima, I. *J. Am. Chem. Soc.* ***1970***, *92*, 395. For another method, see Molander, G.A.; McKie, J.A. *J. Org. Chem.* ***1991***, *56*, 4112, and references cited therein.

[540] Bertini, F.; Grasselli, P.; Zubiani, G.; Cainelli, G. *Tetrahedron* ***1970***, *26*, 1281.

[541] Lajis, N. Hj.; Khan, M.N.; Hassan, H.A. *Tetrahedron* ***1993***, *49*, 3405.

[542] See Morrison, J.D.; Tomaszewski, J.E.; Mosher, H.S.; Dale, J.; Miller, D.; Elsenbaumer, R.L. *J. Am. Chem. Soc.* ***1977***, *99*, 3167; Okuhara, K. *J. Am. Chem. Soc.* ***1980***, *102*, 244.

[543] Pinkus, A.G.; Sabesan, A. *J. Chem. Soc., Perkin Trans. 2* ***1981***, 273.

[544] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 659–674.

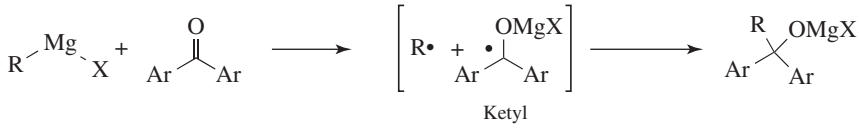
[545] Zong, H.; Huang, H.; Liu, J.; Bian, G.; Song, L. *J. Org. Chem.* ***2012***, *77*, 4645.

[546] Whitmore, F.C.; George, R.S. *J. Am. Chem. Soc.* ***1942***, *64*, 1239.

be prepared by the use of alkyllithium reagents at −80 °C[547] because enolization and reduction are much less important.[548] Other methods of increasing the degree of addition at the expense of reduction include complexing the Grignard reagent with $LiClO_4$ or Bu_4N^+ Br^-,[549] or using benzene or toluene instead of ether as solvent.[550] Both reduction and enolization can be avoided by adding $CeCl_3$ to the Grignard reagent.[551]

There has been controversy regarding the mechanism of addition of Grignard reagents to aldehydes and ketones.[552] The reaction is difficult to study because of the variable nature of the species present in the Grignard solution (the *Schlenk equilibrium*; Sec. 5.B.ii) and because the presence of small amounts of impurities in the Mg seems to have a great effect on the kinetics of the reaction, making reproducible experiments difficult.[553] There seem to be two basic mechanisms, depending on the reactants and the reaction conditions. In one of these, the R group is transferred to the carbonyl carbon with its electron pair,[554] based on the discovery that this reaction proceeds by two paths: one first order in MeMgBr and the other first order in Me_2Mg.[555] According to this proposal, both MeMgBr and Me_2Mg add to the carbonyl carbon, though the exact nature of the step by which MeMgBr or Me_2Mg reacts with the substrate is not certain. One possibility is a four-centered cyclic transition state:[556]

The other type of mechanism is a single-electron transfer (SET) process[557] with a ketyl intermediate.[558] This mechanism, which has been mostly studied with diaryl ketones, is more likely for aromatic and other conjugated aldehydes and ketones than it is for strictly aliphatic aldehydes and ketones.



Ketyl

[547] Bartlett, P.D.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1968***, *90*, 4421. See also, Molle, G.; Briand, S.; Bauer, P.; Dubois, J.E. *Tetrahedron* ***1984***, *40*, 5113.
[548] Buhler, J.D. *J. Org. Chem.* ***1973***, *38*, 904.
[549] Chastrette, M.; Amouroux, R. *Chem. Commun.* ***1970***, 470. See also, Richey Jr., H.G.; DeStephano, J.P. *J. Org. Chem.* ***1990***, *55*, 3281.
[550] Canonne, P.; Foscolos, G.; Caron H.; Lemay, G. *Tetrahedron* ***1982***, *38*, 3563.
[551] Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* ***1989***, *111*, 4392.
[552] See Holm, T. *Acta Chem. Scand. Ser. B* ***1983***, *37*, 567; Ashby, E.C. *Pure Appl. Chem.* ***1980***, *52*, 545; Ashby, E.C.; Laemmle, J.; Neumann, H.M. *Acc. Chem. Res.* ***1974***, *7*, 272. Also see Ashby, E.C.; Laemmle, J. *Chem. Rev.* ***1975***, *75*, 521; Solv'yanov, A.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1987***, *56*, 465.
[553] See, for example, Ashby, E.C.; Neumann, H.M.; Walker, F.W.; Laemmle, J.; Chao, L. *J. Am. Chem. Soc.* ***1973***, *95*, 3330.
[554] Ashby, E.C.; Laemmle, J.; Neumann, H.M. *J. Am. Chem. Soc.* ***1972***, *94*, 5421.
[555] See Laemmle, J.; Ashby, E.C.; Neumann, H.M. *J. Am. Chem. Soc.* ***1971***, *93*, 5120.
[556] Ashby, E.C.; Yu, S.H.; Roling, P.V. *J. Org. Chem.* ***1972***, *37*, 1918. See also, Lasperas, M.; Perez-Rubalcaba, A.; Quiroga-Feijoo, M.L. *Tetrahedron* ***1980***, *36*, 3403.
[557] For a review, see Dagonneau, M. *Bull. Soc. Chim. Fr.* ***1982***, II-269.
[558] See Walling, C. *J. Am. Chem. Soc.* ***1988***, *110*, 6846.

Among the evidence[559] for the SET mechanism are ESR spectra[560] and the fact that $Ar_2C(OH) \rightarrow C(OH)Ar_2$ side products are obtained (from dimerization of the ketyl; see *pinacol coupling* in **19-80**).[561] In the case of addition of RMgX to benzil PhCOCOPh, ESR spectra of two different ketyl radicals were observed, both reported to be quite stable at room temperature.[562] Note that a separate study failed to observe freely defusing radicals in the formation of Grignard reagents.[563] Carbon isotope effect studies with $Ph^{14}COPh$ showed that the rate-determining step with most Grignard reagents is the carbon–carbon bond-forming step, although the rate-determining step is the initial electron-transfer step with allylmagnesium bromide.[564] In the formation of Grignard reagents from bromocyclopropane, diffusing cyclopropyl radical intermediates were found.[565] The concerted versus stepwise mechanism has been probed with chiral Grignard reagents.[566] It has been noted that there are similarities in reactivity for the $S_{RN}1$ (Sec. 13.A.iv) and Grignard mechanisms.[567] Experimental evidence from this work suggests a linear rather than a chain mechanism.

Organolithium reagents (RLi),[568] prepared from alkyl halides and Li metal or by exchange of an alkyl halide with a reactive organolithium (**12-37**), react with aldehydes and ketones by acyl addition to give the alcohol[569] after hydrolysis. Organolithium reagents are more basic than the corresponding *Grignard reagent*, which leads to problems of deprotonation in some cases. Organolithium regents are generally more nucleophilic, however, and can add to hindered ketones with relative ease when compared to the analogous Grignard reagent.[570] Organolithium reagents tend to form aggregates, which influences the reactivity and selectivity of the addition reaction.[571] The addition of lithium amide/butyllithium mixed aggregates has been studied.[572] The organolithium analog of the Barbier reaction is known.[573]

Alkyl, vinyl,[574] and aryl organolithium reagents can be prepared and undergo acyl addition. Structural variations are also possible, including enantioselective 1,2-addition.[575] 1-Bromo-1-lithioethene has been prepared, and it reacts with an aldehyde to give an allylic

[559] Also see Holm, T. *Acta Chem. Scand. Ser. B* ***1988***, *42*, 685; Yamataka, H.; Miyano, N.; Hanafusa, T. *J. Org. Chem.* ***1991***, *56*, 2573.
[560] Maruyama, K.; Katagiri, T. *Chem. Lett.* ***1987***, 731, 735; *J. Phys. Org. Chem.* ***1988***, *1*, 21.
[561] See Holm, T.; Crossland, I. *Acta Chem. Scand.* ***1971***, *25*, 59.
[562] Maruyama, K.; Katagiri, T. *J. Phys. Org. Chem.* ***1989***, *2*, 205. See also, Maruyama, K.; Katagiri, T. *J. Phys. Org. Chem.* ***1991***, *4*, 158.
[563] Walter, R.I. *J. Org. Chem.* ***2000***, *65*, 5014.
[564] Yamataka, H.; Matsuyama, T.; Hanafusa, T. *J. Am. Chem. Soc.* ***1989***, *111*, 4912.
[565] Garst, J.F.; Ungváry, F. *Org. Lett.* ***2001***, *3*, 605.
[566] Hoffmann, R.W.; Hölzer, B. *Chem. Commun.* ***2001***, 491.
[567] Bodineau, N.; Mattalia, J.-M.; Hazimeh, H.; Handoo, K.L.; Timokhin, V.; Négrel, J.-C.; Chanon, M. *Eur. J. Org. Chem.* ***2010***, 2476.
[568] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 580–600.
[569] For Hammett ρ values, see Maclin, K.M.; Richey Jr., H.G. *J. Org. Chem.* ***2002***, *67*, 4370.
[570] Lecomte, V.; Stéphan, E.; Le Bideau, F.; Jaouen, G. *Tetrahedron* ***2003***, *59*, 2169.
[571] See Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron* ***2002***, *58*, 4717.
[572] Liu, J.; Li, D.; Sun, C.; Williard, P.G. *J. Org. Chem.* ***2008***, *73*, 4045.
[573] Guijarro, A.; Yus, M. *Tetrahedron Lett.* ***1993***, *34*, 3487; de Souza-Barboza, J.D.; Pétrier, C.; Luche, J. *J. Org. Chem.* ***1988***, *53*, 1212.
[574] For a discussion of selectivity, see Spino, C.; Granger, M.-C.; Tremblay, M.-C. *Org. Lett.* ***2002***, *4*, 4735.
[575] Granander, J.; Eriksson, J.; Hilmersson, G. *Tetrahedron: Asymmetry* ***2006***, *17*, 2021.

alcohol bearing a vinyl bromide unit.[576] The addition reaction of organolithium reagents is known to be reversible.[577]

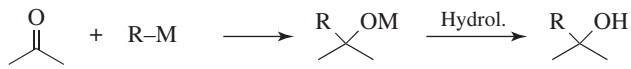
The addition reactions of organolithium compounds can be carried out enantioselectively and diastereoselectively.[578] Chiral secondary alcohols have been obtained with high enantioselectivity by addition of Grignard and organolithium compounds to aromatic aldehydes in the presence of optically active amino alcohols as ligands.[579] The Ti-catalyzed addition of organolithium reagents to aldehydes proceeded with good enantioselectivity.[580] Chiral diol ligands have been developed for the asymmetric addition to aldehydes using organolithium reagents.[581]

Mechanisms for the addition of organolithium reagents have been investigated much less than the mechanism of acyl addition reactions of Grignard reagents.[582] Addition of a cryptand that binds Li^+ inhibited the normal addition reaction, showing that the lithium is necessary for the reaction to take place.[583]

A lithio epoxide was formed by treating an epoxide with *sec*-butyllithium in the presence of sparteine,[584] or with *n*-butyllithium/TMEDA,[585] and subsequent reaction with an aldehyde led to an epoxy alcohol. Alkylidene oxetanes react with lithium and then with an aldehyde to give a conjugated ketone.[586] The reaction of *gem*-dihalides with a carbonyl compound and Li or BuLi give epoxides[587] (see also, **16-46**).

OS **I**, 188; **II**, 406, 606; **III**, 200, 696, 729, 757; **IV**, 771, 792; **V**, 46, 452, 608, 1058; **VI**, 478, 537, 542, 606, 737, 991, 1033; **VII**, 177, 271, 447; **VIII**, 179, 226, 315, 343, 386, 495, 507, 556; **IX**, 9, 103, 139, 234, 306, 391, 472; **75**, 12; **76**, 214; **X**, 200.

16-23 The Addition of Other Organometallics to Aldehydes and Ketones



A variety of organometallic reagents other than RMgX and RLi (which are discussed in **16-22**) add to aldehydes and ketones. Many organometallic reagents have been reported

[576] Novikov, Y.Y.; Sampson, P. *J. Org. Chem.* ***2005***, *70*, 10247.
[577] Benkeser, R.A.; Siklosi, M.P.; Mozdzen, E.C. *J. Am. Chem. Soc.* ***1978***, *100*, 2134.
[578] See Solladié, G. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***, pp. 157–199 (pp. 158–183); Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 160–193; Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed.* ***1991***, *30*, 49.
[579] Schön, M.; Naef, R. *Tetrahedron: Asymmetry* ***1999***, *10*, 169; Arvidsson, P.I.; Davidsson, Ö.; Hilmersson, G. *Tetrahedron: Asymmetry* ***1999***, *10*, 527.
[580] Veguillas, M.; Solà, R.; Shaw, L.; Maciá, B. *Eur. J. Org. Chem.* ***2016***, 1788.
[581] Zong, H.; Huang, H.; Song, L. *Tetrahedron: Asymmetry* ***2017***, *27*, 1069. Also see Rönnholm, P.; Gräfenstein, J.; Norrby, P.-O.; Hilmersson, G.; Nilsson Lill, S.O. *Org. Biomol. Chem.* ***2012***, *10*, 2807.
[582] See Yamataka, H.; Kawafuji, Y.; Nagareda, K.; Miyano, N.; Hanafusa, T. *J. Org. Chem.* ***1989***, *54*, 4706.
[583] Perraud, R.; Handel, H.; Pierre, J. *Bull. Soc. Chim. Fr.* ***1980***, II-283.
[584] Hodgson, D.M.; Kirton, E.H.M.; Miles, S.M.; Norsikian, S.L.M.; Reynolds, N.J.; Coote, S.J. *Org. Biomol. Chem.* ***2005***, *3*, 11893.
[585] Florio, S.; Aggarwal, V.; Salomone, A. *Org. Lett.* ***2004***, *6*, 4191.
[586] Hashemsadeh, M.; Howell, A.R. *Tetrahedron Lett.* ***2000***, *41*, 1855, 1859.
[587] Cainelli, G.; Tangari, N.; Umani-Ronchi, A. *Tetrahedron* ***1972***, *28*, 3009, and references cited therein.

for the addition of allylic groups,[588] and there are enantioselective reactions.[589] One of the most common methods is the *Barbier reaction* noted in **16-22**, which uses metals and metal compounds other than Mg or Li. With other metals, good yields are obtained with systems other than allylic compounds. Enantioselective In-mediated Barbier reactions are known.[590] Indium reacts with allylic bromides and ketones in aqueous media.[591] When allyl iodide is mixed with indium and TMSCl, reaction with a conjugated ketone proceed by 1,4-addition, but in the presence of 10% CuI, the major product is that of 1,2-addition.[592] Allyl bromide reacts with Mn/TMSCl and an In catalyst in water to give homoallylic alcohols from aldehydes.[593] Elimination of the homoallylic alcohol to form a conjugated diene can accompany the addition in some cases.[594]

Allyl bromide reacts with a ketone and Sm[595] or SmI_2[596] to give the homoallylic alcohol. Other metals can be used with allylic halides to give homoallylic alcohols from aldehydes or ketones,[597], including Zn,[598] La,[599] Mg/Cd,[600] or Rh,[601] and compounds of Ti,[602] Mn,[603] Fe,[604] Ga,[605] Ge,[606] Zr,[607] Nb,[608] Cd,[609] Ir,[610] Sb,[611] Te,[612] Ba,[613] Ce,[614] Nd,[615]

[588] For a list of reagents and references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1156–1170. Also see Gajewski, J.J.; Bocian, W.; Brichford, N.L.; Henderson, J.L. *J. Org. Chem.* ***2002***, *67*, 4236.

[589] See Denmark, S.E.; Fu, J. *Chem. Rev.* ***2003***, *103*, 2763.

[590] Haddad, T.D.; Hirayama, L.C.; Taynton, P.; Singaram, B. *Tetrahedron Lett.* ***2008***, *49*, 508. For an example in ionic liquids, see Teo, Y.-C.; Goh, E.-L.; Loh, T.-P. *Tetrahedron Lett.* ***2005***, *46*, 4573.

[591] Chan, T.H.; Yang, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 3228; Paquette, L.A.; Bennett, G.D.; Isaac, M.B.; Chhatriwalla, A. *J. Org. Chem.* ***1998***, *63*, 1836; Li, X.-R.; Loh, T.-P. *Tetrahedron: Asymmetry* ***1996***, *7*, 1535.

[592] Lee, P.H.; Ahn, H.; Lee, K.; Sung, S.-y.; Kim, S. *Tetrahedron Lett.* ***2001***, *42*, 37.

[593] Augé, J.; Lubin-Germain, N.; Thiaw-Woaye, A. *Tetrahedron Lett.* ***1999***, *40*, 9245.

[594] Kumar, V.; Chimni, S.; Kumar, S. *Tetrahedron Lett.* ***2004***, *45*, 3409.

[595] Basu, M.K.; Banik, B.K. *Tetrahedron Lett.* ***2001***, *42*, 187.

[596] Hélion, F.; Namy, J.-L. *J. Org. Chem.* ***1999***, *64*, 2944.

[597] See Knochel, P.; Rao, S.A. *J. Am. Chem. Soc.* ***1990***, *112*, 6146; Wada, M.; Ohki, H.; Akiba, K. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 1738.

[598] Wang, J.-x.; Jia, X.; Meng, T.; Xin, L. *Synthesis* ***2005***, 2838. For a discussion of waste management, see Prathihar, S.; Kakoty, A.; Sarmah, K. *New J. Chem.* ***2016***, 5347.

[599] In water: Bian, Y.-J.; Zhang, J.-Q.; Xia, J.-P.; Li, J.-T. *Synth. Commun.* ***2006***, *36*, 2475.

[600] Narsaiah, A.V.; Reddy, A.R.; Rao, Y.G.; Kumar, E.V.; Prakasham, R.S.; Reddy, B.V.S.; Yadav, J.S. *Synthesis* ***2008***, 3461.

[601] Gellrich, U.; Meißner, A.; Steffani, A.; Kähny, M.; Drexler, H.-J.; Heller, D.; Plattner, D.A.; Breit, B. *J. Am. Chem. Soc.* ***2014***, *136*, 1097; Toyoshima, T.; Miura, T.; Murakami, M. *Angew. Chem. Int. Ed.* ***2011***, *50*, 10436.

[602] Estévez, R.E.; Justicia, J.; Bazdi, B.; Fuentes, N.; Paradas, M.; Choquesillo-Lazarte, D.; García-Ruiz, J.M.; Robles, R.; Gansäuer, A.; Cuerva, J.M.; Oltra, J.E. *Chem. Eur. J.* ***2009***, *15*, 2774.

[603] See Berkessel, A.; Menche, D.; Sklorz, C.A.; Schröder, M.; Paterson, I. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1032.

[604] Chan, T.C.; Lau, C.P.; Chan, T.H. *Tetrahedron Lett.* ***2004***, *45*, 4189.

[605] Wang, Z.; Yuan, S.; Li, C.-J. *Tetrahedron Lett.* ***2002***, *43*, 5097. For a reaction in ionic liquid, see Goswami, D.; Chattopadhyay, A.; Sharma, A.; Chattopadhyay, S. *J. Org. Chem.* ***2012***, *77*, 11064.

[606] Hashimoto, Y.; Kagoshima, H.; Saigo, K. *Tetrahedron Lett.* ***1994***, *35*, 4805.

[607] Hanzawa, Y.; Tabuchi, N.; Saito, K.; Noguchi, S.; Taguchi, T. *Angew. Chem. Int. Ed.* ***1999***, *38*, 2395.

[608] Andrade, C.K.Z.; Azevedo, N.R.; Oliveira, G.R. *Synthesis* ***2002***, 928.

[609] Zheng, Y.; Bao, W.; Zhang, Y. *Synth. Commun.* ***2000***, *30*, 3517.

[610] Gao, X.; Townsend, I.A.; Krische, M.J. *J. Org. Chem.* ***2011***, *76*, 2350.

[611] Li, L.-H.; Chan, T.H. *Can. J. Chem.* ***2001***, *79*, 1536.

[612] See Avilov, D.V.; Malasare, M.G.; Arslancan, E.; Dittmer, D.L. *Org. Lett.* ***2004***, *6*, 2225.

[613] Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* ***1994***, *116*, 6130.

[614] Loh, T.-P.; Zhou, J.-R. *Tetrahedron Lett.* ***1999***, *40*, 9115.

[615] Evans, W.J.; Workman, P.S.; Allen, N.T. *Org. Lett.* ***2003***, *5*, 2041.

Hg,[616] Pr,[617] Bi,[618] In,[619] and Pb.[620] In addition, $BiCl_3/NaBH_4$,[621] $Mg/BiCl_3$,[622] and $CrCl_2/NiCl_2$[623] have been used. Allylic alcohols have been converted to organometallic reagents with diethylzinc and a Pd[624] or Ru catalyst,[625] leading to the homoallylic alcohol upon reaction with an aldehyde. Allylic acetates add to aldehydes in the presence of a Ru catalyst.[626] Organocerium reagents, generated from cerium chloride ($CeCl_3$ and a Grignard reagent or an organolithium reagent) give an organometallic reagent that adds chemoselectively.[627] Furthermore, organotitanium[628] reagents can be made to add chemoselectively to aldehydes in the presence of ketones.[629]

Enantioselective reactions are known.[630] A Cu-catalyzed reaction is known that proceeds with good enantioselectivity.[631] Allylzinc bromide adds to aldehydes under solvent-free conditions.[632] A chiral Cr/Mn complex has been used with allylic bromides in conjunction with trimethylsilyl chloride.[633] The enantioselective addition of methyltriisopropoxytitanium to aldehydes has been reported, for example.[634] Aryl halides that have a pendant ketone unit react with a Pd catalyst to give cyclization via acyl addition.[635] An enantioselective α-vinylation of aldehydes occured by reaction of vinyl iodonium triflate salts with aldehydes using a synergistic combination of Cu and chiral amine catalysts to give the β,γ-unsaturated aldehydes.[636]

As noted in **16-22**, enolate formation and reduction complicate some Grignard reactions. One way to avoid complications is to add Ti (or Zr) compounds to the Grignard or organolithium reagent.[637] The resulting organotitanium (or organozirconium) compounds are much more selective than Grignard or organolithium reagents.[638] Premixing an allylic Grignard reagent with $ScCl_3$ prior to reaction with the aldehyde gives direct

[616] Chan, T.H.; Yang, Y. *Tetrahedron Lett.* ***1999***, *40*, 3863.
[617] Wu, S.; Li, Y.; Zhang, S. *J. Org. Chem.* ***2016***, *81*, 8070.
[618] See Jadhav, B.D.; Pardeshi, S.K. *Tetrahedron Lett.* ***2014***, *55*, 4948.
[619] Kim, Y.M.; Lee, S.; Kim, S.H.; Kim, J.N. *Tetrahedron Lett.* ***2011***, *52*, 3240; Du, Z.; Li, Y.; Wang, F.; Zhou, W.; Wang, J.-X. *Synth. Commun.* ***2010–2011***, *41*, 1664. For a review, see Bowyer, W.J.; Singaram, B.; Sessler, A.M. *Tetrahedron* ***2011***, *67*, 7449.
[620] Zhou, J.-Y.; Jia, Y.; Sun, G.-F.; Wu, S.-H. *Synth. Commun.* ***1997***, *27*, 1899.
[621] Ren, P.-D.; Shao, D.; Dong, T.-W. *Synth. Commun.* ***1997***, *27*, 2569.
[622] Wada, M.; Fukuma, T.; Morioka, M.; Takahashi, T.; Miyoshi, N. *Tetrahedron Lett.* ***1997***, *38*, 8045.
[623] Taylor, R.E.; Ciavarri, J.P. *Org. Lett.* ***1999***, *1*, 467.
[624] Kimura, M.; Shimizu, M.; Shibata, K.; Tazoe, M.; Tamaru, Y. *Angew. Chem. Int. Ed.* ***2003***, *42*, 3392.
[625] Wang, M.; Yang, X.-F.; Li, C.-J. *Eur. J. Org. Chem.* ***2003***, 998.
[626] Denmark, S.E.; Nguyen, S.T. *Org. Lett.* ***2009***, *11*, 781.
[627] See Dimitrov, V.; Bratovanov, S.; Simova, S.; Kostova, K. *Tetrahedron Lett.* ***1994***, *35*, 6713.
[628] For a review of 1,2-addition reactions, see Pellissier, H. *Tetrahedron* ***2015***, *71*, 2487.
[629] Reetz, M.T. *Organotitanium Reagents in Organic Synthesis*, Springer, NY, ***1986*** (monograph), pp. 75–86. See also, Kim, S.-H.; Rieke, R.D. *Tetrahedron Lett.* ***1999***, *40*, 4931.
[630] Appelt, H.R.; Limberger, J.B.; Weber, M.; Rodrigues, O.E.D.; Oliveira, J.S.; Lüdtke, D.S.; Braga, A.L. *Tetrahedron Lett.* ***2008***, *49*, 4956.
[631] Fandrick, D.R.; Fandrick, K.R.; Reeves, J.T.; Tan, Z.; Tang, W.; Capacci, A.G.; Rodriguez, S.; Song, J.J.; Lee, H.; Yee, N.K.; Senanayake, C.H. *J. Am. Chem. Soc.* ***2010***, *132*, 7600.
[632] Zhang, Y.; Jia, X.; Wang, J.-X. *Eur. J. Org. Chem.* ***2009***, 2983.
[633] Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.* ***2003***, *125*, 1140.
[634] Veguillas, M.; Solà, R.; Fernández-Ibañez, M.Á.; Maciá, B. *Tetrahedron: Asymmetry* ***2017***, *27*, 643.
[635] Quan, L.G.; Lamrani, M.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2000***, *122*, 4827.
[636] Skucas, E.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2012***, *134*, 9090.
[637] See Reetz, M.T.; Kyung, S.H.; Hüllmann, M. *Tetrahedron* ***1986***, *42*, 2931.
[638] Reetz, M.T. *Organotitanium Reagents in Organic Synthesis*, Springer, NY, ***1986***. See Weidmann, B.; Seebach, D. *Angew. Chem. Int. Ed.* ***1983***, *22*, 31; Reetz, M.T. *Top. Curr. Chem.* ***1982***, *106*, 1.

acyl addition without allylic rearrangement as the major product, favoring the *trans*-alkene unit.[639]

Allyltin compounds readily add to aldehydes and ketones,[640] and the reaction of tributylallyltin with an aldehyde has been called the *Keck allylation*.[641] Maleic acid promotes the reaction in aqueous media.[642] Allylic bromides react with Sn to generate the organometallic compound *in situ*, which then adds to aldehydes.[643] Allylic chlorides react with aldehydes in the presence of di-tin compounds such as $Me_3Sn{-}SnMe_3$ and a Pd catalyst.[644] Allyltrialkyltin compounds[645] and tetraallyltin react with aldehydes or ketones in the presence compounds of Cu,[646] Ce,[647] Bi,[648] Pb,[649] Ag,[650] Cd,[651] Cr,[652] Pd,[653] Re,[654] Gd,[655] Ti,[656] Rh,[657] Zr,[658] Co,[659] or La.[660] The Sn-mediated reaction of aldehydes or ketones with allyl bromide in the ionic liquid [BMIM][BF_4] gave the homoallylic alcohol.[661] A Ti-exchanged ZSM-5 catalyst was used for the reaction of aldehydes with allyltributylstannane to give the homoallylic alcohol.[662] Tetraallyltin reacts via 1,2-addition to give conjugated ketones in methanol at reflux.[663] Tetraallyltin reacts with aldehydes in ionic liquids[664] and on wet silica,[665] and allyltributyltin adds to aldehydes in ionic liquids with $InCl_3$.[666] Tetraallyltin

[639] Matsukawa, S.; Funabashi, Y.; Imamoto, T. *Tetrahedron Lett.* ***2003***, *44*, 1007.
[640] Zha, Z.; Qiao, S.; Jiang, J.; Wang, Y.; Miao, Q.; Wang, Z. *Tetrahedron* ***2005***, *61*, 2521. See Li, G.-l.; Zhao, G. *J. Org. Chem.* ***2005***, *70*, 4272.
[641] For a review, see Fattah, T.A.; Saeed, A. *New J. Chem.* ***2017***, *41*, 14804; Keck, G.E.; Krishnamurthy, D.; Grier, M.C. *J. Org. Chem.* ***1993***, *58*, 6543; Faller, J.W.; Sams, D.W.I.; Liu, X. *J. Am. Chem. Soc.* ***1996***, *118*, 1217; Denmark, S.E.; Hosoi, S. *J. Org. Chem.* ***1994***, *59*, 5133.
[642] Li, G.-l.; Zhao, G. *Synlett* ***2005***, 2540.
[643] Tan, K.-T.; Chng, S.-S.; Cheng, H.-S.; Loh, T.-P. *J. Am. Chem. Soc.* ***2003***, *125*, 2958.
[644] Wallner, O.A.; Szabó, K.J. *J. Org. Chem.* ***2003***, *68*, 2934.
[645] See Issacs, N.S.; Maksimovic, L.; Rintoul, G.B.; Young, D.J. *J. Chem. Soc., Chem. Commun.* ***1992***, 1749; Isaacs, N.S.; Marshall, R.L.; Young, D.J. *Tetrahedron Lett.* ***1992***, *33*, 3023.
[646] Kalita, H.R.; Borah, A.J.; Phukan, P. *Tetrahedron Lett.* ***2007***, *48*, 5047.
[647] Yadav, J.S.; Reddy, B.V.S.; Kondaji, G.; Reddy, J.S.S. *Tetrahedron* ***2005***, *61*, 879.
[648] Choudary, B.M.; Chidara, S.; Sekhar, Ch.V.R. *Synlett* ***2002***, 1694.
[649] Shibata, I.; Yoshimura, N.; Yabu, M.; Baba, A. *Eur. J. Org. Chem.* ***2001***, 3207.
[650] Yanagisawa, A.; Nakashima, H.; Nakatsuka, Y.; Ishiba, A.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 1129.
[651] Kobayashi, S.; Aoyama, N.; Manabe, K. *Synlett* ***2002***, 483.
[652] Kwiatkowski, P.; Chaładaj, W.; Jurczak, J. *Tetrahedron* ***2006***, *62*, 5116.
[653] Zhang, T.; Shi, M.; Zhao, M. *Tetrahedron* ***2008***, *64*, 2412.
[654] Nishiyama, Y.; Kakushou, F.; Sonoda, N. *Tetrahedron Lett.* ***2005***, *46*, 787.
[655] Lingaiah, B.V.; Ezikiel, G.; Yakaiah, T.; Reddy, G.V.; Rao, P.S. *Tetrahedron Lett.* ***2006***, *47*, 4315.
[656] Kii, S.; Maruoka, K. *Tetrahedron Lett.* ***2001***, *42*, 1935.
[657] Andrade, C.K.Z.; Azevedo, N.R. *Tetrahedron Lett.* ***2001***, *42*, 6473.
[658] Kurosa, M.; Lorca, M. *Tetrahedron Lett.* ***2002***, *43*, 1765.
[659] Chaudhuri, M.K.; Dehury, S.K.; Hussain, S. *Tetrahedron Lett.* ***2005***, *46*, 6247. Also see Tang, L.; Ding, L.; Chang, W.-X.; Li, J. *Tetrahedron Lett.* ***2006***, *47*, 303.
[660] Aspinall, H.C.; Bissett, J.S.; Greeves, N.; Levin, D. *Tetrahedron Lett.* ***2002***, *43*, 319.
[661] Slaton, R.; Petrone, A.; Manchanayakage, R. *Tetrahedron Lett.* ***2011***, *52*, 5073.
[662] Bhuyan, B.K.; Borah, A.J.; Senapati, K.K.; Phukan, P. *Tetrahedron Lett.* ***2011***, *52*, 2649; Bora, P.P.; Sema, H.A.; Wahlang, B.; Bez, G. *Can. J. Chem.* ***2012***, *90*, 167.
[663] Khan, A.T.; Mondal, E. *Synlett* ***2003***, 694.
[664] Gordon, C.M.; McCluskey, A. *Chem. Commun.* ***1999***, 1431.
[665] Jin, Y.Z.; Yasuda, N.; Furuno, H.; Inanaga, J. *Tetrahedron Lett.* ***2003***, *44*, 8765.
[666] Lu, J.; Ji, S.-J.; Qian, R.; Chen, J.-P.; Liu, Y.; Loh, T.-P. *Synlett* ***2004***, 534.

adds to ketones or aldehydes to give homoallylic alcohols with good enantioselectivity in the presence of a chiral Ti complex[667] or a chiral In complex.[668] Asymmetric induction has been reported.[669] The use of chiral Rh[670] or Ti[671] catalysts leads to enantioselective addition of allyltributyltin to aldehydes. Allyltributyltin reacts with aldehydes in the presence of $SiCl_4$ and a chiral phosphoramide to give the homoallylic alcohol with moderate enantioselectivity.[672] Tetravinyltin adds to ketones in the presence of an In catalyst.[673] Trifluoromethylation of aldehydes and ketone used Bu_3SnCF_3.[674]

Aluminum catalysts such as methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide), MABR, facilitate addition of allyltributyltin to aldehydes.[675] Triphenylaluminum reacts with aryl aldehydes in the presence of a Ti catalyst.[676] Trimethylaluminum[677] and dimethyltitanium dichloride[678] exhaustively methylate ketones to give *gem*-dimethyl compounds[679] (see also, **10-63**). The alkyl group of trialkylaluminum compounds, such as $AlEt_3$, adds to aldehydes enantioselectively in the presence of chiral transition metal complexes.[680] Vinylaluminum reagents have been used in reactions with aldehydes.[681] The Ti-catalyzed reaction of pyridyl aluminum reagents with aldehydes gave optically active diarylmethanols that contain various pyridyl groups.[682]

A complex of Me_3Ti•MeLi has been shown to be selective for 1,2-addition with conjugated ketones in the presence of nonconjugated ketones.[683] Chiral amides react with aldehydes in the presence of $TiCl_4$ to give *syn*-selective addition products,[684] and Ti-catalyzed enantioselective additions are known.[685] Chiral dendritic Ti catalysts have been used to give moderate enantioselectivity.[686] Allyltitanocenes, cinnamyltitanocenes, and crotyltitanocenes reacted with five- to seven-membered cyclic enones to give the corresponding alcohol.[687] Allyltitanocenes also reacted with α-chiral ketones to give the homoallylic

[667] Kim, J.G.; Waltz, K.M.; Garcia, I.F.; Kwiatkowski, D.; Walsh, P.J. *J. Am. Chem. Soc.* ***2004***, *126*, 12580.
[668] See Teo, Y.-C.; Goh, J.-D.; Loh, T.-P. *Org. Lett.* ***2005***, *7*, 2743.
[669] Xia, G.; Shibatomi, K.; Yamamoto, H. *Synlett* ***2004***, 2437; Jennequin, T.; Wencel-Delord, J.; Rix, D.; Daubignard, J.; Crévisy, C.; Mauduit, M. *Synlett* ***2010***, 1661.
[670] Moloyama, Y.; Narusawa, H.; Nishiyama, H. *Chem. Commun.* ***1999***, 131.
[671] Doucet, H.; Santelli, M. *Tetrahedron: Asymmetry* ***2000***, *11*, 4163.
[672] Denmark, S.E.; Wynn, T. *J. Am. Chem. Soc.* ***2001***, *123*, 6199.
[673] Zhang, X.; Chen, D.; Liu, X.; Feng, X. *J. Org. Chem.* ***2007***, *72*, 5227.
[674] Sanhueza, I.A.; Bonney, K.J.; Nielsen, M.C.; Schoenebeck, F. *J. Org. Chem.* ***2013***, *78*, 7749.
[675] Marx, A.; Yamamoto, H. *Synlett* ***1999***, 584.
[676] Wu, K.-H.; Gau, H.-M. *J. Am. Chem. Soc.* ***2006***, *128*, 14808.
[677] Meisters, A.; Mole, T. *Aust. J. Chem.* ***1974***, *27*, 1655. See also, Jeffery, E.A.; Meisters, A.; Mole, T. *Aust. J. Chem.* ***1974***, *27*, 2569. For discussions of the mechanism, see Ashby, E.C.; Smith, R.S. *J. Organomet. Chem.* ***1982***, *225*, 71. See Maruoka, H.; Yamamoto, H. *Tetrahedron* ***1988***, *44*, 5001.
[678] Reetz, M.T.; Westermann, J.; Kyung, S. *Chem. Ber.* ***1985***, *118*, 1050.
[679] See Araki, S.; Katsumura, N.; Ito, H.; Butsugan, Y. *Tetrahedron Lett.* ***1989***, *30*, 1581.
[680] Alegre, S.; Diéguez, M.; Pàmies, O. *Tetrahedron: Asymmetry* ***2011***, *22*, 834; Fernández-Mateos, E.; Maciá, B.; Yus, M. *Tetrahedron: Asymmetry* ***2012***, *23*, 789.
[681] Kumar, R.; Kawasaki, H.; Harada, T. *Chem. Eur. J.* ***2013***, *19*, 17707.
[682] Zhang, L.; Tu, B.; Ge, M.; Li, Y.; Chen, L.; Wang, W.; Zhou, S. *J. Org. Chem.* ***2015***, *80*, 8307.
[683] Markó, I.E.; Leung, C.W. *J. Am. Chem. Soc.* ***1994***, *116*, 371.
[684] Crimmins, M.T.; Chaudhary, K. *Org. Lett.* ***2000***, *2*, 775.
[685] See Walsh, P.J. *Acc. Chem. Res.* ***2003***, *36*, 739.
[686] Fan, O.-H.; Liu, G.-H.; Chen, X.-M.; Deng, G.-J.; Chan, A.S.C. *Tetrahedron: Asymmetry* ***2001***, *12*, 1559.
[687] Takeda, T.; Nishimura, T.; Yoshida, S.; Saiki, F.; Tajima, Y.; Tsubouchi, A. *Org. Lett.* ***2012***, *14*, 2042.

alcohol.[688] The titanocene-promoted Mn-mediated Barbier reaction of crotyl halides to carbonyls gave the alcohol.[689]

Organozinc compounds add to aldehydes and ketones;[690] dimethylzinc and diethylzinc are probably the most common reagents. An intramolecular version is possible by reaction of an allene aldehyde with dimethylzinc. Aryl halides react with Zn/Ni complexes to give acyl addition of the aryl group to an aldehyde.[691] The reaction of an allylic halide and Zn[692] or Zn/TMSCl[693] leads to acyl addition of aldehydes.

An enantioselective reaction of a carbonyl with a dialkylzinc or an organozinc halide[694] is possible when chiral catalysts are employed,[695] or when chiral ligands[696] are employed.[697] A comparison of the stereoselectivity for reactions of diphenylzinc and diethylzinc[698] has been reported.[699] A chiral ionic liquid has been developed for the addition of diethylzinc to aldehydes.[700] Dialkylzinc reagents, in the presence of a chiral Ti complex,[701] a Zn[702] or Al complex,[703] a chiral Cr complex,[704] a chiral Schiff base,[705] and other chiral complexes,[706] reacted with aldehydes or ketones to give the corresponding

[688] Takeda, T.; Yoshida, S.; Nishimura, T.; Tsubouchi, A. *Tetrahedron Lett.* ***2012***, *53*, 3930.

[689] Sancho-Sanz, I.; Miguel, D.; Millán, A.; Estévez, R.E.; Oller-López, J.L.; Álvarez-Manzaneda, E.; Robles, R.; Cuerva, J.M.; Justicia, J. *J. Org. Chem.* ***2011***, *76*, 732.

[690] Hatano, M.; Mizuno, T.; Ishihara, K. *Tetrahedron* ***2011***, *67*, 4417; Huelgas, G.; LaRochelle, L.K.; Rivas, L.; Luchinina, Y.; Toscano, R.A.; Carroll, P.J.; Walsh, P.J.; de Parrodi, C.A. *Tetrahedron* ***2011***, *67*, 4467. Łowicki, D.; Baś, S.; Mlynarski, J. *Tetrahedron* ***2015***, *71*, 1339; Wu, H.-L.; Wu, P.-Y.; Cheng, Y.-N.; Uang, B.J. *Tetrahedron* ***2016***, *72*, 2656.

[691] Majumdar, K.K.; Cheng, C.-H. *Org. Lett.* ***2000***, *2*, 2295.

[692] See Felpin, F.-X.; Bertrand, M.-J.; Lebreton, J. *Tetrahedron* ***2002***, *58*, 7381.

[693] Ito, T.; Ishino, Y.; Mizuno, T.; Ishikawa, A.; Kobyashi, J.-i. *Synlett* ***2002***, 2116.

[694] Kinoshita, Y.; Kanehira, S.; Hayashi, Y.; Harada, T. *Chem. Eur. J.* ***2013***, *19*, 3311.

[695] See Wujkowska, Z.; Jarzyński, S.; Pieczonka, A.M.; Leśniak, S.; Rachwalski, M. *Tetrahedron: Asymmetry* ***2016***, *27*, 1238; Cheng, Y.-N.; Wu, H.-L.; Wu, P.-Y.; Shen, Y.-Y.; Uang, B.-J. *Chem. Asian J.* ***2012***, *7*, 2921. For a review, see Wu, H.-L.; Chang, C.-A.; Wu, P.-Y.; Uang, B.-J. *Tetrahedron Lett.* ***2017***, *58*, 706.

[696] See Nottingham, C.; Benson, R.; Müller-Bunz, H.; Guiry, P.J. *J. Org. Chem.* ***2015***, *80*, 10163; Wang, M.-C.; Huang, P.-J.; Yang, X.-C.; Song, X.; Lu, H.-J. *Tetrahedron: Asymmetry* ***2014***, *25*, 781; Karabuga, S.; Karakaya, I.; Ulukanli, S. *Tetrahedron: Asymmetry* ***2014***, *25*, 851.

[697] For a review, see Binder, C.M.; Singara, B. *Org. Prep. Proceed. Int.* ***2011***, *43*, 139.

[698] Hirose, T.; Sugawara, K.; Kodama, K. *J. Org. Chem.* ***2011***, *76*, 5413; Zong, H.; Huang, H.; Bian, G.; Song, L. *Tetrahedron Lett.* ***2013***, *54*, 2722; Aga, M.A.; Kumar, B.; Rouf, A.; Shah, B.A.; Taneja, S.C. *Tetrahedron Lett.* ***2014***, *55*, 2639; Gök, Y.; Kekeç, L. *Tetrahedron Lett.* ***2014***, *55*, 2727; Faigl, F.; Erdélyi, Z.; Deák, S.; Nyerges, M.; Mátravölgyi, B. *Tetrahedron Lett.* ***2014***, *55*, 6891; Frensch, G.; Labes, R.; Wosch, C.-L.; dos Santos Munaretto, L.; Salomé, K.S.; Guerrero Jr., P.G.; Marques, F.A. *Tetrahedron Lett.* ***2016***, *57*, 420; Yang, T.; Zhang, Y.; Cao, P.; Wang, M.; Li, L.; Li, D.; Liao, J. *Tetrahedron* ***2016***, *72*, 2707.

[699] Rudolph, J.; Bolm, C.; Norrby, P.-O. *J. Am. Chem. Soc.* ***2005***, *127*, 1548. See Wang, M.-C.; Li, G.-W.; Hu, W.-B.; Hua, Y.-Z.; Song, X.; Lu, H.-J. *Tetrahedron: Asymmetry* ***2014***, *25*, 1360.

[700] Bach, M.F.; Griebeler, C.H.; Jacoby, C.G.; Schneider, P.H. *Eur. J. Org. Chem.* ***2017***, 6997.

[701] For a review, see Pu, L. *Tetrahedron* ***2003***, *59*, 9873. See Li, Z.-B.; Pu, L. *Org. Lett.* ***2004***, *6*, 1065; Dahmen, S. *Org. Lett.* ***2004***, *6*, 2113; Kang, Y.-F.; Liu, L.; Wang, R.; Yan, W.-J.; Zhou, Y.-F. *Tetrahedron: Asymmetry* ***2004***, *15*, 3155.

[702] Hatano, M.; Miyamoto, T.; Ishihara, K. *Org. Lett.* ***2007***, *9*, 4535.

[703] Wieland, L.C.; Deng, H.; Snapper, M.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2005***, *127*, 1545. Alse see Friel, D.K.; Snapper, M.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2008***, *130*, 9942.

[704] Cozzi P.G.; Kotrusz, P. *J. Am. Chem. Soc.* ***2006***, *128*, 4940.

[705] Tanaka, T.; Yasuda, Y.; Hayashi, M. *J. Org. Chem.* ***2006***, *71*, 7091.

[706] Milburn, R.R.; Hussain, S.M.S.; Prien, O.; Ahmed, Z.; Snieckus, V. *Org. Lett.* ***2007***, *9*, 4403; Infante, R.; Nieto, J.; Andrés, C. *Synthesis* ***2012***, *44*, 1343.

alcohol with good enantioselectivity.[707] High enantioselectivity was obtained from R_2Zn reagents (R = alkyl)[708] and aromatic aldehydes[709] by the use of a small amount of various catalysts.[710] The enantioselectivity is influenced by additives, such as LiCl.[711] Silica-immobilized chiral ligands[712] can be used in conjunction with dialkylzinc reagents, and polymer-supported ligands have been used.[713] The 1,2-addition of (*E*)-di- and (*E*)-trisubstituted vinylzinc reagents to β-silyloxy aldehydes, with alkyl zinc triflate and with nonaflate Lewis acids, gave the *anti*-allylic alcohol.[714] The reaction of benzaldehyde with RZnOAcMg(OAc)Br in the presence of Mg/TADDOLate gave the alcohol with good enantioselectivity.[715] Vinylzinc reagents were prepared by the reaction of vinyl iodides with $ZnEt_2$ and added to aldehydes in the presence of chiral additives to give the allylic alcohols.[716]

Organochromium compounds add to aldehydes or ketones.[717] The reaction of an organochromium reagent with an aldehyde or ketone is known as the *Nozaki-Hiyama reaction.* In the original version, a Cr(II) solution was prepared by reduction of chromic chloride by $LiAlH_4$, and this was subsequently treated with an aldehyde and an allylic halide.[718] The coupling of allylic halides and aldehydes or ketones in the presence of a Cr catalyst and a chiral ligand gives products with good enantioselectivity.[719] Enantioselective coupling reactions catalyzed by Cr compounds are of increasing interest.[720] The organochromium reagent may be derived from vinyl halides, triflates, or aryl derivatives.[721] The Cr-catalyzed reaction of allylic chlorides with aldehydes, mediated by Mn, gave the homoallylic alcohol.[722]

Other metals facilitate addition of groups to an aldehyde, including the coupling of an alkene to an aldehyde using a Ni catalyst.[723] Vinyl bromides react with $NiBr_2/CrCl_3$/TMSCl to give a reagent that adds to aldehydes to give the allylic alcohol.[724] Vinyl complexes generated from alkynes and SmI_2 add intramolecularly, and eight-membered rings have been

[707] See Braga, A.L.; Paixão, M.W.; Westermann, B.; Schneider, P.H.; Wessjohann, L.A. *J. Org. Chem.* ***2008***, *73*, 2879.
[708] See Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* ***2001***, *123*, 2464.
[709] See Soai, K.; Yokoyam, S.; Hayasaka, T. *J. Org. Chem.* ***1991***, *56*, 4264.
[710] Pu, L.; Yu, H.-B. *Chem. Rev.* ***2001***, *101*, 757. See also, Harada, T.; Kanda, K.; Hiraoka, Y.; Marutani, Y.; Nakatsugawa, M. *Tetrahedron: Asymmetry* ***2004***, *15*, 3879.
[711] Sosa-Rivadeneyra, M.; Muñoz-Muñiz, O.; de Parrodi, C.A.; Quintero, L.; Juaristi, E. *J. Org. Chem.* ***2003***, *68*, 2369; García, C.; La Rochelle, L.K.; Walsh, P.J. *J. Am. Chem. Soc.* ***2002***, *124*, 10970.
[712] Fraile, J.M.; Mayoral, J.A.; Servano, J.; Pericàs, M.A.; Solà, L.; Castellnou, D. *Org. Lett.* ***2003***, *5*, 4333.
[713] See Lipshutz, B.H.; Shin, Y.-J. *Tetrahedron Lett.* ***2000***, *41*, 9515.
[714] See Raffier, L.; Stanton, G.R.; Walsh, P.J. *Org. Lett.* ***2013***, *15*, 6174.
[715] Jagtap, R.S.; Joshi, N.N. *Tetrahedron Lett.* ***2011***, *52*, 6501.
[716] DeBerardinis, A.M.; Turlington, M.; Pu, L. *Angew. Chem. Int. Ed.* ***2011***, *50*, 2368.
[717] See Wessjohann, L.A.; Schmidt, G.; Schrekker, H.S. *Tetrahedron* ***2008***, *64*, 2134.
[718] Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* ***1977***, *99*, 3179. See Takai, K. *Org. React.* ***2004***, *64*, 253.
[719] Hargaden, G.C.; O'Sullivan, T.P.; Guiry, P.J. *Org. Biomol. Chem.* ***2008***, *6*, 562; Huang, X.-R.; Chen, C. *Tetrahedron: Asymmetry* ***2010***, *21*, 2999.
[720] Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* ***2006***, *128*, 2554; Shimada, Y.; Katsuki, T. *Chem. Lett.* ***2005***, *34*, 786.
[721] Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* ***1983***, *24*, 5281.
[722] Xiong, Y.; Zhang, G. *Org. Lett.* ***2016***, *18*, 5094.
[723] Ng, S.-S.; Ho, C.-Y.; Jamison, T.F. *J. Am. Chem. Soc.* ***2006***, *128*, 11513.
[724] Kuroboshi, M.; Tanaka, M.; Kishimoto, S.; Goto, K.; Mochizuki, M.; Tanaka, H. *Tetrahedron Lett.* ***2000***, *41*, 81.

formed in this way.[725] Vinyl reagents are formed *in situ* via organozirconium compounds with Me_2Zn, Ti compounds, and terminal alkynes.[726]

Lithium dimethylcopper (Me_2CuLi) reacts with aldehydes[727] and with certain ketones[728] to give the expected alcohols. Vinyltellurium compounds react with $BF_3{\bullet}OEt_2$ and cyanocuprates [R(2-thienyl)$CuCNLi_2$] to give a reagent that adds 1,2- to the carbonyl of a conjugated ketone.[729] Vinyltellurium compounds also react with *n*-butyllithium to give a reagent that adds to nonconjugated ketones.[730] In conjunction with $BeCl_2$, organolithium reagents add to conjugated ketones. In THF, 1,4-addition is observed, but in diethyl ether the 1,2-addition product is formed.[731] The lithium cation has been shown to play a key role in the transition state of the addition of allenyl cuprates to aldehydes.[732]

Alkynes add to aldehydes elsewhere in the same molecule in the presence of BEt_3 and a Ni catalyst to give a cyclic allylic alcohol.[733] Alkene aldehydes react similarly using Me_3SiOTf.[734] In a similar manner, dienes[735] or alkynes[736] add to aldehydes in the presence of a Ni catalyst. Allenes add to aldehydes in the presence of a Ni catalyst, using a chiral imidazolinyl carbene ligand, and the product is trapped as the triethylsilyl ether by addition of Et_3SiI.[737] Terminal alkynes react with Zr complexes and Me_2Zn to give an allylic tertiary alcohol.[738] Internal alkynes also give allylic alcohols in the presence of BEt_3 and a Ni catalyst.[739] Reaction of an aldehyde containing a conjugated diene unit with diethylzinc and a Ni catalyst leads to cyclic alcohols having a pendant allylic unit.[740] A similar reaction was reported using a Cu catalyst.[741] The intramolecular addition of an alkene to an aldehyde leads to a saturated cyclic alcohol using $PhSiH_3$ and a Co catalyst.[742]

Aryl halides react with a Ni complex under electrolytic conditions to add the aryl group to aldehydes.[743] α-Iodo phosphonate esters react with aldehydes and SmI_2 to give a β-hydroxy phosphonate ester.[744] Addition to the allene in the presence of a Ni catalyst[745] or a $CeCl_3$ catalyst[746] is followed by addition of the intermediate organometallic to the aldehyde to give the cyclic product.

[725] Hölemann, A.; Reissig, H.-U. *Synlett* ***2004***, 2732.
[726] Li, H.; Walsh, P.J. *J. Am. Chem. Soc.* ***2005***, *127*, 8355.
[727] See Reetz, M.T.; Rölfing, K.; Griebenow, N. *Tetrahedron Lett.* ***1994***, *35*, 1969.
[728] See Matsuzawa, S.; Isaka, M.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* ***1989***, *30*, 1975.
[729] Araújo, M.A.; Barrientos-Astigarraga, R.E.; Ellensohn, R.M.; Comasseto, J.V. *Tetrahedron Lett.* ***1999***, *40*, 5115.
[730] Dabdoub, M.J.; Jacob, R.G.; Ferreira, J.T.B.; Dabdoub, V.B.; Marques, F.de A. *Tetrahedron Lett.* ***1999***, *40*, 7159.
[731] Krief, A.; de Vos, M.J.; De Lombart, S.; Bosret, J.; Couty, F. *Tetrahedron Lett.* ***1997***, *38*, 6295.
[732] Mangeney, P.; Gérard, H.; Vrancken, E. *Synthesis* ***2017***, *49*, 526.
[733] Miller, K.M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T.F. *J. Am. Chem. Soc.* ***2004***, *126*, 4130.
[734] Suginome, M.; Iwanami, T.; Yamamoto, A.; Ito, Y. *Synlett* ***2001***, 1042. For a reaction using a Ni catalyst, see Ng, S.-S.; Jamison, T.F. *J. Am. Chem. Soc.* ***2005***, *127*, 14194.
[735] Sawaki, R.; Sato, Y.; Mori, M. *Org. Lett.* ***2004***, *6*, 1131.
[736] See Yang, Y.; Zhu, S.-F.; Zhou, C.-Y.; Zhou, Q.-L. *J. Am. Chem. Soc.* ***2008***, *130*, 14052.
[737] Ng, S.-S.; Jamison, T.F. *J. Am. Chem. Soc.* ***2005***, *127*, 7320.
[738] Li, H.; Walsh, P.J. *J. Am. Chem. Soc.* ***2004***, *126*, 6538.
[739] Miller, K.M.; Jamison, T.F. *J. Am. Chem. Soc.* ***2004***, *126*, 15342.
[740] Shibata, K.; Kimura, M.; Shimizu, M.; Tamaru, Y. *Org. Lett.* ***2001***, *3*, 2181.
[741] Agapiou, K.; Cauble, D.F.; Krische, M.J. *J. Am. Chem. Soc.* ***2004***, *126*, 4528.
[742] Baik, T.-G.; Luis, A.L.; Wang, L.-C.; Krische, M.J. *J. Am. Chem. Soc.* ***2001***, *123*, 5112.
[743] Durandetti, M.; Nédélec, J.-Y.; Périchon, J. *Org. Lett.* ***2001***, *3*, 2073.
[744] Orsini, F.; Caselli, A. *Tetrahedron Lett.* ***2002***, *43*, 7255.
[745] Montgomery, J.; Song, M. *Org. Lett.* ***2002***, *4*, 4009.
[746] Fischer, S.; Groth, U.; Jeske, M.; Schütz, T. *Synlett* ***2002***, 1922.

Intramolecular addition of a conjugated ester (via the β carbon) to an aldehyde generates a cyclic ketone.[747] This type of coupling has been called the *Stetter reaction*,[748] which actually involves the addition of aldehydes to activated double bonds (**15-30**), mediated by a catalytic amount of thiazolium salt in the presence of a weak base. The intramolecular addition of the allene moiety to an aldehyde is catalyzed by a Pd complex in the presence of $Me_3SiSnBu_3$.[749] A highly enantio- and diastereoselective intramolecular Stetter reaction has been developed.[750] Alkynyl aldehydes react with silanes such as Et_3SiH and a Ni catalyst to give a cyclic compound having a silyl ether and an exocyclic vinylidene unit.[751] Alkene aldehydes give cyclic alcohols via intramolecular addition of the C═C unit to the carbonyl under electrolytic conditions using a phase-transfer catalyst.[752] A similar cyclization was reported using $SnCl_4$.[753] Vinylidene cycloalkanes react with aldehydes in the presence of a Pd catalyst to give a homoallylic alcohol where addition occurs at the carbon exocyclic to the ring.[754] Allenes react with benzaldehyde using $HCl/SnCl_2$ with a Pd catalyst.[755] Silyl allenes react with aldehydes in the presence of a chiral Sc catalyst to give homopropargylic alcohols with good enantioselectivity.[756] Intramolecular cyclization of allenyl aldehydes via reaction with PhI and a Pd catalyst gave cyclic alcohols with a pendant phenyl alkene unit.[757] Allenes add to ketones to give homoallylic alcohols in the presence of SmI_2 and HMPA.[758] Conjugated dienes react with aldehydes via acyl addition of a terminal carbon of the diene in the presence of $Ni(acac)_2$ and Et_2Zn.[759]

The reaction of Na or K alkyne anions (e.g., RC≡C─M, **16-38**) with ketones or aldehydes gives the propargylic alcohol via acyl addition.[760] The problems associated with propargyl allenyl systems in their addition reactions with carbonyl compounds has been reviewed.[761] In the reaction with terminal acetylenes,[762] sodium acetylides are the most common reagents, but lithium acetylides are commonly used.[763] While Na is the metal of choice for the addition of acetylenic groups, vinylic alanes (prepared as in **15-12**) are the reagents of choice for the addition of vinylic groups.[764] A chiral phosphoric acid was used with an Ir catalyst for the addition of terminal alkynes to aldehydes to give the homoallylic

[747] Kerr, M.S.; Rovis, T. *J. Am. Chem. Soc.* ***2004***, *126*, 8876.
[748] Stetter, H.; Schreckenberg, M. *Angew. Chem. Int. Ed.* ***1973***, *12*, 81; Stetter, H.; Kuhlmann, H. *Org. React.* ***1991***, *40*, 407; Kerr, M.S.; Rovis, T. *J. Am. Chem. Soc.* ***2004***, *126*, 8876; Mennen, S.; Blank, J.; Tran-Dube, M.B.; Imbriglio, J.E.; Miller, S.J. *Chem. Commun.* ***2005***, 195. See Mattson, A.E.; Bharadwaj, A.R.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2004***, *126*, 2314.
[749] Kang, S.-K.; Ha, Y.-H.; Ko, B.-S.; Lim, Y.; Jung, J. *Angew. Chem. Int. Ed.* ***2002***, *41*, 343.
[750] Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* ***2005***, *127*, 6284.
[751] Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* ***1999***, *121*, 6098.
[752] Locher, C.; Peerzada, N. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 179.
[753] Alcaide, B.; Pardo, C.; Rodríguez-Ranera, C.; Rodríguez-Vicente, A. *Org. Lett.* ***2001***, *3*, 4205.
[754] Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* ***2000***, *2*, 4059.
[755] Chang, H.-M.; Cheng, C.-H. *Org. Lett.* ***2000***, *2*, 3439.
[756] Evans, D.A.; Sweeney, Z.K.; Rovis, T.; Tedrow, J.S. *J. Am. Chem. Soc.* ***2001***, *123*, 12095.
[757] Kang, S.-K.; Lee, S.-W.; Jung, J.; Lim, Y. *J. Org. Chem.* ***2002***, *67*, 4376.
[758] Hölemann, A.; Reißig, H.-U. *Chem. Eur. J.* ***2004***, *10*, 5493.
[759] Loh, T.-P.; Song, H.-Y.; Zhou, Y. *Org. Lett.* ***2002***, *4*, 2715.
[760] See Guillarme, S.; Plé, K.; Banchet, A.; Liard, A.; Haudrechy, A. *Chem. Rev.* ***2006***, *106*, 2355.
[761] Wisniewska, H.M.; Jarvo, E.R. *J. Org. Chem.* ***2013***, *78*, 11629.
[762] Ziegenbein, W. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 207–241; Ried, W. *Newer Methods Prep. Org. Chem.* ***1968***, *4*, 95.
[763] Tanaka, K.; Kukita, K.; Ichibakase, T.; Kotani, S.; Nkajima, M. *Chem. Commun.* ***2011***, *47*, 5614.
[764] See Jacob III, P.; Brown, H.C. *J. Org. Chem.* ***1977***, *42*, 579.

alcohol.[765] The Cu-catalyzed reaction of enynes gave an organocopper intermediate that reacted with a carbonyl compound to give the homoallylic yne enol.[766]

A solvent-free reaction was reported that mixed a ketone, a terminal alkyne, and potassium *tert*-butoxide.[767] The reaction is sometimes called the *Nef reaction*. Li,[768] Mg, and other metallic acetylides have also been used. A particularly convenient reagent is lithium acetylide/ethylenediamine complex,[769] a stable, free-flowing powder that is commercially available. Alternatively, the substrate may be treated with the alkyne itself in the presence of a base, so that the acetylide is generated *in situ*. This procedure is called the *Favorskii reaction* – not to be confused with the Favorskii rearrangement (**18-7**).[770]

Zinc(II) chloride facilitates the addition of a terminal alkyne to an aldehyde to give a propargylic alcohol.[771] Zinc(II) triflate can also be used for alkyne addition to aldehydes,[772] and in the presence of a chiral ligand leads to good enantioselectivity in the propargyl alcohol product.[773] The reagents Et_3Al, Et_2Zn, and a terminal alkyne react with ketones, and in the presence of a *Cinchona* alkaloid gives the alkynyl alcohol in moderate enantiomeric excess.[774] Other enantioselective alkynylation reactions are known using various catalysts.[775] Terminal alkynes add to aryl aldehydes in the presence of $InBr_3$ and NEt_3,[776] SmI_2,[777] or Me_2Zn.[778] A Zn-mediated reaction using iodoalkynes is known,[779] and catalytically generated zinc acetylides add to aldehydes.[780] An In-catalyzed addition of alkynes to aldehydes used a catalytic amount of BINOL and gave the alkynyl alcohol with high enantioselectivity.[781] Other enantioselective addition reactions of terminal alkynes are known.[782]

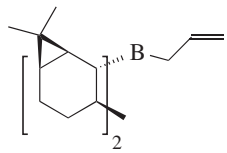
Propargylic acetate adds to aldehydes with good *anti* selectivity in the presence of Et_2Zn and a Pd catalyst.[783] Aldehydes reacted with propargyl bromide using $FeCl_3$/Zn or

[765] Miura, T.; Nishida, Y.; Morimoto, M.; Murakami, M. *J. Am. Chem. Soc.* ***2013***, *135*, 11497.
[766] Wei, X.-F.; Xie, X.-W.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* ***2017***, *139*, 4647.
[767] Miyamoto, H.; Yasaka, S.; Tanaka, K. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 185.
[768] See Midland, M.M. *J. Org. Chem.* ***1975***, *40*, 2250.
[769] Beumel Jr., O.F.; Harris, R.F. *J. Org. Chem.* ***1963***, *28*, 2775.
[770] See Kondrat'eva, L.A.; Potapova, I.M.; Grigina, I.N.; Glazunova, E.M.; Nikitin, V.I. *J. Org. Chem. USSR* ***1976***, *12*, 948.
[771] Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* ***2002***, *43*, 8323.
[772] Frantz, D.E.; Fässler, R.; Carreira, E.M. *J. Am. Chem. Soc.* ***2000***, *122*, 1806.
[773] Boyall, D.; Frantz, D.E.; Carreira, E.M. *Org. Lett.* ***2002***, *4*, 2605; Xu, Z.; Chen, C.; Xu, J.; Miao, M.; Yan, W.; Wang, R. *Org. Lett.* ***2004***, *6*, 1193. For an example using zinc(II) diflate, see Chen, Z.; Xiong, W.; Jiang, B. *Chem. Commun.* ***2002***, 2098.
[774] Liu, L.; Wang, R.; Kang, Y.-F.; Chen, C.; Xu, Z.-Q.; Zhou, Y.-F.; Ni, M.; Cai, H.-Q.; Gong, M.-Z. *J. Org. Chem.* ***2005***, *70*, 1084. For a review of asymmetric alkynylations, see Bisai, V.; Singh, V.K. *Tetrahedron Lett.* ***2016***, *57*, 4771.
[775] See Li, H.; Huang, Y.; Jin, W.; Xue, F.; Wan, B. *Tetrahedron Lett.* ***2008***, *49*, 1686; Mao, J.; Bao, Z.; Guo, J.; Ji, S. *Tetrahedron* ***2008***, *64*, 9901.
[776] Sakai, N.; Hirasawa, M.; Konakahara, T. *Tetrahedron Lett.* ***2003***, *44*, 4171.
[777] Kwon, D.W.; Cho, M.S.; Kim, Y.H. *Synlett* ***2001***, 627.
[778] Wolf, C.; Liu, S. *J. Am. Chem. Soc.* ***2006***, *128*, 10996; Cozzi, P.G.; Rudolph, J.; Bolm, C.; Norrby, P.-O.; Tomasini, C. *J. Org. Chem.* ***2005***, *70*, 5733.
[779] Srihari, P.; Singh, V.K.; Bhunia, D.C.; Yadav, J.S. *Tetrahedron Lett.* ***2008***, *49*, 7132.
[780] Downey, C.W.; Mahoney, B.D.; Lipari, V.R. *J. Org. Chem.* ***2009***, *74*, 2904.
[781] Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* ***2005***, *127*, 13760. See Turlington, M.; Pu, L. *Synlett* ***2012***, *23*, 649.
[782] Ekström, J.; Zaitsev, S.B.; Adolfsson, H. *Synlett* ***2006***, 885.
[783] Marshall, J.A.; Adams, N.D. *J. Org. Chem.* ***1999***, *64*, 5201.

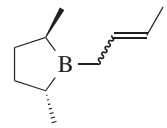
$CuCl_2$•H_2O/Zn to give the homopropargyl alcohol.[784] The Pd-catalyzed reaction of aldehydes and allylic bromides was mediated by $SnCl_2$•2 H_2O and gave the homoallylic alcohol.[785] The Ag-catalyzed addition of terminal alkynes to cyclic ketones was reported using aqueous media.[786] The Ni-catalyzed, indium-mediated reaction of propargyl mesylates or carbonates with aldehydes has been reported.[787] The In-mediated reaction of aldehydes and ketones with propargyl bromides gave the 1,2-addition product, the homoallylic alcohol.[788] The Cr-catalyzed reaction of propargyl chlorides with ketones, mediated by Mn, gave the homopropargylic alcohol.[789]

16-24 The Addition of Organoboranes to Aldehydes and Ketones

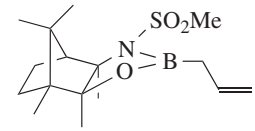
Although organoboranes do not generally add to aldehydes and ketones,[790] allylic boranes are exceptions.[791] When they add, an allylic rearrangement always takes place. The use of a chiral catalyst leads to asymmetric induction[792] and chiral allylic boranes have been prepared.[793] It is noted that chloroboranes (R_2BCl) react with aldehydes via acyl addition of the alkyl group, giving the corresponding alcohol after treatment with water.[794] Treatment with catecholborane gives addition to the conjugated ketone, and subsequent cyclization of the resulting organometallic at the nonconjugated ketone gives a cyclic alcohol with a pendant ketone unit, after treatment with methanol.[795] Addition of trialkylboranes to aldehydes is catalyzed by a Ni complex.[796]



20



21



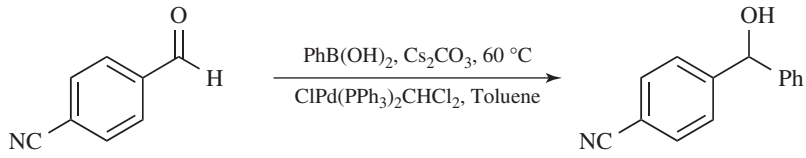
22

A number of optically active allylic boron compounds have been used, including[797] *B*-allylbis(2-isocaranyl)borane (**20**),[798] (*E*)- and (*Z*)-crotyl-(*R*,*R*)-2,5-dimethylborolanes

[784] Ghosh, P.; Chattopadhyay, A. *Tetrahedron Lett.* ***2012***, *53*, 5202.
[785] Kashyap, B.; Phukan, P. *Tetrahedron Lett.* ***2013***, *54*, 6324.
[786] Jia, Z.; Li, X.; Chan, A.S.C.; Li, C.-J. *Synlett* ***2012***, *23*, 2758.
[787] Hirashita, T.; Suzuki, Y.; Tsuji, H.; Sato, Y.; Naito, K.; Araki, S. *Eur. J. Org. Chem.* ***2012***, 5668.
[788] Haddad, T.D.; Hirayama, L.C.; Buckley, J.J.; Singaram, B. *J. Org. Chem.* ***2012***, *77*, 889; Woo, S.K.; Geary, L.M.; Krische, M.J. *Angew. Chem. Int. Ed.* ***2012***, *51*, 7830.
[789] Harper, K.C.; Vilardi, S.C.; Sigman, M.S. *J. Am. Chem. Soc.* ***2013***, *135*, 2482.
[790] See Satoh, Y.; Tayano, T.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* ***1989***, *30*, 5153.
[791] See Hoffmann, R.W.; Niel, G.; Schlapbach, A. *Pure Appl. Chem.* ***1990***, *62*, 1993; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 310–318; Buynak, J.D.; Geng, B.; Uang, S.; Strickland, J.B. *Tetrahedron Lett.* ***1994***, *35*, 985.
[792] Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2004***, *126*, 8910. For an enantioselective reaction with an alkoxyborane, see Lou, S.; Moquist, P.N.; Schaus, S.E. *J. Am. Chem. Soc.* ***2006***, *128*, 12660.
[793] See Schneider, U.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* ***2008***, *130*, 13824.
[794] Kabalka, G.W.; Wu, Z.; Ju, Y. *Tetrahedron* ***2002***, *58*, 3243.
[795] Huddleston, R.R.; Cauble, D.F.; Krische, M.J. *J. Org. Chem.* ***2003***, *68*, 11.
[796] Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2005***, *7*, 4689.
[797] See Roush, W.R.; Ando, K.; Powers, D.B.; Palkowitz, A.D.; Halterman, R.L. *J. Am. Chem. Soc.* ***1990***, *112*, 6339; Brown, H.C.; Randad, R.S. *Tetrahedron Lett.* ***1990***, *31*, 455; Stürmer, R.; Hoffmann, R.W. *Synlett* ***1990***, 759.
[798] Racherla, U.S.; Brown, H.C. *J. Org. Chem.* ***1991***, *56*, 401, and references cited therein.

(**21**),[799] and the borneol derivative **22**,[800] all of which add an allyl group to aldehydes, with good enantioselectivity. A recyclable 10-TMS-9-borabicyclo[3.3.2]decane has been used for asymmetric allyl and crotyl addition to aldehydes.[801] Where the substrate possesses an aryl group or a triple bond, using a metal carbonyl complex of the substrate enhances enantioselectivity.[802] Chiral biphenols catalyze the enantioselective reaction of allenyldioxoborolane with ketones, in the absence of solvent and under microwave irradiation, to give the homopropargylic alcohol.[803]

In the presence of Ru,[804] Cu,[805] Ni,[806] or Pd[807] compounds, $RB(OH)_2$ and arylboronic acids ($ArB(OH)_2$, see **12-27**) add to aldehydes to give the corresponding alcohol, as in the Pd-catalyzed reaction that gave **23**.[807]



23

The Pd-catalyzed addition of arylboronic acids to aryl aldehydes gave the diaryl alcohol and it was observed that the solvent played a role in the course of the reaction.[808] Aldehydes reacted with arylboronic acids in the presence of a Rh catalyst.[809] The Rh-catalyzed 1,2-addition of arylboronic acids to α-diketones gave α-hydroxy ketones.[810] The sealed-vessel microwave heating of aromatic and aliphatic aldehydes with arylboronic acids at 180 °C in toluene, with a Ni catalyst, gave the alcohol.[811] The Co-catalyzed reaction of a vinylboronic acid and carbonyl compounds gave the corresponding allylic alcohols.[812]

Arylboronic acids add to aldehydes in the presence of a chiral ligand to give an alcohol with good enantioselectivity.[813] An enantioselective intramolecular reaction of an arylboronic acid to a pendant ketone moiety used a Pd catalyst.[814] The Ru-catalyzed reaction

[799] Garcia, J.; Kim, B.M.; Masamune, S. *J. Org. Chem.* ***1987***, *52*, 4831.
[800] Reetz, M.T.; Zierke, T. *Chem. Ind. (London)* ***1988***, 663.
[801] Burgos, C.H.; Canales, E.; Matos, K.; Soderquist, J.A. *J. Am. Chem. Soc.* ***2005***, *127*, 8044.
[802] Roush, W.R.; Park, J.C. *J. Org. Chem.* ***1990***, *55*, 1143.
[803] Barnett, D.S.; Schaus, S.E. *Org. Lett.* ***2011***, *13*, 4020.
[804] Ueda, M.; Miyaura, N. *J. Org. Chem.* ***2000***, *65*, 4450 and references cited therein; Duan, H.-F.; Xie, J.-H.; Shi, W.-J.; Zhang, Q.; Zhou, Q.-L. *Org. Lett.* ***2006***, *8*, 1479. See Son, S.U.; Kim, S.B.; Reingold, J.A.; Carpenter, G.B.; Sweigart, D.A. *J. Am. Chem. Soc.* ***2005***, *127*, 12238.
[805] Zheng, H.; Zhang, Q.; Chen, J.; Liu, M.; Cheng, S.; Ding, J.; Wu, H.; Su, W. *J. Org. Chem.* ***2009***, *74*, 943.
[806] Zhou, L.; Du, X.; He, R.; Ci, Z.; Bao, M. *Tetrahedron Lett.* ***2009***, *50*, 406.
[807] Yamamoto, T.; Ohta, T.; Ito, Y. *Org. Lett.* ***2005***, *7*, 4153.
[808] Das, T.; Chakraborty, A.; Sarkar, A. *Tetrahedron Lett.* ***2014***, *55*, 5174.
[809] Yang, J.; Chen, X.; Wang, Z. *Tetrahedron Lett.* ***2015***, *56*, 5673.
[810] Feng, X.; Nie, Y.; Yang, J.; Du, H. *Org. Lett.* ***2012***, *14*, 624; Zhu, T.-S.; Jin, S.-S.; Xu, M.-H. *Angew. Chem. Int. Ed.* ***2012***, *51*, 780.
[811] Chen, W.; Baghbanzadeh, M.; Kappe, C.O. *Tetrahedron Lett.* ***2011***, *52*, 1677.
[812] Huang, Y.; Huang, R.-Z.; Zhao, Y. *J. Am. Chem. Soc.* ***2016***, *138*, 6571.
[813] Duan, H.-F.; Xie, J.-H.; Qiao, X.-C.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* ***2008***, *47*, 4351; Jumde, V.R.; Facchetti, S.; Iuliano, A. *Tetrahedron: Asymmetry* ***2010***, *21*, 2775.
[814] Liu, G.; Lu, X. *J. Am. Chem. Soc.* ***2006***, *128*, 6504.

of arylboronic acids with aryl aldehydes gave chiral diarylmethanols with excellent enantioselectivity.[815] An intramolecular version of the phenylboronic acid-induced reaction is known, where a molecule with ketone and conjugated ketone units is converted to a cyclic alcohol using a chiral Rh catalyst.[816]

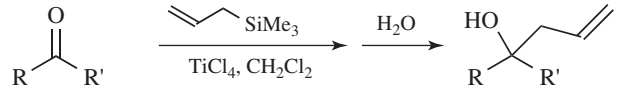
Boronic esters (boronates) can also be used in this acyl addition reaction. Allylic boronates add to aldehydes,[817] and there are enantioselective reactions.[818] The Cu-catalyzed reaction of aryl aldehydes with $[(Pin)B]_2CH(Me)$ gave the *syn*-1,2-hydroxyboronate.[819] The Cu-catalyzed propargylation of aldehydes with trimethylsilyl propargyl boronates gave 1-TMS homopropargyl alcohols.[820] Cyclopropylmethyl boronates reacted with aldehydes in the presence of $PhBCl_2$ to give bis(homoallyl) alcohols.[821] Allenyl boronates reacted with aldehydes to give the homopropargyl alcohols, catalyzed by (BINOL)-derived phosphoric acids.[822] 1-Alkenyl boronates generated a transient allylic boronate intermediate that reacted with aldehydes to give the *anti*-homoallylic alcohol.[823] The $ZnEt_2$-catalyzed reaction of allenyl boronate and aldehydes or ketones gave the allenyl alcohol.[824] Polymer-bound aryl borates add an aryl group to aldehydes in the presence of a Rh catalyst.[825] The CuCl/bipyridine-catalyzed addition reaction of arylboroxines with aldehydes gave the corresponding alcohol.[826] A Rh/diene-catalyzed reaction of arylboroxines/arylboronic acids with ketones gave the tertiary alcohol.[827]

The Pd-catalyzed reaction of aryl aldehydes with $PhBF_3K$ gave a diaryl alcohol.[828] A Ru-catalyzed reaction of aryltrifluoroborates led to sterically hindered diaryl ketones.[829] Aliphatic aldehydes react with trifluoroborates, in the presence of $BF_3{\bullet}OEt_2$, to give the homoallylic alcohol with allylic rearrangement and a preference for the *syn* diastereomer,[830] and aryl aldehydes react as well.[831] Allylic trifluoroborates (**12-27**) reacted with aldehydes to give the homoallylic alcohol. Aldehydes reacted with potassium allyltrifluoroborate to give the allylated product using a lanthanide catalyst.[832] The propargylation of aldehydes

[815] Li, K.; Hu, N.; Luo, R.; Yuan, W.; Tang, W. *J. Org. Chem.* ***2013***, *78*, 6350.
[816] Cauble, D.F.; Gipson, J.D.; Krische, M.J. *J. Am. Chem. Soc.* ***2003***, *125*, 1110.
[817] See Bouffard, J.; Itami, K. *Org. Lett.* ***2009***, *11*, 4410.
[818] Schneider, U.; Kobayashi, S. *Angew. Chem. Int. Ed.* ***2007***, *46*, 5909; Hall, D.G. *Synlett* ***2007***, 1644. See Barnett, D.S.; Moquist, P.N.; Schaus, S.E. *Angew. Chem. Int. Ed.* ***2009***, *48*, 8679.
[819] Joannou, M.V.; Moyer, B.S.; Meek, S.J. *J. Am. Chem. Soc.* ***2015***, *137*, 6176.
[820] Fandrick, K.R.; Fandrick, D.R.; Reeves, J.T.; Gao, J.; Ma, S.; Li, W.; Lee, H.; Grinberg, N.; Lu, B.; Senanayake, C.H. *J. Am. Chem. Soc.* ***2011***, *133*, 10332.
[821] Lin, H.; Pei, W.; Wang, H.; Houk, K.N.; Krauss, I.J. *J. Am. Chem. Soc.* ***2013***, *135*, 82.
[822] Grayson, M.N.; Goodman, J.M. *J. Am. Chem. Soc.* ***2013***, *135*, 6142. See Jain, P.; Wang, H.; Houk, K.N.; Antilla, J.C. *Angew. Chem. Int. Ed.* ***2012***, *51*, 1391; Huang, Y.; Yang, X.; Lv, Z.; Cai, C.; Kai, C.; Pei, Y.; Feng, Y. *Angew. Chem. Int. Ed.* ***2015***, *54*, 7299; Reddy, L.R. *Chem. Commun.* ***2012***, *48*, 9189.
[823] Shimizu, H.; Igarashi, T.; Miura, T.; Murakami, M. *Angew. Chem. Int. Ed.* ***2011***, *50*, 11465.
[824] Fandrick, D.R.; Saha, J.; Fandrick, K.R.; Sanyal, S.; Ogikubo, J.; Lee, H.; Roschangar, F.; Song, J.J.; Senanayake, C.H. *Org. Lett.* ***2011***, *13*, 5616.
[825] See Rudolph, J.; Schmidt, F.; Bolm, C. *Synthesis* ***2005***, 840.
[826] Liao, Y.-X.; Hu, Q.-S. *J. Org. Chem.* ***2011***, *76*, 7602.
[827] Liao, Y.-X.; Xing, C.-H.; Hu, Q.-S. *Org. Lett.* ***2012***, *14*, 1544.
[828] Kuriyama, M.; Shimazawa, R.; Enomoto, T.; Shirai, R. *J. Org. Chem.* ***2008***, *73*, 6939.
[829] Chuzel, O.; Roesch, A.; Genet, J.-P.; Darses, S. *J. Org. Chem.* ***2008***, *73*, 7800.
[830] Batey, R.A.; Thadani, A.N.; Smil, D.V. *Tetrahedron Lett.* ***1999***, *40*, 4289.
[831] Batey, R.A.; Thadani, A.N.; Smil, D.V.; Lough, A.J. *Synthesis* ***2000***, 990.
[832] Freitas, J.C.R.; de Oliveira, C.K.; Cunha, E.C.; Malvestiti, I.; Alves Jr., S.; Longo, R.L.; Menezes, P.H. *Tetrahedron Lett.* ***2013***, *54*, 1558.

using potassium allenyltrifluoroborate was promoted by tonsil clay.[833] Potassium alkynyltrifluoroborates (**12-27**) reacted with aldehydes and a secondary amine, in an ionic liquid, to give a propargylic amine.[834]

16-25 The Addition of Trialkylallylsilanes to Aldehydes and Ketones



24

Allylic alcohols can be treated with TMS-Cl and NaI, and then Bi, to give an organometallic reagent that adds to aldehydes.[835] Allyltrichlorosilanes have also been used in addition reactions with aldehydes.[836] Hünig's base (i-Pr_2NEt) and a sulfoxide have also been used to facilitate the addition of an allyl group to an aldehyde from allyltrichlorosilane.[837] The mechanism of this reaction has been examined.[838] The *Sakurai reaction*, also called the *Hosomi-Sakurai reaction*,[839] is the reaction of allyltrimethylsilanes with aldehydes or ketones in the presence of Lewis or Brønsted acid to give homoallylic alcohols such as **24**.[839] Alternative catalysts include $HClO_4$ supported on silica gel,[840] and organocatalysts.[841] The zinc-catalyzed hydrosilation of ketones is known.[842] The transition state for the bipyridine *N*-oxide-catalyzed, enantioselective propargylation of aromatic aldehydes with allenyltrichlorosilanes was examined using density functional theory.[843]

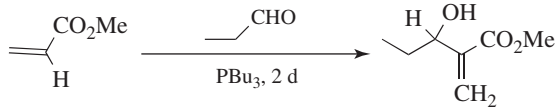
Allylic trialkyl, trialkoxy, and trihalosilanes add to aldehydes to give the homoallylic alcohols in the presence of a Lewis acid[844] (including $TaCl_5$[845] and $YbCl_3$[846]), fluoride ion,[847] proazaphosphatranes,[848] or a catalytic amount of iodine.[849] A Ru catalyst has been

[833] See Freitas, J.J.R.; Couto, T.R.; Cavalcanti, I.H.; Freitas, J.C.R.; Barbosa, Q.P.S.; Oliveira, R.A. *Tetrahedron Lett.* ***2016***, *57*, 760.
[834] Kabalka, G.W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* ***2004***, *45*, 729.
[835] Miyoshi, N.; Nishio, M.; Murakami, S.; Fukuma, T.; Wada, M. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 689.
[836] Kobayashi, S.; Nishio, K. *J. Org. Chem.* ***1994***, *59*, 6620.
[837] Massa, A.; Malkov, A.V.; Kocovský, P.; Scettri, A. *Tetrahedron Lett.* ***2003***, *44*, 7179.
[838] Bottoni, A.; Costa, A.L.; Di Tommaso, D.; Rossi, I.; Tagliavini, E. *J. Am. Chem. Soc.* ***1997***, *119*, 12131; Denmark, S.E.; Weber, E.J.; Wilson, T.; Willson, T.M. *Tetrahedron* ***1989***, *45*, 1053; Keck, G.E.; Andrus, M.B.; Castellino, S. *J. Am. Chem. Soc.* ***1989***, *111*, 8136.
[839] Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* ***1976***, *17*, 1295; Denmark, S.E.; Almstead, N.G. in *Modern Carbonyl Chemistry*, Otera, J., Ed., Wiley-VCH, Marshall, J.A. *Chem. Rev.* ***2000***, *100*, 3163; Marshall, J.A. *Chem. Rev.* ***1996***, *96*, 31; Yamamoto, Y.; Asao, N. *Chem. Rev.* ***1993***, *93*, 2207.
[840] Murugan, K.; Chen, C. *Tetrahedron Lett.* ***2011***, *52*, 5827.
[841] Kaib, P.S.J.; Schreyer, L.; Lee, S.; Properzi, R.; List, B. *Angew. Chem. Int. Ed.* ***2016***, *55*, 13200.
[842] Surzhko, V.; Roisnel, T.; Le Grel, B.; Le Grel, P.; Lalli, C.; Argouarch, G. *Tetrahedron Lett.* ***2017***, *58*, 1343.
[843] Lu, T.; Zhu, R.; An, Y.; Wheeler, S.E. *J. Am. Chem. Soc.* ***2012***, *134*, 3095.
[844] Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* ***1989***, *37*, 57 (pp. 113–125, 290–328); Parnes, Z.N.; Bolestova, G.I. *Synthesis* ***1984***, 991 (see pp. 997–1000). See Aggarwal, V.K.; Vennall, G.P. *Tetrahedron Lett.* ***1996***, *37*, 3745.
[845] Chandrasekhar, S.; Mohanty, P.K.; Raza, A. *Synth. Commun.* ***1999***, *29*, 257.
[846] Fang, X.; Watkin, J.G.; Warner, B.P. *Tetrahedron Lett.* ***2000***, *41*, 447.
[847] See Cossy, J.; Lutz, F.; Alauze, V.; Meyer, C. *Synlett* ***2002***, 45.
[848] Wang, Z.; Kisanga, P.; Verkade, J.G. *J. Org. Chem.* ***1999***, *64*, 6459.
[849] Yadav, J.S.; Chand, P.K.; Anjaneyulu, S. *Tetrahedron Lett.* ***2002***, *43*, 3783.

used in conjunction with an arylsilane and an aldehyde.[850] Allyl(trimethoxy)silane adds an allyl group to aldehydes using a CdF_2[851] catalyst or a chiral AgF complex.[852] Aldehydes and ketones reacted with $PhSiH_3$ in the presence of a cationic ruthenium nitrido compound to give the alcohol product.[853] The reaction of an aldehyde with an α-substituted allylsilane and $TiCl_4$ gave the homoallylic alcohol.[854]

Allyltrichlorosilane reacts with aldehydes in the presence of certain additives to give the corresponding alcohol,[855] and the reaction proceeds with good enantioselectivity by addition of a chiral additive.[856] The enhanced *N*-oxide selectivity shown for allylation when compared to propargylation has been discussed.[857] Other chiral additives have been used,[858] as well as chiral catalysts[859] and chiral complexes of allylsilanes.[860] Trimethoxyallylsilanes react with aldehydes in the presence of a Cu catalyst and a chiral ligand to give the chiral alcohol.[861] Chiral allylic silyl derivatives add to aldehydes to give the chiral homoallylic alcohol.[862]

16-26 The Addition of Conjugated Alkenes to Aldehydes: the Morita-Baylis-Hillman Reaction[863]



In the presence of a base,[864] such as 1,4-diazabicyclo[2.2.2]octane (DABCO) or trialkylphosphines, conjugated carbonyl compounds [ketones, esters (including lactones)[865] thioesters,[866] and amides[867]] add to aldehydes via the α carbon to give α-alkenyl-β-hydroxy

[850] Fujii, T.; Koike, T.; Mori, A.; Osakada, K. *Synlett* ***2002***, 298.
[851] Aoyama, N.; Hamada, T.; Manabe, K.; Kobayashi, S. *Chem. Commun.* ***2003***, 676.
[852] Yanagisawa, A.; Kageyama, H.; Nakatsuka, Y.; Asakawa, K.; Matsumoto, Y.; Yamamoto, H. *Angew. Chem. Int. Ed.* ***1999***, *38*, 3701.
[853] Truong, T.V.; Kastl, E.A.; Du, G. *Tetrahedron Lett.* ***2011***, *52*, 1670.
[854] Albury, A.M.M.; Jennings, M.P. *Tetrahedron Lett.* ***2013***, *54*, 4487.
[855] Malkov, A.V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kocovský, P. *J. Org. Chem.* ***2003***, *68*, 9659.
[856] Malkov, A.V.; Ramírez-López, P.; Biedermannová (née Bendová), L.; Rulíšek, L.; Dufková, L.; Kotora, M.; Zhu, F.; Kocovský, P. *J. Am. Chem. Soc.* ***2008***, *130*, 5341; De Sio, V.; Massa, A.; Scettri, A. *Org. Biomol. Chem.* ***2010***, *8*, 3055; Oh, Y.S.; Kotani, S.; Sugiura, M.; Nakajima, M. *Tetrahedron: Asymmetry* ***2010***, *21*, 1833.
[857] Lu, T.; Porterfield, M.A.; Wheeler, S.E. *Org. Lett.* ***2012***, *14*, 5310.
[858] Angell, R.M.; Barrett, A.G.M.; Braddock, D.C.; Swallow, S.; Vickery, B.D. *Chem. Commun.* ***1997***, 919.
[859] Malkov, A.V.; Dufková, L.; Farrugia, L.; Kocovsky, P. *Angew. Chem Int. Ed.* ***2003***, *42*, 3802.
[860] Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* ***1999***, *55*, 977.
[861] Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2005***, *127*, 4138; Yamamoto, H.; Wadamoto, M. *Chem. Asian J.* ***2007***, *2*, 692.
[862] See Hackman, B.M.; Lombardi, P.J.; Leighton, J.L. *Org. Lett.* ***2004***, *6*, 4375.
[863] See Basavaiah, D.; Rao, A.J.; Satyanarayana, T. *Chem. Rev.* ***2003***, *103*, 811.
[864] See Luo, S.; Mi, X.; Xu, H.; Wang, P.G.; Cheng, J.-P. *J. Org. Chem.* ***2004***, *69*, 8413.
[865] See Karur, S.; Hardin, J.; Headley, A.; Li, G. *Tetrahedron Lett.* ***2003***, *44*, 2991.
[866] See Tarsis, E.; Gromova, A.; Lim, D.; Zhou, G.; Coltart, D.M. *Org. Lett.* ***2008***, *10*, 4819.
[867] See Faltin, C.; Fleming, E.M.; Connon, S.J. *J. Org. Chem.* ***2004***, *69*, 6496.

esters or amides. This sequence is called the *Baylis-Hillman reaction* (or *Morita-Baylis-Hillman reaction*).[868] Mechanistic investigations of the reaction have been reported.[869] Methyl vinyl ketone gave other products in the Baylis-Hillman reaction, whereas conjugated esters do not.[870] Methods that are catalytic in base have been developed for the Baylis-Hillman reaction.[871] There is a protein-catalyzed reaction[872] and organocatalysts have been used.[873] It is known that DABCO accelerates the reaction.[874] Both microwave irradiation[875] and ultrasound[876] have been used to induce the reaction.[877] Baylis-Hillman reactions have been done in aqueous acidic media.[878] The reaction has been done in ionic liquids[879] and polyethylene glycol (PEG)[880] or sulfolane,[881] and without an organic solvent.[882] The mechanism of this reaction in ionic liquids has been probed.[883] A computational mechanistic study, using *N*-heterocyclic carbenes as catalysts, has been reported.[884] Transition metal compounds can facilitate the Baylis-Hillman reaction,[885] and BF_3•OEt_2 has been used.[886] A sila variation is known, involving the reaction of vinylsilanes and aldehydes.[887] The *aza-Baylis-Hillman reaction* is discussed in reaction **16-31**.

Ethoxyacetylene reacted with carbonyl compounds to prepare Baylis-Hillman adducts.[888] The reaction of cyclic unsaturated ketones with aldehydes gave the Morita-Baylis-Hillman product upon treatment with a catalytic amount of *N*-methylpyrrolidine

[868] Baylis, A.B.; Hillman, M.E.D. *Ger. Offen.* 2,155,133 (*Chem. Abstr.* ***1972***, *77*, 34174q, *U.S. Patent* 3,743,668). For a review, see Basavaiah, D.; Rao, P.D.; Hyma, R.S. *Tetrahedron* ***1996***, *52*, 8001; Rafel, S.; Leahy, J.W. *J. Org. Chem.* ***1997***, *62*, 1521. For a case study of a mechanism, see Plata, R.E.; Singleton, D.A. *J. Am. Chem. Soc.* ***2015***, *137*, 3811.

[869] Robiette, R.; Aggarwal, V.K.; Harvey, J.N. *J. Am. Chem. Soc.* ***2007***, *129*, 15513 (computational); Roy, D.; Sunoj, R.B. *Org. Lett.* ***2007***, *9*, 4873 (computational).

[870] Shi, M.; Li, C.-Q.; Jiang, J.-K. *Chem. Commun.* ***2001***, 833.

[871] See Pereira, S.I.; Adrio, J.; Silva, A.M.S.; Carretero, J.C. *J. Org. Chem.* ***2005***, *70*, 10175. For an ionic liquid immobilized base, see Mi, X.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* ***2005***, *70*, 2338.

[872] Reetz, M.T.; Mondière, R.; Carballeira, J.D. *Tetrahedron Lett.* ***2007***, *48*, 1679. Also see Shairgojray, B.A.; Dar, A.A.; Bhat, B.A. *Tetrahedron Lett.* ***2013***, *54*, 2391.

[873] Thorat, P.B.; Goswami, S.V.; Khade, B.C.; Bhusare, S.R. *Tetrahedron: Asymmetry* ***2012***, *23*, 1320; Song, H.L.; Yua, K; Wu, X.-Y. *Chem. Commun.* ***2011***, *47*, 1012.

[874] See Brezinsku, L.J.; Rafel, S.; Leahy, J.W. *Tetrahedron* ***1997***, *53*, 16423; Cai, J.; Park, K.S.; Kim, J.; Choo, H.; Chong, Y. *Synlett* ***2007***, 395. See Dordonne, S.; Crousse, B. Bonnet-Delpon, D.; Legros, J. *Chem. Commun.* ***2011***, *47*, 5855. For a discussion of salt effects, see Kumar, A.; Pawar, S.S. *Tetrahedron* ***2003***, *59*, 5019.

[875] Kundu, M.K.; Mukherjee, S.B.; Balu, N.; Padmakumar, R.; Bhat, S.V. *Synlett* ***1994***, 444.

[876] Coelho, F.; Almeida, W.P.; Veronese, D.; Mateus, C.R.; Lopes, E.C.S.; Rossi, R.C.; Silveira, G.P.C.; Pavam, C.H. *Tetrahedron* ***2002***, *58*, 7437.

[877] For improved procedures: Zhao, S.-H.; Bie, H.-Y.; Chen, Z.-B. *Org. Prep. Proceed. Int.* ***2005***, *37*, 231.

[878] Caumul, P.; Hailes, H.C. *Tetrahedron Lett.* ***2005***, *46*, 8125; Gomes, J.C.; Rodrigues Jr., M.T.; Moyano, A.; Coelho, F. *Eur. J. Org. Chem.* ***2012***, 6861.

[879] Fall, A.; Seck, I.; Diouf, O.; Gaye, M.; Seck, M.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* ***2015***, *56*, 5128; Mendoza-Espinosa, D.; González-Olvera, R.; Osornio, C.; Negrón-Silva, G.E.; Santillan, R. *New J. Chem.* ***2015***, 1587. For an example in a chiral ionic liquid, see Pégot, B.; Vo-Thanh, G.; Gori, D.; Loupy, A. *Tetrahedron Lett.* ***2004***, *45*, 6425.

[880] Chandrasekhar, S.; Narsihmulu, Ch.; Saritha, B.; Sultana, S.S. *Tetrahedron Lett.* ***2004***, *45*, 5865.

[881] Krishna, P.R.; Manjuvani, A.; Kannan, V.; Sharma, G.V.M. *Tetrahedron Lett.* ***2004***, *45*, 1183.

[882] See Inani, H.; Jha, A.K.; Easwar, S. *Synlett* ***2017***, *28*, 128.

[883] Singh, A.; Kumar, A. *J. Org. Chem.* ***2012***, *77*, 8775.

[884] Zhao, L.; Chen, X.Y.; Ye, S.; Wang, Z.-X. *J. Org. Chem.* ***2011***, *76*, 2733.

[885] See Oh, K.; Li, J.-Y. *Synthesis* ***2011***, *43*, 1960.

[886] Walsh, L.M.; Winn, C.L.; Goodman, J.M. *Tetrahedron Lett.* ***2002***, *43*, 8219.

[887] Chuprakov, S.; Malyshev, D.A.; Trofimov, A.; Gevorgyan, V. *J. Am. Chem. Soc.* ***2007***, *129*, 14868.

[888] Ng, K.; Minehan, T.G. *Org. Lett.* ***2016***, *18*, 4028.

and $Ba(OH)_2$ in aqueous methanol.[889] An intramolecular version of the Baylis-Hillman reaction generated cyclopentenone derivatives from alkyne aldehydes and a Rh catalyst.[890] Other intramolecular cyclization reactions are known.[891] Less reactive ketones and acrylamides gave an intramolecular Baylis-Hillman reaction with DABCO to give functionalized α-methylene-γ-lactams.[892]

Enantioselective Baylis-Hillman reactions[893] are possible using a chiral auxiliary via an amide[894] or ester.[895] Organocatalysts can be used to give products with good enantioselectivity.[896] Sugars have been used as ester auxiliaries, and in reaction with aryl aldehydes and 20% DABCO gave the allylic alcohol with modest enantioselectivity.[897]

Another variation is the *Rauhut-Currier cyclization* reaction,[898] which involves the reaction of a conjugated carbonyl with the allylic site of a second conjugated system. Intramolecular variations of this latter method are known.[899] The coupling of aldehydes with conjugated ketones used $TiCl_4$,[900] dialkylaluminum halides,[901] or with (polymethyl)hydrosiloxane and a Cu catalyst.[902] Conjugated esters were coupled to aldehydes with DABCO and a La catalyst.[903]

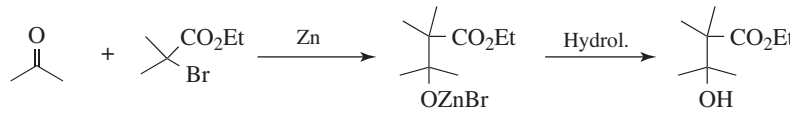
Alkyl halides are coupled with conjugated carbonyls to give the alkylated derivative in what is known as *Morita-Baylis-Hillman alkylation.*[904] α-Bromomethyl esters react with the α carbon of the C═C unit of conjugated ketones in the presence of DABCO to give the alkylated alkene coupling product, which is a nonconjugated diene.[905] The asymmetric organocatalytic allylic substitution of Baylis-Hillman carbonates with allylamines has been used for the preparation of 2,5-dihydropyrroles.[906] The allylic alkylation of Baylis-Hillman carbonates with allyl ketones has been reported.[907] The preparation of γ-alkylidenebutenolides was achieved via sequential indium-mediated Barbier-type reaction

[889] Guerra, K.P.; Afonso, C.A.M. *Tetrahedron* ***2011***, *67*, 2562.
[890] Tanaka, K.; Fu, G.C. *J. Am. Chem. Soc.* ***2001***, *123*, 11492.
[891] Keck, G.E.; Welch, D.S. *Org. Lett.* ***2000***, *4*, 3687; Krafft, M.E.; Seibert, K.A.; Haxell, T.F.N.; Wright, J.A.; Hirosawa, C.; Abboud, K.A. *Tetrahedron* ***2011***, *67*, 9922.
[892] Basavaiah, D.; Reddy, G.C.; Bharadwaj, K.C. *Tetrahedron* ***2014***, *70*, 7991.
[893] See Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem. Int. Ed.* ***2007***, *46*, 4614; Also see, Markó, I.E.; Giles, P.R.; Hindley, N.J. *Tetrahedron* ***1997***, *53*, 1015.
[894] Brzezinski, L.J.; Rafel, S.; Leahy, J.W. *J. Am. Chem. Soc.* ***1997***, *119*, 4317.
[895] See Wei, H.-X.; Chen, D.; Xu, X.; Li, G.; Paré, P.W. *Tetrahedron: Asymmetry* ***2003***, *14*, 971.
[896] For reviews, see Pellissier, H. *Tetrahedron* ***2017***, *73*, 2831; Wei, Y.; Shi, M. *Chem. Rev.* ***2013***, *113*, 6659. See also, Nakayama, Y.; Gotanda, T.; Ito, K. *Tetrahedron Lett.* ***2011***, *52*, 6234; Kotani, S.; Ito, M.; Nozaki, H.; Sugiura, M.; Ogasawara, M.; Nakajima, M. *Tetrahedron Lett.* ***2013***, *54*, 6430; Han, X.; Wang, Y.; Zhong, F.; Lu, Y. *Org. Biomol. Chem.* ***2011***, *9*, 6734; Verma, P.; Verma, P.; Sunoj, R.B. *Org. Biomol. Chem.* ***2014***, *12*, 2176.
[897] Filho, E.P.S.; Rodrigues, J.A.R.; Moran, P.J.S. *Tetrahedron: Asymmetry* ***2001***, *12*, 847.
[898] Rauhut, M.M.; Currier, H. *U.S. Patent* 3,074,999, American Cyanamid Co., ***1963***.
[899] Aroyan, C.E.; Miller, S.J. *J. Am. Chem. Soc.* ***2007***, *129*, 256.
[900] Li, G.; Wei, H.-X.; Gao, J.J.; Caputo, T.D. *Tetrahedron Lett.* ***2000***, *41*, 1; Shi, M.; Jiang, J.-K.; Feng, Y.-S. *Org. Lett.* ***2000***, *2*, 2397.
[901] Pei, W.; Wei, H.X.; Li, G. *Chem. Commun.* ***2002***, 2412.
[902] Arnold, L.A.; Imbos, R.; Mandoli, A.; de Vries, A.H.M.; Naasz, R.; Feringa, B.L. *Tetrahedron* ***2000***, *56*, 2865.
[903] Yang, K.-S.; Lee, W.-D.; Pan, J.-F.; Chen, K. *J. Org. Chem.* ***2003***, *68*, 915. For a reaction with conjugated ketones and other transition metal catalysts and organocatalysts, see Li, Y.-Q.; Wang, H.-J.; Huang, Z.-Z. *J. Org. Chem.* ***2016***, *81*, 4429.
[904] See Krafft, M.E.; Haxell, T.F.M.; Seibert, K.A.; Abboud, K.A. *J. Am. Chem. Soc.* ***2006***, *128*, 4174.
[905] Basavaiah, D.; Sharada, D.S.; Kumaragurubaran, N.; Reddy, R.M. *J. Org. Chem.* ***2002***, *67*, 7135.
[906] Sun, W.; Ma, X.; Hong, L.; Wang, R. *J. Org. Chem.* ***2011***, *76*, 7826.
[907] Tong, G.; Zhu, B.; Lee, R.; Yang, W.; Tan, D.; Yang, C.; Han, Z.; Yan, L.; Huang, K.-W.; Jiang, Z. *J. Org. Chem.* ***2013***, *78*, 5067.

of Morita-Baylis-Hillman bromides with an aldehyde, followed by lactonization, and finally double bond isomerization.[908] The reaction can be modified to give additional products, as with the reaction of *o*-hydroxybenzaldehyde and methyl vinyl ketone with DABCO, where the initial Baylis-Hillman product cyclized via conjugate addition of the phenolic oxygen to the conjugated ketone (**15-27**).[909]

See OS ***2010***, 87, 201.

16-27 The Reformatsky Reaction

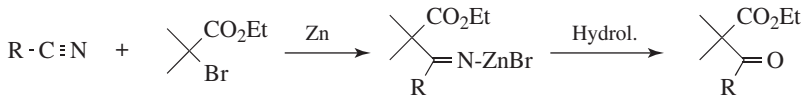


The *Reformatsky reaction*[910] is very similar to **16-24**. An aldehyde or ketone is treated with Zn and a halide; the halide is usually an α-halo ester or a vinylog (Sec. 6.B) of an α-halo ester (e.g., RCHBrCH=CHCOOEt), although α-halo nitriles,[911] α-halo ketones,[912] and α-halo *N*,*N*-disubstituted amides have also been used. Especially high reactivity can be achieved with activated Zn[913] and with Zn and ultrasound.[914] The reaction is catalytic in Zn in the presence of iodine and ultrasound.[915] Metals other than Zn can be used, including In,[916] Mn,[917] low valent Ti,[918] metal compounds of Ti,[919] Sn,[920] Sm,[921] Ce,[922] or Sc.[923] The use of additives, such as Ge[924] or Me_2Zn,[925] can lead to highly selective reactions.[926] The aldehyde or ketone can be aliphatic, aromatic, or heterocyclic or contain various functional groups. Solvents used are generally ethers, including Et_2O, THF, and 1,4-dioxane, although the reaction can be done in water[927] using dibenzoyl peroxide and $MgClO_4$. Dialkylzinc compounds are an alternative source of Zn in the Reformatsky reaction. The reaction of an α-bromo ester, an aldehyde, and diethylzinc in THF, with a Rh catalyst, gave a β-hydroxy ester.[928]

[908] Park, B.R.; Kim, K.H.; Lim, J.-W.; Kim, J.N. *Tetrahedron Lett.* ***2012***, *53*, 36.
[909] Kaye, P.T.; Nocanda, X.W. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 1331.
[910] See Fürstner, A. *Synthesis* ***1989***, 571; Rathke, M.W. *Org. React.* ***1975***, *22*, 423; Gaudemar, M. *Organomet. Chem. Rev. Sect. A* ***1972***, *8*, 183; Ocampo, R.; Dolbier Jr., W.R. *Tetrahedron* ***2004***, *60*, 9325.
[911] Palomo, C.; Aizpurua, J.M.; López, M.C.; Aurrekoetxea, N. *Tetrahedron Lett.* ***1990***, *31*, 2205; Zheng, J.; Yu, Y.; Shen, Y. *Synth. Commun.* ***1990***, *20*, 3277.
[912] See Huang, Y.; Chen, C.; Shen, Y. *J. Chem. Soc., Perkin Trans. 1* ***1988***, 2855.
[913] Rieke, R.D.; Uhm, S.J. *Synthesis* ***1975***, 452; Bouhlel, E.; Rathke, M.W. *Synth. Commun.* ***1991***, *21*, 133.
[914] Han, B.; Boudjouk, P. *J. Org. Chem.* ***1982***, *47*, 5030.
[915] Ross, N.A.; Bartsch, R.A. *J. Org. Chem.* ***2003***, *68*, 360.
[916] Araki, S.; Yamada, M.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* ***1994***, *67*, 1126.
[917] Suh, Y.S.; Rieke, R.D. *Tetrahedron Lett.* ***2004***, *45*, 1807.
[918] Aoyagi, Y.; Tanaka, W.; Ohta, A. *J. Chem. Soc., Chem. Commun.* ***1994***, 1225.
[919] See Parrish, J.D.; Shelton, D.R.; Little, R.D. *Org. Lett.* ***2003***, *5*, 3615.
[920] Shibata, I.; Kawasaki, M.; Yasuda, M.; Baba, A. *Chem. Lett.* ***1999***, 689.
[921] Park, H.S.; Lee, I.S.; Kim, Y.H. *Tetrahedron Lett.* ***1995***, *36*, 1673; Molander, G.A.; Etter, J.B. *J. Am. Chem. Soc.* ***1987***, *109*, 6556.
[922] Rodrigues, S.M.M.; Nardini, V.; Constantino, M.G.; da Silva, G.V.J. *Tetrahedron Lett.* ***2012***, *53*, 6136.
[923] Kagoshima, H.; Hashimoto, Y.; Saigo, K. *Tetrahedron Lett.* ***1998***, *39*, 8465.
[924] Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Saigo, K. *J. Org. Chem.* ***1998***, *63*, 691.
[925] Cozzi, P.G. *Angew. Chem. Int. Ed.* ***2006***, *45*, 2951.
[926] Cozzi, P.G. *Angew. Chem. Int. Ed.* ***2007***, *46*, 2568.
[927] Bieber, L.W.; Malvestiti, I.; Storch, E.C. *J. Org. Chem.* ***1997***, *62*, 9061.
[928] Kanai, K.; Wakabyashi, H.; Honda, T. *Org. Lett.* ***2000***, *2*, 2549.

Using chiral auxiliaries[929] or chiral catalysts,[930] and organocatalysts,[931] good enantioselectivity[932] can be achieved. Formally, the reaction is somewhat analogous to the *Grignard reaction* (**16-22**), with $EtO_2C{-}C{-}ZnBr$ as an intermediate analogous to RMgX.[933] There is a cyclic intermediate, which is a coordination complex of the ester carbonyl oxygen and Zn, and the structure has been characterized by X-ray crystallography of the solid intermediate prepared from *t*-$BuOCOCH_2Br$ and Zn.[934]

After hydrolysis, the alcohol is the usual product, but sometimes (especially with aryl aldehydes) elimination follows directly and the product is an alkene. By the use of Bu_3P along with Zn, the alkene can be made the main product,[935] making this an alternative to the *Wittig reaction* (**16-44**). Since *Grignard reagents* cannot be formed from α-halo esters, the method is quite useful, but competing reactions sometimes lead to low yields. A similar reaction (called the *Blaise reaction*) has been carried out on nitriles:[936]

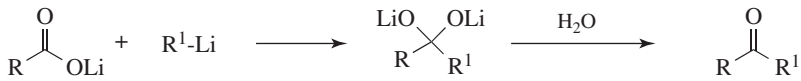


Carboxylic esters have also been used as substrates, but then, as might be expected (Sec. 16.A), the result is substitution to give a β-keto ester, and not addition. The product in this case is the same as with the corresponding nitrile, although the pathways are different.

Aza-Reformatsky reactions have been reported.[937]

OS **3**, 408; **4**, 120, 444; **6**, 598; **IX**, 275.

16-28 The Reaction of Carboxylic Acids or Acyl Halides With Organometallic Compounds to Give Ketones[938]



Good yields of ketones can often be obtained by treatment of the lithium salt of a carboxylic acid with an alkyllithium reagent, followed by hydrolysis.[939] The carboxylate salt is formed

[929] See Orsini, F.; Sello, G.; Manzo, A.M.; Lucci, E.M. *Tetrahedron: Asymmetry* ***2005***, *16*, 1913.

[930] Fernández-Ibáñez, M.A.; Maciá, B.; Minnaard, A.J.; Feringa, B.L. *Angew. Chem. Int. Ed.* ***2008***, *47*, 1317; Cozzi, P.G.; Mignogna, A.; Zoli, L. *Pure Appl. Chem.* ***2008***, *80*, 891.

[931] Wolf, C.; Moskowitz, M. *J. Org. Chem.* ***2011***, *76*, 6372.

[932] See Formalczyk, M.; Singh, K.; Stuart, A.M. *Chem. Commun.* ***2012***, *48*, 3500; Li, Y.; He, B. *Synth. Commun.* ***2014***, *44*, 1938. See Fernández-Ibáñez, M.Á.; Maciá, B.; Alonso, D.A.; Pastor, I.M. *Eur. J. Org. Chem.* ***2013***, 7028.

[933] See Maiz, J.; Arrieta, A.; Lopez, X.; Ugalde, J.M.; Cossio, F.P.; Fakultatea, K.; Unibertsitatea, E.H.; Lecea, B. *Tetrahedron Lett.* ***1993***, *34*, 6111.

[934] Dekker, J.; Budzelaar, P.H.M.; Boersma, J.; van der Kerk, G.J.M.; Spek, A.L. *Organometallics* ***1984***, *3*, 1403.

[935] Shen, Y.; Xin, Y.; Zhao, J. *Tetrahedron Lett.* ***1988***, *29*, 6119. For another method, see Huang, Y.; Shi, L.; Li, S.; Wen, X. *J. Chem. Soc., Perkin Trans. 1* ***1989***, 2397.

[936] See Sakthivel, K.; Srinivasan, K. *J. Org. Chem.* ***2014***, *79*, 3244; Xuan, Z.; Jung, D.J.; Jeon, H.J.; Lee, S.-g. *J. Org. Chem.* ***2016***, *81*, 10094; Chun, Y.S.; Lee, J.H.; Kim, J.H.; Ko, Y.O.; Lee, S.-g. *Org. Lett.* ***2011***, *13*, 6390.

[937] Rodríguez-Solla, H.; Díaz-Pardo, A.; Concellón, C.; del Amo, V. *Synlett* ***2014***, *25*, 1709.

[938] For a review, see Cais, M.; Mandelbaum, A. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 303–330.

[939] See Jorgenson, M.J. *Org. React.* ***1970***, *18*, 1; Rubottom, G.M.; Kim, C. *J. Org. Chem.* ***1983***, *48*, 1550.

by reaction of the carboxylic acid with a large excess of R^1Li. The R′ group may be aryl or primary, secondary, or tertiary alkyl and R may be alkyl or aryl. Tertiary alcohols are side products. Using R(PrNH)Mg, carboxylic acid salts react to form ketones.[940] A related reaction treats the lithium carboxylate with lithium metal and the alkyl halide, with sonication, to give the ketone.[941] Phenylboronic acid (**12-27**) reacts with aryl carboxylic acids in the presence of a Pd catalyst and disuccinoyl carbonate to give a diaryl ketone.[942] Carboxylic acids were converted directly into methyl, *n*-butyl, and isopropyl ketones by reaction with an excess of cyanocuprates $R_2CuLi{\cdot}LiCN$.[943] Trimethylaluminum, which exhaustively methylates ketones (**16-22**), also exhaustively methylates carboxylic acids to give *tert*-butyl compounds[944] (see also **10-63**).

OS **V**, 775.

Acyl halides react cleanly and under mild conditions with lithium dialkylcopper reagents (see **10-58**)[945] to give high yields of ketones.[946] The R′ group may be primary, secondary, or tertiary alkyl or aryl and may contain iodo, keto, ester, nitro, or cyano groups. The R groups that have been used successfully are methyl, primary alkyl, and vinylic. Secondary and tertiary alkyl groups can be introduced by the use of PhS(R)CuLi (**10-58**) instead of R_2CuLi,[947] or by the use of either the mixed homocuprate $(R'SO_2CH_2CuR)^-Li^+$,[948] or a magnesium dialkylcopper reagent "RMeCuMgX."[949] Secondary alkyl groups can also be introduced with the copper/zinc reagents RCu(CN)ZnI.[950] Organocopper reagents generated *in situ* from highly reactive copper, and containing such functional groups as cyano, chloro, and ester, react with acyl halides to give ketones.[951]

When the organometallic compound is a *Grignard reagent*,[952] ketones are generally not obtained because the initially formed ketone reacts with a second molecule of RMgX to give the salt of a tertiary alcohol (**16-29**). Ketones *have* been prepared in this manner by the use of low temperatures, inverse addition (i.e., addition of the Grignard reagent to the acyl halide rather than the other way), excess acyl halide, and so on, but the yields are usually

[940] Ohki, M.; Asaoka, M. *Chem. Lett.* ***2009***, *38*, 856.

[941] Aurell, M.J.; Danhui, Y.; Einhorn, J.; Einhorn, C.; Luche, J.L. *Synlett* ***1995***, 459. Also see, Aurell, M.J.; Einhorn, C.; Einhorn, J.; Luche, J.L. *J. Org. Chem.* ***1995***, *60*, 8.

[942] Gooßen, L.J.; Ghosh, K. *Chem. Commun.* ***2001***, 2084.

[943] Genna, D.T.; Posner, G.H. *Org. Lett.* ***2011***, *13*, 5358.

[944] Meisters, A.; Mole, T. *Aust. J. Chem.* ***1974***, *27*, 1665.

[945] See Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, ***1980***, pp. 81–85. Ryu, I.; Ikebe, M.; Sonoda, N.; Yamamoto, S.-y.; Yamamura, G.-h.; Komatsu, M. *Tetrahedron Lett.* ***2002***, *43*, 1257.

[946] Posner, G.H.; Whitten, C.E.; McFarland, P.E. *J. Am. Chem. Soc.* ***1972***, *94*, 5106; Luong-Thi, N.; Rivière, H. *J. Organomet. Chem.* ***1974***, *77*, C52.

[947] See Bennett, G.B.; Nadelson, J.; Alden, L.; Jani, A. *Org. Prep. Proceed. Int.* ***1976***, *8*, 13.

[948] Johnson, C.R.; Dhanoa, D.S. *J. Org. Chem.* ***1987***, *52*, 1885.

[949] Bergbreiter, D.E.; Killough, J.M. *J. Org. Chem.* ***1976***, *41*, 2750.

[950] Knochel, P.; Yeh, M.C.P.; Berk, S.C.; Talbert, J. *J. Org. Chem.* ***1988***, *53*, 2390.

[951] Stack, D.E.; Dawson, B.T.; Rieke, R.D. *J. Am. Chem. Soc.* ***1992***, *114*, 5110.

[952] See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood, NJ, ***1954***, pp. 712–724. See Wang, X.-j.; Zhang, L.; Sun, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C.H. *Org. Lett.* ***2005***, *7*, 5593.

low, although high yields have been reported in THF at −78 °C.[953] Pretreatment with a trialkylphosphine followed by the Grignard reagent gave the ketone.[954] Using CuBr[955] or a Ni catalyst[956] with the Grignard reagent can lead to the ketone. Some ketones are unreactive toward Grignard reagents for steric or other reasons; these can be prepared in this way.[957] Certain metallic halides, notably ferric and cuprous halides, are catalysts that improve the yields of ketone at the expense of tertiary alcohol.[958] Both free-radical and ionic mechanisms have been proposed for this catalysis.[959]

Other organometallic reagents[960] give good yields of ketones when treated with acyl halides. A particularly useful class of organometallic reagent is the organocadmium reagents R_2Cd, prepared from Grignard reagents (**12-22**). In this case, R may be aryl or primary alkyl. In general, secondary and tertiary alkylcadmium reagents are not stable enough to be useful in this reaction.[961] Direct treatment of the acid chloride with an alkyl halide and Cd metal leads to the ketone in some cases.[962] Organozinc compounds behave similarly to dialkylcadmium reagents, but are used less often.[963] Allylic halides and In metal react with acyl chlorides to give the ketone.[964] Other reagents include organomanganese,[965] organobismuth,[966] and organothallium compounds.[967]

Acid chlorides are generally so reactive that the initially formed ketone reacts further, giving the alcohol as the product. However, it is possible for the ketone to be isolated, and the use of lithium dialkylcuprates (or dialkylcadmium reagents) are common. Grignard reagents react with acid chlorides to give the ketones, mediated by simple amides such as NMP or DMF.[968] Aryl heteroaryl ketones were prepared by reaction of an aryl carboxylic acid with *i*-PrMgBr, followed by reaction with 2-iodopyridine, and, finally, treatment with EtMgBr.[969] The Ni-catalyzed coupling of carboxylic acid chlorides and alkyl iodides or benzylic chlorides gave unsymmetrical dialkyl ketones.[970] Aryl acid chlorides were

[953] Föhlisch, B.; Flogaus, R. *Synthesis* ***1984***, 734.
[954] Maeda, H.; Okamoto, J.; Ohmori, H. *Tetrahedron Lett.* ***1996***, *37*, 5381.
[955] Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* ***1996***, *52*, 13513.
[956] Malanga, C.; Aronica, L.A.; Lardicci, L. *Tetrahedron Lett.* ***1995***, *36*, 9185. See Lemoucheux, L.; Rouden, J.; Lasne, M.-C. *Tetrahedron Lett.* ***2000***, *41*, 9997.
[957] See Dubois, J.E.; Lion, C.; Arouisse, A. *Bull. Soc. Chim. Belg.* ***1984***, *93*, 1083.
[958] See Fujisawa, T.; Sato, T. *Org. Synth.* ***66***, 116; Babudri, F.; D'Ettole, A.; Fiandanese, V.; Marchese, G.; Naso, F. *J. Organomet. Chem.* ***1991***, *405*, 53.
[959] See MacPhee, J.A.; Boussu, M.; Dubois, J.E. *J. Chem. Soc., Perkin Trans. 2* ***1974***, 1525.
[960] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1389–1400.
[961] Cason, J.; Fessenden, R. *J. Org. Chem.* ***1960***, *25*, 477.
[962] Baruah, B.; Boruah, A.; Prajapati, D.; Sandhu, J.S. *Tetrahedron Lett.* ***1996***, *37*, 9087.
[963] See Grey, R.A. *J. Org. Chem.* ***1984***, *49*, 2288; Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Org. Synth.* ***67***, 98. Filon, H.; Gosmini, C.; Périchon, J. *Tetrahedron* ***2003***, *59*, 8199.
[964] Yadav, J.S.; Srinivas, D.; Reddy, G.S.; Bindu, K.H. *Tetrahedron Lett.* ***1997***, *38*, 8745. Also see, Bryan, V.J.; Chan, T.-H. *Tetrahedron Lett.* ***1997***, *38*, 6493 for a similar reaction with an acyl imidazole.
[965] Kim, S.-H.; Rieke, R.D. *J. Org. Chem.* ***1998***, *63*, 6766; Cahiez, G.; Martin, A.; Delacroix, T. *Tetrahedron Lett.* ***1999***, *40*, 6407.
[966] Rao, M.L.N.; Venkatesh, V.; Banerjee, D. *Tetrahedron* ***2007***, *63*, 12917.
[967] Markó, I.E.; Southern, J.M. *J. Org. Chem.* ***1990***, *55*, 3368.
[968] Gowda, M.S.; Pande, S.S.; Ramakrishna, R.A.; Ramaiah, K. *Org. Biomol. Chem.* ***2011***, *9*, 5365.
[969] Demkiw, K.; Araki, H.; Elliott, E.L.; Franklin, C.L.; Fukuzumi, Y.; Hicks, F.; Hosoi, K.; Hukui, T.; Ishimaru, Y.; O'Brien, E.; Omori, Y.; Mineno, M.; Mizufune, H.; Sawada, N.; Sawai, Y.; Zhu, L. *J. Org. Chem.* ***2016***, *81*, 3447.
[970] Wotal, A.C.; Weix, D.J. *Org. Lett.* ***2012***, *14*, 1476.

coupled with secondary alkyl halides using a Ni catalyst, 3 equivalents of Zn, and 15 equivalents of $MgCl_2$ to give the ketone.[971] The reaction of acid chlorides with alkynylzinc reagents gave the ynone using a Pd catalyst.[972] The Pd-catalyzed reaction of aryl- or alkenylboronic acids with acid chlorides in the presence of copper(I) thiophene-2-carboxylate as an activator gave diaryl ketones.[973] Arylboronic acids were heated with Bu_3SnOMe and then the Pd-catalyzed reaction with aryl acid chlorides gave the diaryl ketone.[974] The Pd-catalyzed reaction of an acyl chloride and an arylboronic acid[975] or an alkenylboronic acid[976] gives a ketone. Surfactants are known to promote arylboronic acid coupling reactions.[977] Arylboronic esters add to carbamoyl halides, in the presence of a Pd catalyst, to give the corresponding benzamide.[978] Arylboronic acids also react with anhydrides to give a ketone in the presence of a Pd catalyst.[979]

In the presence of BCl_3, ynones were prepared by the reaction of acyl chlorides and potassium alkynyltrifluoroborate salts.[980] Silica-supported zinc bromide ($ZnBr_2/SiO_2$) catalyzed the reaction of acid chlorides with terminal alkynes to give the ynone.[981]

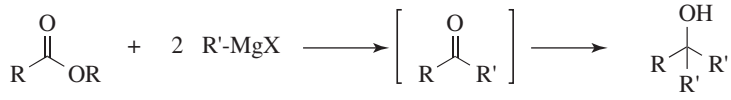
Conjugated alkynyl ketones can be prepared from an acyl halide, a terminal alkyne, catalyzed by CuI,[982] Pd,[983] Fe,[984] or an In metal.[985] Terminal alkynes react with chloroformates and a Pd catalyst to give the corresponding propargyl ester.[986] Similar reaction of an alkyne with an acid chloride and a Pd/Cu[987] or CuI catalyst,[988] both with microwave irradiation, gave alkynyl ketones.

It is noted that arylboronic acids also react with dialkyl anhydrides, with a Rh catalyst[989] or a Pd catalyst,[990] to give the ketone. Aryl iodides react with acetic anhydride, with a Pd catalyst, to give the aryl methyl ketone.[991]

OS **II**, 198; **III**, 601; **IV**, 708; **VI**, 248, 991; **VII**, 226, 334; **VIII**, 268, 274, 371, 441, 486.

[971] Wu, F.; Lu, W.; Qian, Q.; Ren, Q.; Gong, H. *Org. Lett.* ***2012***, *14*, 3044.
[972] Yuan, H.; Shen, Y.; Yu, S.; Shan, L.; Sun, Q.; Zhang, W. *Synth. Commun.* ***2013***, *43*, 2817; Yuan, H.; Jin, H.; Li, B.; Shen, Y.; Yue, R.; Shan, L.; Sun, Q.; Zhang, W. *Can. J. Chem.* ***2013***, *91*, 333.
[973] Ogawa, D.; Hyodo, K.; Suetsugu, M.; Li, J.; Inoue, Y.; Fujisawa, M.; Iwasaki, M.; Takagi, K.; Nishihara, Y. *Tetrahedron* ***2013***, *69*, 2565.
[974] Oikawa, A.; Kindaichi, G.; Shimotori, Y.; Okimoto, M.; Hoshi, M. *Tetrahedron* ***2015***, *71*, 1705.
[975] Ekoue-Kovi, K.; Xu, H.; Wolf, C. *Tetrahedron Lett.* ***2008***, *49*, 5773. For a Cu-mediated reaction, see Nishihara, Y.; Inoue, Y.; Fujisawa, M.; Takagi, K. *Synlett* ***2005***, 2309.
[976] Thimmaiah, M.; Zhang, X.; Fang, S. *Tetrahedron Lett.* ***2008***, *49*, 5605.
[977] Xin, B.; Zhang, Y.; Cheng, K. *Synthesis* ***2007***, 1970.
[978] Lysén, M.; Kelleher, S.; Begtrup, M.; Kristensen, J.L. *J. Org. Chem.* ***2005***, *70*, 5342.
[979] Xin, B.; Zhang, Y.; Cheng, K. *J. Org. Chem.* ***2006***, *71*, 5725.
[980] Taylor, C.; Bolshan, Y. *Org. Lett.* ***2014***, *16*, 488.
[981] Keivanloo, A.; Bakherad, M.; Bahramian, B.; Baratnia, S. *Tetrahedron Lett.* ***2011***, *52*, 1498.
[982] Chowdhury, C.; Kundu, N.G. *Tetrahedron* ***1999***, *55*, 7011; Wang, J.-X.; Wei, B.; Hu, Y.; Liua, Z.; Kang, L. *J. Chem. Res. (S)* ***2001***, 146.
[983] Karpov, A.S.; Müller, T.J.J. *Org. Lett.* ***2003***, *5*, 3451.
[984] Wang, B.; Wang, S.; Li, P.; Wang, L. *Chem. Commun.* ***2010***, 5891.
[985] Iwai, T.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* ***2009***, *131*, 6668.
[986] Böttcher, A.; Becker, H.; Brunner, M.; Preiss, T.; Henkelmann, J.; De Bakker, C.; Gleiter, R. *J. Chem. Soc., Perkin Trans.1* ***1999***, 3555.
[987] Wang, J.-X.; Wei, B.; Huang, D.; Hu, Y.; Bai, L. *Synth. Commun.* ***2001***, *31*, 3337.
[988] Wang, J.-X.; Wei, B.; Hu, Y.; Liu, Z.; Fu, Y. *Synth. Commun.* ***2001***, *31*, 3527.
[989] Frost, C.G.; Wadsworth, K.J. *Chem. Commun.* ***2001***, 2316.
[990] Gooßen, L.J.; Ghosh, K. *Eur. J. Org. Chem.* ***2002***, 3254.
[991] Cacchi, S.; Fabrizi, G.; Gavazza, F.; Goggiamani, A. *Org. Lett.* ***2003***, *5*, 289.

16-29 The Reaction of Organometallic Compounds With Carboxylic Acid Derivatives



As is the case with acyl halides (**16-28**), anhydrides and carboxylic esters give tertiary alcohols (**16-29**) when treated with Grignard reagents.[992] Low temperatures,[993] the solvent HMPA,[994] and inverse addition have been used to increase the yields of ketone.[995] Esters or amides can be used in reactions with organometallic compounds to give ketones.[996]

When carboxylic esters are treated with Grignard reagents, addition to the carbonyl initially generates a ketone (**16-22**). Under the reaction conditions, the initially formed ketone is more reactive than the ester and usually undergoes further reaction to give a tertiary alcohol in which two R groups are the same. Possible side reactions include enolization, condensations, and cleavages. Organolithium compounds have been used to give ketones from carboxylic esters, but a high-boiling solvent such as toluene is required, since reaction at lower temperatures gives tertiary alcohols.[997] Isolation of the ketone as the major product is possible in some cases, particularly when the reaction is done at low temperature[998] and when there is steric hindrance to the carbonyl in the first-formed ketone. Esters of formic acid, dialkyl formamides, and lithium or sodium formate[999] give good yields of aldehydes when treated with Grignard reagents. Formates react to give secondary alcohols and carbonates give tertiary alcohols in which all three R groups are the same:

$$(EtO)_2C{=}O + RMgX \rightarrow R_3COMgX$$

Symmetrical aromatic 1,3-diols were prepared by the reaction of substituted aryl Grignard reagents with isopropenyl acetate in a one-step reaction.[1000] Tertiary alcohols were prepared by the CuO-catalyzed reaction of Mg and unactivated alkyl or aryl bromides with an ester.[1001] When 1,4-dimagnesium compounds are used, carboxylic esters are converted to cyclopentanols.[1002] 1,5-Dimagnesium compounds give cyclohexanols, but in lower yields.[1003]

[992] See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 549–766, 846–869.
[993] See Newman, M.S.; Smith, A.S. *J. Org. Chem.* ***1948***, *13*, 592; Edwards Jr., W.R.; Kammann Jr., K.P. *J. Org. Chem.* ***1964***, *29*, 913; Araki, M.; Sakat, S.; Takei, H.; Mukaiyama, T. *Chem. Lett.* ***1974***, 687.
[994] Huet, F.; Pellet, M.; Conia, J.M. *Tetrahedron Lett.* ***1976***, 3579.
[995] For a list of reactions with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1386–1389, 1400–1419.
[996] See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood, NJ, ***1954***, pp. 561–562, 846–908. Prosser, A.R.; Liotta, D.C. *Tetrahedron Lett.* ***2015***, *56*, 3006.
[997] Petrov, A.D.; Kaplan, E.P.; Tsir, Ya. *J. Gen. Chem. USSR* ***1962***, *32*, 691.
[998] Deskus, J.; Fan, D.; Smith, M.B. *Synth. Commun.* ***1998***, *28*, 1649.
[999] Bogavac, M.; Arsenijevic, L.; Pavlov, S.; Arsenijevic, V. *Tetrahedron Lett.* ***1984***, *25*, 1843.
[1000] Jiao, Y.; Cao, C.; Zhou, Z. *Org. Lett.* ***2011***, *13*, 180.
[1001] Gao, F.; Deng, X.-J.; Tang, Y.; Tang, J.-P.; Yang, J.; Zhang, Y.-M. *Tetrahedron Lett.* ***2014***, *55*, 880.
[1002] Canonne, P.; Bernatchez, M. *J. Org. Chem.* ***1986***, *51*, 2147; ***1987***, *52*, 4025.
[1003] Kresge, A.J.; Weeks, D.P. *J. Am. Chem. Soc.* ***1984***, *106*, 7140. See also, Amyes, T.L.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 7888, 7900.

Sodium naphthalenide reacts with esters to give naphthyl ketones.[1004] Trimethylaluminum reacts with esters to form ketones in the presence of *N*,*N*′-dimethylethylenediamine.[1005] Trialkylboranes have been used to convert thioesters to ketones.[1006] Thioesters (RCOSR′) react with arylboronic acids, in the presence of a Pd catalyst, to give the corresponding ketone,[1007] and esters react similarly with arylboronic acids (Pd catalyst)[1008] or arylboronates (Ru catalyst).[1009] Thioesters are converted to ketones with organoindium compounds.[1010] Thioesters give good yields of ketones when treated with lithium dialkylcopper reagents $R^2{}_2CuLi$ (R^2 = primary or secondary alkyl or aryl).[1011] Organozinc reagents convert thioesters to ketones.[1012] Diaryl- or dialkylzinc reagents react with anhydrides and a Pd[1013] or Ni catalyst[1014] to give the ketone. The reaction of alkylzinc halides and thioesters leads to ketones in the presence of 1.5% Pd/C,[1015] in what has been called *Fukuyama coupling*.[1016] The Fukuyama reaction couples a thioester with an organozinc compound, using a Pd catalyst, to give the corresponding ketone.[1017] The Pd-catalyzed Fukuyama cross coupling of secondary organozinc reagents with thioesters or acid chlorides using a $ZnCl_2$ mediator gave the ketone.[1018]

Amides give better yields of the ketone at room temperature, but yields are still not very high.[1019] Anhydrides can react with arylmagnesium halides at low temperature, and in the presence of (−)-sparteine, to give a keto acid with good enantioselectivity.[1020] Organocadmium reagents are less successful with these substrates than with acyl halides (**16-28**). Tertiary amides reacted with Grignard reagents to give the ketone and an amine.[1021] The reaction of Grignard reagents with thioamides and thioformamides has been reviewed.[1022]

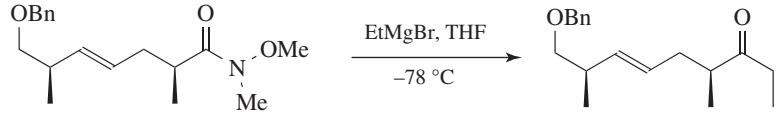
Organolithium reagents also give good yields of carbonyl compounds with *N*,*N*-disubstituted amides.[1023] Dialkylformamides react to give aldehydes, other disubstituted

[1004] Periasamy, M.; Reddy, M.R.; Bharathi, P. *Synth. Commun.* ***1999***, *29*, 677.
[1005] Chung, E.-A.; Cho, C.-W.; Ahn, K.H. *J. Org. Chem.* ***1998***, *63*, 7590.
[1006] Yu, Y.; Liebeskind, L.S. *J. Org. Chem.* ***2004***, *69*, 3554.
[1007] Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L.S. *Org. Lett.* ***2003***, *5*, 3033.
[1008] Tatamidani, H.; Kakiuchi, F.; Chatani, N. *Org. Lett.* ***2004***, *6*, 3597.
[1009] Tatamidani, H.; Yokota, K.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* ***2004***, *69*, 5615.
[1010] Fausett, B.W.; Liebeskind, L.S. *J. Org. Chem.* ***2005***, *70*, 4851.
[1011] Anderson, R.J.; Henrick, C.A.; Rosenblum, L.D. *J. Am. Chem. Soc.* ***1974***, *96*, 3654. See also, Kim, S.; Lee, J.I. *J. Org. Chem.* ***1983***, *48*, 2608.
[1012] Shimizu, T.; Seki, M. *Tetrahedron Lett.* ***2002***, *43*, 1039.
[1013] Bercot, E.A.; Rovis, T. *J. Am. Chem. Soc.* ***2004***, *126*, 10248.
[1014] O'Brien, E.M.; Bercot, E.A.; Rovis, T. *J. Am. Chem. Soc.* ***2003***, *125*, 10498.
[1015] Shimizu, T.; Seki, M. *Tetrahedron Lett.* ***2001***, *42*, 429.
[1016] See Mori, Y.; Seki, M. *Tetrahedron Lett.* ***2004***, *45*, 7343. For a different but related cross-coupling, see Zhang, Y.; Rovis, T. *J. Am. Chem. Soc.* ***2004***, *126*, 15964.
[1017] Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* ***1998***, *39*, 3189; Mori, Y.; Seki, M. *Org. Synth.* ***2007***, *84*, 285; *Coll. Vol*. ***11***, pp. 281.
[1018] Cherney, A.H.; Reisman, S.E. *Tetrahedron* ***2014***, *70*, 3259.
[1019] See Olah, G.S.; Prakash, G.K.S.; Arvanaghi, M. *Synthesis* ***1984***, 228; Martín, R.; Romea, P.; Tey, C.; Urpí, F.; Vilarrasa, J. *Synlett* ***1997***, 1414. Also see Kashima, C.; Kita, I.; Takahashi, K.; Hosomi, A. *J. Heterocycl. Chem.* ***1995***, *32*, 25 for a related reaction.
[1020] Shintani, R.; Fu, G.C. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1057.
[1021] Huang, P.-Q.; Wang, Y.; Xiao, K.-J.; Huang, Y.-H. *Tetrahedron* ***2015***, *71*, 4248.
[1022] Murai, T.; Mutoh, Y. *Chem. Lett.* ***2012***, *41*, 2.
[1023] Evans, E.A. J. *Chem. Soc.* ***1956***, 4691. See Clark, C.T.; Milgram, B.C.; Scheidt, K.A. *Org. Lett.* ***2004***, *6*, 3977. See Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, pp. 82–88.

amides give ketones, and other acid derivatives have been used.[1024] Disubstituted formamides can react with 2 molar equivalents of Grignard reagent. The products of this reaction when R = H (called *Bouveault reaction*) are an aldehyde and a tertiary amine.[1025]

The use of an amide other than a formamide can give a ketone instead of an aldehyde, but yields are generally low. However, the addition of 2 molar equivalents of phenyllithium to a carbamate gave good yields of the ketone.[1026]

Ketones can be prepared by treatment of thioamides with organolithium compounds (alkyl or aryl).[1027] Cerium reagents, such as $MeCeCl_2$, also add two R groups to an amide.[1028] More commonly, an organolithium reagent is treated with $CeCl_3$ to generate the organocerium reagent *in situ*.[1029] It has proven possible to add two different R groups by sequential addition of two Grignard reagents.[1030] When an amide having a *gem*-dibromocyclopropyl unit elsewhere in the molecule was treated with methyllithium, Li–Br exchange was accompanied by intramolecular acyl addition to the amide carbonyl, giving a bicyclic amino alcohol.[1031]



25 **26**

N-Methoxy *N*-methyl amides, such as **25**, are referred to as a *Weinreb amide*.[1032] When a *Weinreb amide* reacts with a *Grignard reagent* or an organolithium reagent,[1033] the product is the ketone. The reaction of **25** (Bn = benzyl) with ethylmagnesium bromide to give ketone **26** is a typical example, taken from the Goswami and Kuilya synthesis of carolacton.[1034] Intramolecular displacement of a Weinreb amide by an organolithium reagent generated *in situ* from an iodide precursor leads to cyclic ketones.[1035] Reaction with vinylmagnesium bromide led to a β-*N*-methoxy-*N*-methylamino ketone, presumably by initial formation of the conjugated ketone followed by *Michael addition* (**15-20**) of the liberated amine.[1036] By the use of the compound *N*-methoxy-*N*,*N*′,*N*′-trimethylurea, it is possible to add two R

[1024] Mueller-Westerhoff, U.T.; Zhou, M. *Synlett* ***1994***, 975.
[1025] Spialter, L.; Pappalardo, J.A. *The Acyclic Aliphatic Tertiary Amines*, Macmillan, NY, ***1965***, pp. 59–63.
[1026] Prakash, G.K.S.; York, C.; Liao, Q.; Kotian, K.; Olah, G.A. *Heterocycles* ***1995***, *40*, 79.
[1027] Tominaga, Y.; Kohra, S.; Hosomi, A. *Tetrahedron Lett.* ***1987***, *28*, 1529.
[1028] Calderwood, D.J.; Davies, R.V.; Rafferty, P.; Twigger, H.L.; Whelan, H.M. *Tetrahedron Lett.* ***1997***, *38*, 1241.
[1029] Ahn, Y.; Cohen, T. *Tetrahedron Lett.* ***1994***, *35*, 203.
[1030] Comins, D.L.; Dernell, W. *Tetrahedron Lett.* ***1981***, *22*, 1085.
[1031] Baird, M.S.; Huber, F.A.M.; Tverezovsky, V.V.; Bolesov, I.G. *Tetrahedron* ***2001***, *57*, 1593.
[1032] Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* ***1981***, *22*, 3815. For a review, see Balasubramaniam, S.; Aidhen, I.S. Sy*nthesis* ***2008***, 3707. Also see Pace, V.; Holzer, W. *Aust. J. Chem.* ***2013***, *66*, 507.
[1033] See Tallier, C.; Bellosta, V.; Meyer, C.; Cossy, J. *Org. Lett.* ***2004***, *6*, 2145.
[1034] Kuilya, T.K.; Goswami, R.K. *Org. Lett.* ***2017***, *19*, 2366.
[1035] Ruiz, J.; Sotomayor, N.; Lete, E. *Org. Lett.* ***2003***, *5*, 1115.
[1036] See Hansford, K.A.; Dettwiler, J.E.; Lubell, W.D. *Org. Lett.* ***2003***, *5*, 4887.

groups as RLi, with the two R groups being the same or different, to a CO group.[1037] Another variant used organocerium reagents with (*Z*)-α,β-unsaturated Weinreb amides to give (*Z*)-α,β-unsaturated ketones.[1038] Halomethyllithium reagents reacted with Weinreb amides to give the ketone.[1039] The Ti-catalyzed reaction of alkynes with Weinreb amides gave the ketone.[1040] The reaction of an organolithium reagent and a Weinreb amide followed by reaction with a Pd catalyst and then an organolithium reagent gave the ketone.[1041] The Pd-catalyzed reaction of aryl boronic acids and geometrically activated amides gave the aryl ketone.[1042]

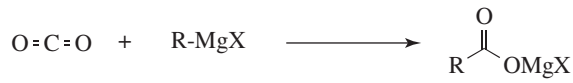
N,*N*-Disubstituted amides can be converted to alkynyl ketones by treatment with alkynylboranes:[1043]

$$RCONR_2{}^2 + (R'C{\equiv}C)_3B \rightarrow RCOC{\equiv}CR'$$

Triallylborane reacts with the carbonyl group of lactams, and after treatment with methanol and then aqueous NaOH gives the *gem*-diallyl amine. For example, 2-pyrrolidinone gives 2,2-diallylpyrrolidine.[1044] *N*,*N*-Disubstituted amides give ketones in high yields when treated with alkyllanthanum triflates $RLa(OTf)_2$.[1045]

OS **I**, 226; **II**, 179, 602; **III**, 237, 831, 839; **IV**, 601; **VI**, 240, 278; **VIII**, 474, 505. OS **II**, 282; **72**, 32; **III**, 353; **IV**, 285; **VI**, 611; **VII**, 323, 451; **81**, 14.

16-30 The Addition of Organometallic Compounds to CO_2 and CS_2



Grignard reagents add to one C═O bond of CO_2 (O═C═O) as they do with an aldehyde or a ketone,[1046] but the product is the salt of a carboxylic acid. The reaction is usually performed by adding the Grignard reagent to dry ice. Many carboxylic acids have been prepared in this manner, and this constitutes an important way of increasing a carbon chain by one unit. Since labeled CO_2 is commercially available, this is a good method for the preparation of carboxylic acids labeled in the carboxyl group. Other organometallic compounds have also

[1037] Hlasta, D.J.; Court, J.J. *Tetrahedron Lett.* ***1989***, *30*, 1773. See also, Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* ***1981***, *22*, 3815.
[1038] Kojima, S.; Hidaka, T.; Yamakaw, A. *Chem. Lett.* ***2005***, *34*, 470.
[1039] Pace, V.; Castoldi, L.; Holzer, W. *J. Org. Chem.* ***2013***, *78*, 7764.
[1040] Silwal, S.; Rahaim, R.J. *J. Org. Chem.* ***2014***, *79*, 8469.
[1041] Giannerini, M.; Vila, C.; Hornillos, V.; Feringa, B.L. *Chem. Commun.* ***2016***, *52*, 1206.
[1042] Meng, G.; Szostak, M. *Org. Lett.* ***2015***, *17*, 4364.
[1043] Yamaguchi, M.; Waseda, T.; Hirao, I. *Chem. Lett.* ***1983***, 35.
[1044] Bubnov, Yu.N.; Klimkina, E.V.; Zhun', I.V.; Pastukhov, F.V.; Yampolsky, I.V. *Pure Appl. Chem.* ***2000***, *72*, 1641.
[1045] Collins, S.; Hong, Y. *Tetrahedron Lett.* ***1987***, *28*, 4391.
[1046] See Volpin, M.E.; Kolomnikov, I.S. *Organomet. React.* ***1975***, *5*, 313; Sneeden, R.P.A. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 137–173; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 913–948. For a more general review, see Lapidus, A.L.; Ping, Y.Y. *Russ. Chem. Rev.* ***1981***, *50*, 63.

been used (RLi,[1047] RNa, RCaX, RBa,[1048] etc.), but much less often. The formation of the salt of a carboxylic acid after the addition of CO_2 to a reaction mixture is regarded as a positive test for the presence of a carbanion or of a reactive organometallic intermediate in that reaction mixture (see also **16-42**).

Aryl organoboronates react with CO_2, in the presence of a Ru catalyst, to give the corresponding aryl carboxylic acid.[1049] Aryl and alkenyl boronic esters are carboxylated in the presence of a Cu catalyst.[1050] Vinyl halides react with CO and water, with a Pd catalyst in an ionic liquid, to give the conjugated carboxylic acid.[1051] Organozinc compounds are carboxylated with CO_2 and a Ni catalyst.[1052] Metal-free carboxylation of organozinc reagents is also known.[1053] In the presence of CO_2 and an organocatalyst, aromatic aldehydes are converted to the corresponding carboxylic acid.[1054] Direct carboxylation of aryl bromides is possible using CO_2 and a Pd catalyst.[1055] Allenes are converted to β,γ-unsaturated acids with CO_2 in the presence of Et_2Zn.[1056]

When chiral additives such as (−)-sparteine have been added to the initial reaction with the organolithium reagent, quenching with CO_2 produces carboxylic acids with good asymmetric induction.[1057]

Heating *N*-tosylhydrazones and CO_2 with 3 equivalents of Cs_2CO_3 in DMSO gave the corresponding α-arylacrylic acid.[1058] Benzoic acid (de)carboxylases reacted with styrene derivatives to selectively give *o*-hydroxybenzoic acid derivatives, whereas phenolic acid (de)carboxylases reacted at the β carbon atom of styrenes to give (*E*)-cinnamic acids.[1059] The Cu(I)/NHC-catalyzed reaction of allylboronic pinacol esters with CO_2 gave the more substituted β,γ-unsaturated carboxylic acid.[1060] The reaction of alkenylzirconocenes with CO_2 using (IMes)CuCl as a catalyst gave the α,β-unsaturated carboxylic acids.[1061] A Cu-containing ionic liquid was used to catalyze the reaction of terminal alkynes with ambient CO_2 in the presence of iodobutane to give a butyl propiolate derivative.[1062] The Ni-catalyzed carboxylation of benzyl halides with CO_2 gave phenylacetic acids.[1063] The Ni-catalyzed carboxylation of primary alkyl bromides and sulfonates with CO_2 gave the aliphatic carboxylic acid.[1064] Allylic carboxylic acids were generated by the Ni-catalyzed reaction of allylic acetates with CO_2.[1065] In a closely related reaction, Grignard reagents add to CS_2

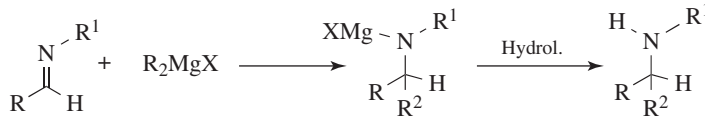
[1047] See Nudelman, N.S.; Doctorovich, F. *J. Chem. Soc., Perkin Trans. 2* ***1994***, 1233.
[1048] Yanagisawa, A.; Yasue, K.; Yamamoto, H. *Synlett* ***1992***, 593.
[1049] Ukai, K.; Aoki, M.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* ***2006***, *128*, 8706.
[1050] Takaya, J.; Tadami, S.; Ukai, K.; Iwasawa, N. *Org. Lett.* ***2008***, *10*, 2697.
[1051] Zhao, X.; Alper, H.; Yu, Z. *J. Org. Chem.* ***2006***, *71*, 3988.
[1052] Ochiai, H.; Jang, M.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2008***, *10*, 2681.
[1053] Kobayashi, K.; Kondo, Y. *Org. Lett.* ***2009***, *11*, 2035.
[1054] Nair, V.; Varghese, V.; Paul, R.P.; Jose, A.; Sinu, C.R.; Menon, R.S. *Org. Lett.* ***2010***, *12*, 2653.
[1055] Correa, A.; Martín, R. *J. Am. Chem. Soc.* ***2009***, *131*, 15974.
[1056] North, M. *Angew. Chem. Int. Ed.* ***2009***, *48*, 4104.
[1057] Park, Y.S.; Beak, P. *J. Org. Chem.* ***1997***, *62*, 1574.
[1058] Sun, S.; Yu, J.-T.; Jiang, Y.; Cheng, J. *J. Org. Chem.* ***2015***, *80*, 2855.
[1059] Wuensch, C.; Glueck, S.M.; Gross, J.; Koszelewski, D.; Schober, M.; Faber, K. *Org. Lett.* ***2012***, *14*, 1974.
[1060] Duong, H.A.; Huleatt, P.B.; Tan, Q.-W.; Shuying, E.L. *Org. Lett.* ***2013***, *15*, 4034.
[1061] Wang, S.; Shao, P.; Chen, C.; Xi, C. *Org. Lett.* ***2015***, *17*, 5112.
[1062] Xie, J.-N.; Yu, B.; Zhou, Z.-H.; Fu, H.-C.; Wang, N.; He, L.-N. *Tetrahedron Lett.* ***2015***, *56*, 7059.
[1063] León, T.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* ***2013***, *135*, 1221.
[1064] See Börjesson, M.; Moragas, T.; Martin, R. *J. Am. Chem. Soc.* ***2016***, *138*, 7504.
[1065] Moragas, T.; Cornella, J.; Martin, R. *J. Am. Chem. Soc.* ***2014***, *136*, 17702.

to give salts of dithiocarboxylic acids.[1066] These salts can be trapped with amines to form thioamides.[1067]

A terminal alkyne can be converted to the anion under electrolytic conditions, in the presence of CO_2, to give propargylic acids, $R{-}C{\equiv}C{-}CO_2H$.[1068]

OS **I**, 361, 524; **II**, 425; **III**, 413, 553, 555; **V**, 890, 1043; **VI**, 845; **IX**, 317.

16-31 The Addition of Organometallic Compounds to C═N Compounds



Aldimines can be converted to secondary amines by treatment with *Grignard reagents*.[1069] Ketimines generally react with Grignard reagents to give reduction instead of addition. However, organolithium compounds react to give the normal addition product with both aldimines and ketimines.[1070] The solvent and the aggregation state of the organolithium play a role in the addition, however.[1071] Addition of R^2MgX or R^2Li to aldimines gives $ArCHR^2NH_2$ after hydrolysis.[1072] An intramolecular version of the addition of organolithium reagents gave 2-phenylpyrrolidine.[1073] Grignard reagents add to imines in the presence of various transition metal catalysts, including $Sc(OTf)_3$[1074] or Cp_2ZrCl_2.[1075] Alkynes add to imines to give propargylic amines.[1076] Allylic alcohols add to imines in the presence of a Pd catalyst to give the homoallylic amine.[1077] Alkyl and aryl halides reacted with imines under electrochemical conditions using zinc electrodes to give the amine.[1078]

When chiral additives are used in conjunction with the organolithium reagent, chiral amines are produced[1079] with good asymmetric induction.[1080] Chiral auxiliaries have been used in addition reactions of organometallic compounds to imines[1081] and to oxime derivatives.[1082] The Cu-mediated and catalyzed asymmetric alkylation of imines has been reviewed.[1083] Chiral catalysts lead to enantioselective addition of alkynes to imines to

[1066] See Ramadas, S.R.; Srinivasan, P.S.; Ramachandran, J.; Sastry, V.V.S.K. *Synthesis* ***1983***, 605.
[1067] Katritzky, A.R.; Moutou, J.-L.; Yang, Z. *Synlett* ***1995***, 99.
[1068] Köster, F.; Dinjus, E.; Duñach, E. *Eur. J. Org. Chem.* ***2001***, 2507.
[1069] See Harada, K. in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 266–272; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 1204–1227; Wang, D.-K.; Dai, L.-X.; Hou, X.-L.; Zhang, Y. *Tetrahedron Lett.* ***1996***, *37*, 4187.
[1070] Huet, J. *Bull. Soc. Chim. Fr.* ***1964***, 952, 960, 967, 973.
[1071] Qu, B.; Collum, D.B. *J. Am. Chem. Soc.* ***2005***, *127*, 10820; *J. Am. Chem. Soc.* ***2006***, *128*, 9355.
[1072] Davis, F.A.; Giangiordano, M.A.; Starner, W.E. *Tetrahedron Lett.* ***1986***, *27*, 3957.
[1073] Yus, M.; Soler, T.; Foubelo, F. *J. Org. Chem.* ***2001***, *66*, 6207.
[1074] Saito, S.; Hatanaka, K.; Yamamoto, H. *Synlett* ***2001***, 1859.
[1075] Gandon, V.; Bertus, P.; Szymoniak, J. *Eur. J. Org. Chem.* ***2001***, 3677.
[1076] Zani, L.; Bolm, C. *Chem. Commun.* ***2006***, 4263.
[1077] Shimizu, M.; Kimura, M.; Watanabe, T.; Tamaru, Y. *Org. Lett.* ***2005***, *7*, 637.
[1078] Huang, J.-M.; Wang, X.-X.; Dong, Y. *Angew. Chem. Int. Ed.* ***2011***, *50*, 924.
[1079] For a review, see Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* ***1997***, *8*, 1895.
[1080] See Kobayashi, S.; Mori, Y.; Fossey, J.S.; Salter, M.M. *Chem. Rev.* ***2011***, *111*, 2626.
[1081] See Ferraris, D. *Tetrahedron* ***2007***, *63*, 9581.
[1082] Dieter, R.K.; Datar, R. *Can. J. Chem.* ***1993***, *71*, 814.
[1083] Yamada, K.-i.; Tomioka, K. *Chem. Rev.* ***2008***, *108*, 2874.

give the amine.[1084] Chiral *N*-sulfinylimines react with lithium silanes to give the α-silylsulfinylamine.[1085] In the presence of a chiral ligand, the metal-catalyzed reaction proceeds with good enantioselectivity.[1086] With a Cu catalyst and a chiral ligand, the amine is formed with good enantioselectivity.[1087]

Zinc metal reacts with allylic bromides to form an allylic zinc complex, which reacts with imines to give the homoallylic amine.[1088] This reaction is catalyzed by TMSCl.[1089] Dialkylzinc reagents add to *N*-tosylimines to give the alkylated tosyl amine.[1090] Dimethylzinc has been used to mediate the addition of terminal alkynes to *N*-tosylimines.[1091]

Other organometallic compounds catalyze addition reactions to aldimines,[1092] including Sn,[1093] Sm,[1094] Ge,[1095] Zn,[1096] Pd,[1097] Hf,[1098] Rh,[1099] Zr,[1100] Ga metal with ultrasound,[1101] Yb with Me_3SiCl,[1102] and In.[1103] Catalytic amounts of a metal compound can be used with an allylic stannane.[1104] Catalytic enantioselective addition reactions with organotin compounds are well known,[1105] including reactions in an ionic liquid.[1106] Reaction with $PhSnMe_3$ and *N*-tosylimines with a Rh catalyst leads to addition of a phenyl group to the carbon of the C=N bond.[1107] Aryltrialkylstannanes add the aryl group to *N*-tosylimines

[1084] Hatano, M.; Asai, T.; Ishihara, K. *Tetrahedron Lett.* ***2008***, *49*, 379; Zani, L.; Eichhorn, T.; Bolm, C. *Chem. Eur. J.* ***2007***, *13*, 2587; Zhou, C.-Y.; Zhu, S.-F.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* ***2010***, *132*, 10955.
[1085] Ballweg, D.M.; Miller, R.C.; Gray, D.L.; Scheidt, K.A. *Org. Lett.* ***2005***, *7*, 1403.
[1086] See Fu, P.; Snapper, M.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2008***, *130*, 5530; Basra, S.; Fennie, M.W.; Kozlowski, M.C. *Org. Lett.* ***2006***, *8*, 2659.
[1087] Fujihara, H.; Nagai, K.; Yomioka, K. *J. Am. Chem. Soc.* ***2000***, *122*, 12055. See Wang, C.-J.; Shi, M. *J. Org. Chem.* ***2003***, *68*, 6229.
[1088] Lee, C.-L.K.; Ling, H.-Y.; Loh, T.-P. *J. Org. Chem.* ***2004***, *69*, 7787. See van der Sluis, M.; Dalmolen, J.; de Lange, B.; Kaptein, B.; Kellogg, R.M.; Broxterman, Q.B. *Org. Lett.* ***2001***, *3*, 3943.
[1089] Legros, J.; Meyer, F.; Coliboeuf, M.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem.* ***2003***, *68*, 6444.
[1090] See Dickstein, J.S.; Fennie, M.W.; Norman, A.L.; Paulose, B.J.; Kozlowski, M.C. *J. Am. Chem. Soc.* ***2008***, *130*, 15794.
[1091] Zani, L.; Alesi, S.; Cozzi, P.G.; Bolm, C. *J. Org. Chem.* ***2006***, *71*, 1558.
[1092] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 847–863.
[1093] See Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* ***1998***, *120*, 4242.
[1094] See Kim, B.; Han, R.; Park, R.; Bai, K.; Jun, Y.; Baik, W. *Synth. Commun.* ***2001***, *31*, 2297.
[1095] Akiyama, T.; Iwai, J.; Onuma, Y.; Kagoshima, H. *Chem. Commun.* ***1999***, 2191.
[1096] Huang, W.-M.; Uang, B.-J. *Chem. Asian J.* ***2015***, *10*, 998; Dahmen, S.; Bräse, S. *Isr. J. Chem.* ***2012***, *52*, 139.
[1097] Fernandes, R.A.; Chaudhari, D.A. *Eur. J. Org. Chem.* ***2012***, 1945.
[1098] Mei, H.; Ji, X.; Han, J.; Pan, Y. *Eur. J. Org. Chem.* ***2011***, 5783.
[1099] Yasukawa, T.; Kuremoto, T.; Miyamura, H.; Kobayashi, S. *Org. Lett.* ***2016***, *18*, 2716.
[1100] With a Cu catalyst, see Sato, A.; Ito, H.; Okada, M.; Nakamura, Y.; Taguchi, T. *Tetrahedron Lett.* ***2005***, *46*, 8381.
[1101] Andrews, P.C.; Peatt, A.C.; Raston, C.L. *Tetrahedron Lett.* ***2004***, *45*, 243.
[1102] Su, W.; Li, J.; Zhang, Y. *Synth. Commun.* ***2001***, *31*, 273.
[1103] Kargbo, R.; Takahashi, Y.; Bhor, S.; Cook, G.R.; Lloyd-Jones, G.C.; Shepperson, I.R. *J. Am. Chem. Soc.* ***2007***, *129*, 3846.
[1104] **Al**: Niwa, Y.; Shimizu, M. *J. Am. Chem. Soc.* ***2003***, *125*, 3720. **La**: Aspinall, H.C.; Bissett, J.S.; Greeves, N.; Levin, D. *Tetrahedron Lett.* ***2002***, *43*, 323. **Nb**: Andrade, C.K.Z.; Oliveira, G.R. *Tetrahedron Lett.* ***2002***, *43*, 1935; Akiyama, T.; Onuma, Y. *J. Chem. Soc., Perkin Trans. 1* ***2002***, 1157. **Pd**: Fernandes, R.A.; Yamamoto, Y. *J. Org. Chem.* ***2004***, *69*, 3562. **Ta**: Shibata, I.; Nose, K.; Sakamoto, K.; Yasuda, M.; Baba, A. *J. Org. Chem.* ***2004***, *69*, 2185. **Zr**: Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. *Angew. Chem. Int. Ed.* ***2001***, *40*, 1896.
[1105] See Kobayashi, Sh.; Ishitani, H. *Chem. Rev.* ***1999***, *99*, 1069.
[1106] Chowdari, N.S.; Ramachary, D.B.; Barbas III, C.F. *Synlett* ***2003***, 1906.
[1107] Oi, S.; Moro, M.; Fukuhara, H.; Kawanishi, T.; Inoue, Y. *Tetrahedron Lett.* ***1999***, *40*, 9259.

using a Rh catalyst and sonication.[1108] Aryl iodides add to *N*-aryl imines in the presence of a Rh catalyst.[1109] Arylation of *N*-tosyl ketimines proceeds with good enantioselectivity using a Rh catalyst.[1110] Propargylic halides add to imines in the presence of In metal, in aqueous THF.[1111]

The addition of catalytically generated benzylcopper derivatives to protected imines [=N(O)Ph_2] gave enantiomerically enriched amines.[1112] The Rh-catalyzed arylation of *N*-Boc imines with polycyclic aromatic compounds gave an aryl-branched *N*-Boc amine.[1113] The Zn-mediated reaction of prenyl bromide with imines gave the homoallylic amine in the environmentally benign 1,3-dimethyl-2-imidazolidinone as the solvent.[1114] A photoredox-mediated coupling of benzylic ethers with Schiff bases using a thiol catalyst with an Ir photocatalyst led to radical–radical coupling and gave β-amino ether products.[1115] The Zn-catalyzed addition of vinylzirconium compounds to *N*-Boc imines gave the *N*-Boc allylic amine product.[1116] The In/Cu-catalyzed addition of phenylacetylene to aldimines gave the amine in aqueous media.[1117] Aromatic compounds added to imines to give the aryl-substituted amine using a Rh catalyst.[1118]

N-Tosyl imines also react with dialkylzinc reagents, giving the sulfonamide with modest enantioselectivity.[1119] *N*-Sulfinyl imines, $R_2CH{=}NS(=O)R'$,[1120] react with Grignard reagents at carbon to give the corresponding *N*-sulfinylamine.[1121] *N*-Carbamoyl imines, formed *in situ*, react with allylic silanes in the presence of an iodine catalyst.[1122] *N*-Carbamoyl imines add acetonitrile (via carbon) using DBU and a Ru catalyst.[1123]

Terminal alkynes react with aryl aldehydes and aryl amines to give propargylic amines without a catalyst.[1124] In addition, with an Ir[1125] or a Cu catalyst,[1126] propargylic amines are formed.[1127] Terminal alkynes add to *N*-substituted imines to give a propargylic amine with good enantioselectivity using a chiral Cu complex.[1128] An Fe_3O_4 nanoparticle-supported copper(I) pybox catalyst promoted the addition reaction of 1-arylethyne derivatives with *N*-aryl imines to give propargylic amine products with good enantioselectivity.[1129]

[1108] Ding, R.; Zhao, C.H.; Chen, Y.J.; Lu, L.; Wang, D.; Li, C.J. *Tetrahedron Lett.* ***2004***, *45*, 2995.
[1109] Ishiyama, T.; Hartwig, J. *J. Am. Chem. Soc.* ***2000***, *122*, 12043.
[1110] Shintani, R.; Takeda, M.; Tsuji, T.; Hayashi, T. *J. Am. Chem. Soc.* ***2010***, *132*, 13168.
[1111] Prajapati, D.; Laskar, D.D.; Gogoi, B.J.; Devi, G. *Tetrahedron Lett.* ***2003***, *44*, 6755.
[1112] Yang, Y.; Perry, I.B.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2016***, *138*, 9787.
[1113] Tsai, A.S.; Tauchert, M.E.; Bergman, R.G.; Ellman, J.A. *J. Am. Chem. Soc.* ***2011***, *133*, 1248.
[1114] Zhao, L.-M.; Zhang, S.-Q.; Jin, H.-S.; Wan, L.-J.; Dou, F. *Org. Lett.* ***2012***, *14*, 886.
[1115] Hager, D.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2014***, *136*, 16986.
[1116] Trost, B.M.; Hung, C.-I.; Koester, D.C.; Miller, Y. *Org. Lett.* ***2015***, *17*, 3778.
[1117] Prajapati, D.; Sarma, R.; Bhuyan, D.; Hu, W. *Synlett* ***2011***, *22*, 627.
[1118] Li, Y.; Li, B.-J.; Wang, W.-H.; Huang, W.-P.; Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Angew. Chem. Int. Ed.* ***2011***, *50*, 2115.
[1119] Soeta, T.; Nagai, K.; Fujihara, H.; Kuriyama, M.; Tomioka, K. *J. Org. Chem.* ***2003***, *68*, 9723.
[1120] See Ellman, J.A.; Owens, T.D.; Tang, T.P. *Acc. Chem. Res.* ***2002***, *35*, 984.
[1121] Tang, T.P.; Volkman, S.K.; Ellman, J.A. *J. Org. Chem.* ***2001***, *66*, 8772.
[1122] Phukan, P. *J. Org. Chem.* ***2004***, *69*, 4005.
[1123] Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2004***, *126*, 13632.
[1124] Li, C.-J.; Wei, C. *Chem. Commun.* ***2002***, 268.
[1125] Fischer, C.; Carreira, E.M. *Synthesis* ***2004***, 1497.
[1126] Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem. Eur. J.* ***2003***, *9*, 2797.
[1127] Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* ***2002***, *124*, 5638.
[1128] See Colombo, F.; Benaglia, M.; Orlandi, S.; Usuelli, F.; Celentano, G. *J. Org. Chem.* ***2006***, *71*, 2064.
[1129] Zeng, T.; Yang, L.; Hudson, R.; Song, G.; Moores, A.R.; Li, C.-J. *Org. Lett.* ***2011***, *13*, 442.

Iminium salts[1130] give tertiary amines directly, via 1,2-addition to the C=N unit. Chloroiminium salts $ClCH{=}NR_2'Cl^-$ (generated *in situ* from an amide, $HCONR_2'$, and phosgene, $COCl_2$) react with 2 molar equivalents of a Grignard reagent RMgX, one adding to the C=N and the other replacing the Cl, to give tertiary amines R_2CHNR_2'.[1131] Alkoxycarbonyl iminium salts were prepared by the oxidation of tetrasubstituted amino ketene silyl acetals, and subsequent nucleophilic addition of Grignard reagents gave α,α-disubstituted α-amino ester derivatives.[1132] The reaction of aldehydes, secondary amines, proton sponge, and silyl triflate generated an iminium salt *in situ*. This salt reacted with difluorocarbene, generated in HMPA from Me_3SiCF_2Br, to give the α-bromodifluoromethyl amine.[1133]

Arylboronic acids (**12-27**) add the aryl group to *N*-tosyl imines using a Rh[1134] or Pd[1135] catalyst. Arylboronic acids react similarly and, in the presence of a chiral Rh[1136] or Ir[1137] catalyst, give a chiral sulfinamide or sulfonamide. The Rh-catalyzed arylation of aliphatic *N*-tosylaldimines with arylboronic acids gave the corresponding tosylamine with good enantioselectivity.[1138] The Pd-catalyzed addition of arylboronic acids to cyclic ketimines gave the amine with good enantioselectivity.[1139] The allylation reaction of organoboron reagents with imines has been reviewed.[1140]

Arylboronates (**12-27**) add to *N*-sulfonyl imines in the presence of a Rh catalyst to give the corresponding sulfonamide.[1141] Chiral Cu complexes have also been used for effective allylation of ketimines.[1142] Allylic boronates also add to aldehydes, and subsequent treatment with ammonia gives the homoallylic amine.[1143] Vinyl boronates add to nitrones in the presence of Me_2Zn, transferring the vinyl group to the C=N unit.[1144] The organocatalyst-mediated reaction of allenyl boronates and *N*-Boc imines gave the α-allenyl *N*-Boc amine.[1145] The enantioselective Cu-catalyzed reactions of (pinacolato)allylborons with aryl-, heteroaryl-, alkyl-, or alkenyl-substituted *N*-phosphinoylimines gave homoallylamides.[1146] Triethylborane was used to initiate a radical coupling reaction of *N*-Boc- and *N*-Cbz-imines and $PivOCH_2I$ to give the corresponding amine product.[1147]

[1130] Paukstelis, J.V.; Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, pp. 275–356. The use of ketene iminium compounds has been reviewed, see Evano, G.; Lecomte, M.; Thilmany, P.; Theunissen, C. *Synthesis* ***2017***, *49*, 3183.
[1131] Wieland, G.; Simchen, G. *Liebigs Ann. Chem.* ***1985***, 2178.
[1132] Hata, S.; Koyama, H.; Shimizu, M. *J. Org. Chem.* ***2011***, *76*, 9670.
[1133] Tsymbal, A.V.; Kosobokov, M.D.; Levin, V.V.; Struchkova, M.I.; Dilman, A.D. *J. Org. Chem.* ***2014***, *79*, 7831.
[1134] See Trincado, M.; Ellman, J.A. *Angew. Chem. Int. Ed.* ***2008***, *47*, 5623.
[1135] Zhang, Q.; Chen, J.; Liu, M.; Wu, H.; Cheng, J.; Qin, C.; Su, W.; Ding, J. *Synlett* ***2008***, 935.
[1136] See Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* ***2007***, *129*, 5336.
[1137] Ngai, M.-Y.; Barchuk, A.; Krische, M.J. *J. Am. Chem. Soc.* ***2007***, *129*, 12644.
[1138] Cui, Z.; Yu, H.-J; Yang, R.-F.; Gao, W.-Y.; Feng, C.-G.; Lin, G.-Q. *J. Am. Chem. Soc.* ***2011***, *133*, 12394.
[1139] Yang, G.; Zhang, W. *Angew. Chem. Int. Ed.* ***2013***, *52*, 7540.
[1140] Ramadhar, T.R.; Batey, R.A. *Synthesis* ***2011***, *43*, 1321.
[1141] Ueda, M.; Saito, A.; Miyaura, N. *Synlett* ***2000***, 1637.
[1142] Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2006***, *128*, 7687.
[1143] Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* ***2004***, *126*, 7182.
[1144] Pandya, A.; Pinet, S.U.; Chavant, P.Y.; Vallée, Y. *Eur. J. Org. Chem.* ***2003***, 3621.
[1145] Wu, H.; Haeffner, F.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2014***, *136*, 3780.
[1146] Vieira, E.M.; Snapper, M.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2011***, *133*, 3332.
[1147] Yamada, K.-i.; Konishi, T.; Nakano, M.; Fujii, S.; Cadou, R.; Yamamoto, Y.; Tomioka, K. *J. Org. Chem.* ***2012***, *77*, 1547.

Potassium allyltrifluoroborates react with *N*-tosylimines in the presence of a Pd catalyst.[1148] Potassium alkenyltrifluoroborates added to *N*-tosylimines using a rhodium catalyst to give the *N*-tosylallylic amine with good enantioselectivity.[1149]

Allylic silanes, such as allyltrimethylsilane, add to *N*-substituted imines in the presence of a Pd catalyst to give the homoallylic amine.[1150] Similar results are obtained when the allylic silane and imine are treated with a catalytic amount of tetrabutylammonium fluoride.[1151] Allylic trichlorosilanes add to hydrazones to give homoallylic hydrazine derivatives with excellent *anti* selectivity[1152] and with good enantioselectivity using a chiral ligand.[1153] Chiral allylic silane derivatives have been developed, and add to hydrazones with good enantioselectivity.[1154] The chiral Mg-BINOL phosphate-catalyzed phosphination of imines gave α-amino phosphine oxides.[1155]

There is an *aza-Baylis-Hillman reaction* that converts imines and conjugated carbonyl derivatives to the α-amino-conjugated derivative.[1156] *N*-Tosylimines can be used in place of aldehydes, and the reaction of the imine, a conjugated ester, and DABCO gave the allylic *N*-tosylimine.[1157] A "double Baylis-Hillman" reaction has also been reported using *N*-tosylimines and conjugated ketones.[1158] The use of chiral catalysts leads to enantioselective product formation.[1159] Enantioselective aza-Baylis-Hillman reactions[1160] were reported, including using a chiral reaction medium.[1161] Aldehydes add via the α carbon using proline, to give β-amino aldehydes with good selectivity.[1162]

Nitro compounds add to *N*-carbamoyl imines with a chiral diamine catalyst with some enantioselectivity.[1163] Nitro compounds add via carbon using a Cu catalyst, and with good enantioselectivity, when a chiral ligand is used.[1164] The conjugate bases of nitro compounds (formed by treatment of the nitro compound with BuLi) react with Grignard reagents in the presence of $ClCH{=}NMe_2^+\ Cl^-$ to give oximes.[1165]

Many other C=N systems such as hydrazones and oximes give 1,2-addition when treated with *Grignard reagents*; others give reductions; others give miscellaneous reactions.

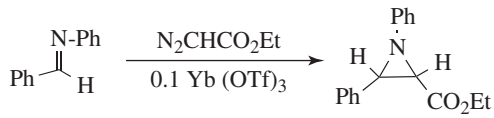
[1148] Solin, N.; Wallner, O.A.; Szabó, K.J. *Org. Lett.* ***2005***, *7*, 689.
[1149] Gopula, B.; Chiang, C.-W.; Lee, W.-Z.; Kuo, T.-S.; Wu, P.-Y.; Henschke, J.P.; Wu, H.-L. *Org. Lett.* ***2014***, *16*, 632. Also see Cui, Z.; Chen, Y.-J.; Gao, W.-Y.; Feng, C.-G.; Lin, C.-Q. *Org. Lett.* ***2014***, *16*, 1016.
[1150] Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* ***1999***, *64*, 2614.
[1151] See Fernandes, R.A.; Yamamoto, Y. *J. Org. Chem.* ***2004***, *69*, 735.
[1152] Hirabayashi, R.; Ogawa, C.; Sugiura, M.; Kobayashi, S. *J. Am. Chem. Soc.* ***2001***, *123*, 9493.
[1153] Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* ***2003***, *125*, 6610.
[1154] Berger, R.; Duff, K.; Leighton, J.L. *J. Am. Chem. Soc.* ***2004***, *126*, 5686.
[1155] Ingle, G.K.; Liang, Y.; Mormino, M.G.; Li, G.; Fronczek, F.R.; Antilla, J.C. *Org. Lett.* ***2011***, *13*, 2054.
[1156] For reviews, see Zhang, W.; Ma, W.; Shen, Y.; Yao, Y. *Org. Prep. Proceed. Int.* ***2011***, *43*, 1; Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* ***2009***, *109*, 1. Linder, C.; Tandon, R.; Liu, Y.; Maryasin, B.; Zipse, H. *Org. Biomol. Chem.* ***2012***, *10*, 3210.
[1157] Xu, Y.-M.; Shi, M. *J. Org. Chem.* ***2004***, *69*, 417.
[1158] Shi, M.; Xu, Y.-M. *J. Org. Chem.* ***2003***, *68*, 4784.
[1159] Qi, M.-J.; Ai, T.; Shi, M.; Li, G. *Tetrahedron* ***2008***, *64*, 1181; Utsumi, N.; Zhang, H.; Tanaka, F.; Barbas III, C.F. *Angew. Chem. Int. Ed.* ***2007***, *46*, 1878.
[1160] Kitagaki, S.; Ohta, Y.; Takahashi, R.; Komizu, M.; Mukai, C. *Tetrahedron Lett.* ***2013***, *54*, 384; Hyodo, K.; Nakamura, S.; Shibata, N. *Angew. Chem. Int. Ed.* ***2012***, *51*, 10337.
[1161] Gausepohl, R.; Buskens, P.; Kleinen, J.; Bruckmann, A.; Lehmann, C.W.; Klankermayer, J.; Leitner, W. *Angew. Chem. Int. Ed.* ***2006***, *45*, 3689.
[1162] See Chowdari, N.S.; Suri, J.T.; Barbas III, C.F. *Org. Lett.* ***2004***, *6*, 2507.
[1163] Nugent, B.M.; Yoder, R.A.; Johnston, J.N. *J. Am. Chem. Soc.* ***2004***, *126*, 3418.
[1164] Nishiwaki, N.; Knudson, K.R.; Gothelf, K.V.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* ***2001***, *40*, 2992.
[1165] Fujisawa, T.; Kurita, Y.; Sato, T. *Chem. Lett.* ***1983***, 1537.

Organocerium reagents add to hydrazones.[1166] Indium metal promotes the addition of alkyl iodides to hydrazones.[1167] Hydrazone derivatives react with iodoalkenes in the presence of $InCl_3$ and $Mn_2(CO)_{10}$ under photochemical conditions to give the hydrazine derivative.[1168] The Sn-catalyzed nucleophilic allyl/Pt addition to hydrazones in the presence of H_2 gave the cyclic *N*-acylhydrazine derivative.[1169] Diarylboronic acids were coupled with tosyl hydrazones by heating to give diarylmethanes.[1170]

Oximes can be converted to hydroxylamines by treatment with 2 molar equivalents of an alkyllithium reagent, followed by methanol.[1171] Oxime ethers add an allyl group upon reaction with allyl bromide and In metal in water.[1172] Nitrones, $R_2C{=}N^+(R')—O^-$, react with allylic bromides and Sm to give homoallylic oximes,[1173] and with terminal alkynes and a Zn catalyst to give propargylic oximes.[1174] *Grignard reagents* also add to nitrones.[1175] Organozinc halides added to nitrones with a TMSCl promoter to give α-branched amines.[1176] Nitrones react with $CH_2{=}CHCH_2InBr$ in aqueous DMF to give the homoallylic oxime[1177] and silyl ketene acetals add in the presence of a chiral Ti catalyst with good enantioselectivity.[1178]

OS **IV**, 605; **VI**, 64. Also see, OS **III**, 329.

16-32 The Addition of Carbenes and Diazoalkanes to C=N Compounds

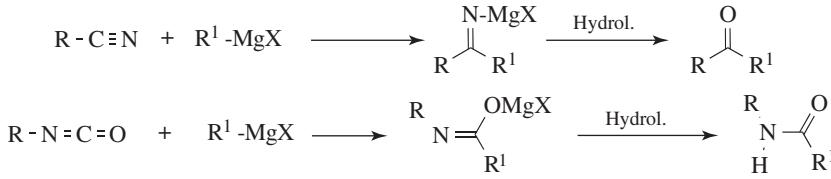


In the presence of metal catalysts such as $Yb(OTf)_3$, diazoalkanes add to imines to generate aziridines.[1179] The reaction is somewhat selective for the *cis* diastereomer. The use of chiral additives in this reaction leads to aziridines enantioselectively.[1180] Imines are formed by the reaction of amines with an aldehyde or ketone (**16-12**). *N*-Tosyl imines react with diazoalkenes to form *N*-tosyl aziridines, with good *cis* selectivity[1181] and modest enantioselectivity in the presence of a chiral Cu catalyst[1182] but with excellent enantioselectivity

[1166] Denmark, S.E.; Edwards, J.P.; Nicaise, O. *J. Org. Chem.* ***1993***, *58*, 569.
[1167] Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Tetrahedron* ***2004***, *60*, 4227.
[1168] Friedstad, G.K.; Qin, J. *J. Am. Chem. Soc.* ***2001***, *123*, 9922.
[1169] Hong, J.-T.; Jang, H.-Y. *J. Org. Chem.* ***2011***, *76*, 6877.
[1170] Li, X.; Feng, Y.; Lin, L.; Zou, G. *J. Org. Chem.* ***2012***, *77*, 10991.
[1171] Richey Jr., H.G.; McLane, R.C.; Phillips, C.J. *Tetrahedron Lett.* ***1976***, 233.
[1172] Bernardi, L.; Cerè, V.; Femoni, C.; Pollicino, S.; Ricci, A. *J. Org. Chem.* ***2003***, *68*, 3348.
[1173] Laskar, D.D.; Prajapati, D.; Sandu, J.S. *Tetrahedron Lett.* ***2001***, *42*, 7883.
[1174] Frantz, D.E.; Fässler, R.; Carreira, E.M. *J. Am. Chem. Soc.* ***1999***, *121*, 11245. See Pinet, S.; Pandya, S.U.; Chavant, P.Y.; Ayling, A.; Vallee, Y. *Org. Lett.* ***2002***, *4*, 1463.
[1175] See Merino, P.; Tejero, T. *Tetrahedron* ***2001***, *57*, 8125.
[1176] Fu, Y.; Liu, Y.; Chen, Y.; Hügel, H.M.; Wang, M.; Huang, D.; Hu, Y. *Org. Biomol. Chem.* ***2012***, *10*, 7669.
[1177] Kumar, H.M.S.; Anjaneyulu, S.; Reddy, E.J.; Yadav, J.S. *Tetrahedron Lett.* ***2000***, *41*, 9311.
[1178] Murahashi, S.-I.; Imada, Y.; Kawakami, T.; Harada, K.; Yonemushi, Y.; Tomita, N. *J. Am. Chem. Soc.* ***2002***, *124*, 2888.
[1179] See Nagayama, S.; Kobayashi, S. *Chem. Lett.* ***1998***, 685. Also see, Rasmussen, K.G.; Jørgensen, K.A. *J. Chem. Soc., Chem. Commun.* ***1995***, 1401.
[1180] See Janardanan, D.; Sunoj, R.B. *J. Org. Chem.* ***2008***, *73*, 8163.
[1181] See Williams, A.L.; Johnston, J.N. *J. Am. Chem. Soc.* ***2004***, *126*, 1612.
[1182] Juhl, K.; Hazell, R.G.; Jørgensen, K.A. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2293.

with a chiral Rh catalyst[1183] or with the use of an organocatalyst.[1184] It is noted that *N*-tosyl aziridines are formed by the reaction of an alkene with PhI=NTs and a Cu catalyst.[1185] *N*-Acylimines react with diazoesters via C–H insertion using a Pt catalyst.[1186] The Pd-catalyzed intramolecular insertion of alkenes into the C–N bond of β-lactams has been reported.[1187]

16-33 The Addition of Grignard Reagents to Nitriles and Isocyanates



The addition of *Grignard reagents* to nitriles, followed by hydrolysis of the initially formed imine anion, gives ketones. When both R groups are alkyl, yields are not high.[1188] Yields can be improved by the use of Cu(I) salts[1189] or by using benzene containing 1 equivalent of ether as the solvent, rather than ether alone.[1190] In general, the ketimine salt does not react with Grignard reagents: hence tertiary alcohols or tertiary alkyl amines are not often side products.[1191] By careful hydrolysis of the salt it is sometimes possible to isolate ketimines ($RR'C{=}NH$),[1192] especially when R and R′ = aryl. The addition of Grignard reagents to the C≡N group is normally slower than to the C=O group, and cyano groups containing aldehydes add the Grignard reagent without disturbing the CN group.[1193] The addition of Grignard reagents to nitriles has been reported using flow conditions (Sec. 7.D).[1194] The mechanism probably involves addition of the carbon group to the nitrile carbon to form an N–MgBr imine, although dialkylmagnesium addition to the nitrile may be involved.[1195]

Organolithium reagents add to nitriles, mediated by LiBr, to form *N*-acetyl enamines.[1196] Secondary thioamides were prepared by the reaction of functionalized organolithium reagents with isothiocyanates followed by aqueous acid hydrolysis.[1197] Other metal compounds have been used, including Sm with allylic halides[1198] and organocerium

[1183] Aggarwal, V.K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem. Int. Ed.* ***2001***, *40*, 1433.
[1184] Lu, Z.; Zhang, Y.; Wulff, W.D. *J. Am. Chem. Soc.* ***2007***, *129*, 7185. Also see Branco, P.S.; Raje, V.P.; Dourado, J.; Gordo, J. *Org. Biomol. Chem.* ***2010***, *8*, 2968.
[1185] Handy, S.T.; Czopp, M. *Org. Lett.* ***2001***, *3*, 1423.
[1186] Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* ***2005***, *127*, 9360.
[1187] Yada, A.; Okajima, S.; Murakami, M. *J. Am. Chem. Soc.* ***2015***, *137*, 8708.
[1188] See Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 767–845.
[1189] Weiberth, F.J.; Hall, S.S. *J. Org. Chem.* ***1987***, *52*, 3901.
[1190] Canonne, P.; Foscolos, G.B.; Lemay, G. *Tetrahedron Lett.* ***1980***, 155.
[1191] See Gauthier, R.; Axiotis, G.P.; Chastrette, M. *J. Organomet. Chem.* ***1977***, *140*, 245.
[1192] Pickard, P.L.; Toblert, T.L. *J. Org. Chem.* ***1961***, *26*, 4886.
[1193] Cason, J.; Kraus, K.W.; McLeod Jr., W.D. *J. Org. Chem.* ***1959***, *24*, 392.
[1194] Mateos, C.; Rincón, J.A.; Villanueva, J. *Tetrahedron Lett.* ***2013***, *54*, 2226.
[1195] Ashby, E.C.; Chao, L.; Neumann, H.M. *J. Am. Chem. Soc.* ***1973***, *95*, 4896, 5186.
[1196] Savarin, C.G.; Boice, G.N.; Murry, J.A.; Corley, E.; DiMichele, L.; Hughes, D. *Org. Lett.* ***2006***, *8*, 3903.
[1197] Pace, V.; Castoldi, L.; Monticelli, S.; Safranek, S.; Roller, A.; Langer, T.; Holzer, W. *Chem. Eur. J.* ***2015***, *21*, 18966.
[1198] Yu, M.; Zhang, Y.; Guo, H. *Synth. Commun.* ***1997***, *27*, 1495.

compounds.[1199] Allylic halides react with an excess of Zn metal in the presence of 40% $AlCl_3$, and in the presence of a nitrile, to give homoallylic ketones after hydrolysis.[1200] The *Blaise reaction* is the reaction of the organozinc reagent derived from a α-bromo ester with Zn metal and a nitrile to give the corresponding β-keto ester.[1201] Arenes add to nitriles in the presence of a Pd catalyst in DMSO/trifluoroacetic acid to give a diaryl ketone.[1202] *N*-Aryl amides were prepared by the Cu-catalyzed reaction of aryl halides and nitriles.[1203]

Arylboronic acids add to nitriles in the presence of a Pd catalyst.[1204] Aryl and alkenylboronic acids add to isocyanates in the presence of a Pd[1205] or Rh[1206] catalyst. Arylboronic acids added to aliphatic nitriles using a Pd catalyst to give alkyl aryl ketones.[1207] The boron trifluoride-mediated double allylboration of nitriles to give bis(allyl) amines by reaction with potassium allyltrifluoroborate proceeded at room temperature.[1208]

The Ag-catalyzed reactions of isocyanides have been reviewed.[1209] It is noted that terminal alkynes add to the carbon of an isonitrile in the presence of a uranium complex, giving a propargylic imine.[1210] The addition of Grignard reagents to isocyanates gives, after hydrolysis, *N*-substituted amides.[1211] This is a very good reaction and can be used to prepare derivatives of alkyl and aryl halides. The reaction has also been performed with alkyllithium compounds.[1212] Isothiocyanates give *N*-substituted thioamides. Nitroso compounds react with activated nitriles in the presence of LiBr and microwave irradiation to give a cyano imine, ArN═C(CN)Ar.[1213] This transformation has been called the *Ehrlich-Sachs reaction*.[1214]

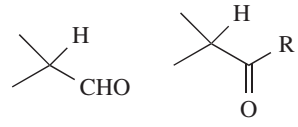
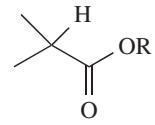
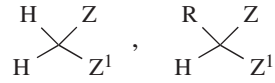
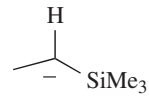
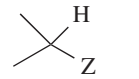
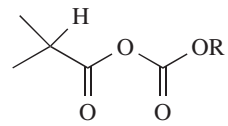
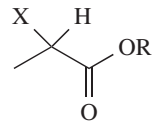
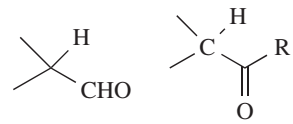
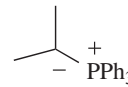
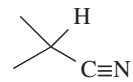
OSCV **III**, 26, 562; **V**, 120, 520.

G. Carbon Attack by Active Hydrogen Compounds

Reactions **16-34** to **16-49** are base-catalyzed condensations (although some of them are also catalyzed by acids).[1215] In **16-34** to **16-44**, a base removes a C—H proton to give a carbanion, which then adds to a C═O. The oxygen acquires a proton, and the resulting alcohol may or may not be dehydrated, depending on whether an α hydrogen is present and on whether

[1199] Ciganek, E. *J. Org. Chem.* ***1992***, *57*, 4521.
[1200] Lee, A.S.-Y.; Lin, L.-S. *Tetrahedron Lett.* ***2000***, *41*, 8803.
[1201] Blaise, E.E. *Compt. Rend.* ***1901***, *132*, 478; Rao, H.S.P.R.; Rafi, S.; Padmavathy, K. *Tetrahedron* ***2008***, *64*, 8037.
[1202] Zhou, C.; Larock, R.C. *J. Am. Chem. Soc.* ***2004***, *126*, 2302.
[1203] Zhang, D.-X.; Xiang, S.-K.; Hu, H.; Tan, W.; Feng, C.; Wang, B.-Q.; Zhao, K.-Q.; Hu, P.; Yang, H. *Tetrahedron* ***2013***, *69*, 10022.
[1204] Zhao, B.; Lu, X. *Tetrahedron Lett.* ***2006***, *47*, 6765.
[1205] Kianmehr, E.; Rajabi, A.; Ghanbari, M. *Tetrahedron Lett.* ***2009***, *50*, 1687.
[1206] Miura, T.; Takahashi, Y.; Murakami, M. *Chem. Commun.* ***2007***, 3577.
[1207] Wang, X.; Wang, X.; Liu, M.; Ding, J.; Chen, J.; Wu, H. *Synthesis* ***2013***, *45*, 2241; Das, T.; Chakraborty, A.; Sarkar, A. *Tetrahedron Lett.* ***2014***, *55*, 7198.
[1208] Ramadhar, T.R.; Bansagi, J.; Batey, R.A. *J. Org. Chem.* ***2013***, *78*, 1216.
[1209] Wang, W.; Kumar, R.K.; Bi, X. *Tetrahedron Lett.* ***2016***, *57*, 5730.
[1210] Barnea, E.; Andrea, T.; Kapon, M.; Berthet, J.-C.; Ephritikhine, M.; Eisen, M.S. *J. Am. Chem. Soc.* ***2004***, *126*, 10860.
[1211] See Screttas, C.G.; Steele, B.R. *Org. Prep. Proced. Int.* ***1990***, *22*, 271.
[1212] See Cooke Jr., M.P.; Pollock, C.M. *J. Org. Chem.* ***1993***, *58*, 7474.
[1213] Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *Synth. Commun.* ***2001***, *31*, 1427.
[1214] Ehrlich, P.; Sachs, F. *Chem. Ber.* ***1899***, *32*, 2341.
[1215] See Reeves, R.L. in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, ***1966***, pp. 567–619. See also, Stowell, J.C. *Carbanions in Organic Synthesis*, Wiley, NY, ***1979***.

TABLE 16.2 Base-catalyzed condensations showing the active-hydrogen components and the carbonyl compounds

	Reaction	Active hydrogen component	Carbonyl component	Subsequent reaction
16-34	**Aldol**		aldehyde, ketone	dehydration may follow
16-36			aldehyde, ketone (usually without α-hydrogens)	dehydration may follow
16-38	**Knoevenagel**	 and similar molecules	aldehyde, ketone (usually without α-hydrogens)	Dehydration usually follows
16-41	**Peterson**		aldehyde, ketone	dehydration may follow
16-42		 Z = COR, COOR, NO_2	CO_2, CS_2	
16-39	**Perkin**		aromatic aldehyde	dehydration usually follows
16-40	**Darzen's**		aldehyde, ketone	epoxidation
16-43	**Tollen's**		formaldehyde	crossed Cannizzaro reaction follows
16-44	**Wittig**		aldehyde, ketone	Dehydration always follows
16-49	**Thorpe**		nitrile	

the new double bond would be in conjugation with double bonds already present. The reactions differ in the nature of the active hydrogen component and the carbonyl component. Table 16.2 illustrates the differences. Reaction **16-49** is an analogous reaction involving addition to C≡N.

16-34 The Aldol Condensation[1216]

In the *aldol reaction* or *aldol condensation* the α carbon of one aldehyde or ketone molecule adds to the carbonyl carbon of another.[1217] Although acid-catalyzed aldol reactions are known,[1218] the most common form of the reaction uses a base. There is evidence that an SET mechanism can intervene when the substrate is an aromatic ketone.[1219] Although hydroxide was commonly used in early versions of this reaction, stronger bases, such as alkoxides (RO^-) or amides (R_2N^-), are also common. Amine bases have been used to catalyze the aldol condensation.[1220] With weaker bases, not all of an aldehyde or ketone is converted to the corresponding enolate ion, so the equilibrium lies well to the left, for both aldehydes and ketones. Nevertheless, enough enolate ion is present for reaction with the carbonyl carbon to give the β-alkoxide product. Hydrolysis gives the aldol product. Homoaldol condensation products are known[1221] as well as vinylogous aldol reactions.[1222] Aza-aldol reactions have been reported.[1223]

The reaction with hydroxide generates water (pK_a 15.7) as the conjugate acid, which is a stronger acid that the carbonyl (pK_a about 20–22), so the water reacts with the enolate anion to shift the equilibrium back to the left. With amide bases, the conjugate acid is the amine (pK_a about 36), which is a much weaker acid than the carbonyl. So, particularly with aprotic solvents, the equilibrium usually lies to the right when compared with alkoxides or hydroxide. Protic solvents have an acidic hydrogen (e.g., water or alcohol), and the solvent is acidic enough to react with the enolate anion and shift the equilibrium to the left. An aprotic solvent, such as ether or THF, does not have an acidic hydrogen atom and cannot react with the enolate anion. A strong amide base, such as lithium diisopropylamide (LDA, Sec. 8.F, category 7), generates a amine conjugate acid that reacts very slowly with the

[1216] See Mahrwald, R. *Modern Aldol Reactions*, 2 Volume Set, Wiley, NJ, ***2004***; Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 681–687. Aleksandr Borodin was the discoverer of the aldol condensation: see Podlech, J. *Angew. Chem. Int. Ed.* ***2010***, *49*, 6490.

[1217] For reviews, see Mandal, S.; Mandal, S.; Ghosh, S.K.; Ghosh, A.; Saha., R.; Banerjee, S.; Saha, B. *Synth. Commun.* ***2016***, *46*, 1327; Gati, W.; Yamamoto, H. *Acc. Chem. Res.* ***2016***, *49*, 1757; Nielsen, A.T.; Houlihan, W.J. *Org. React.* ***1968***, *16*, 1. See Thebtaranonth, C.; Thebtaranonth, Y. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, ***1989***, pp. 199–280; Hajos, Z.G. in Augustine, R.L. *Carbon-Carbon Bond Formation*, Vol. 1, Marcel Dekker, NY, ***1979***, pp. 1–84.

[1218] See Mahrwald, R.; Gündogan, B. *J. Am. Chem. Soc.* ***1998***, *120*, 413.

[1219] Ashby, E.C.; Argyropoulos, J.N. *J. Org. Chem.* ***1986***, *51*, 472.

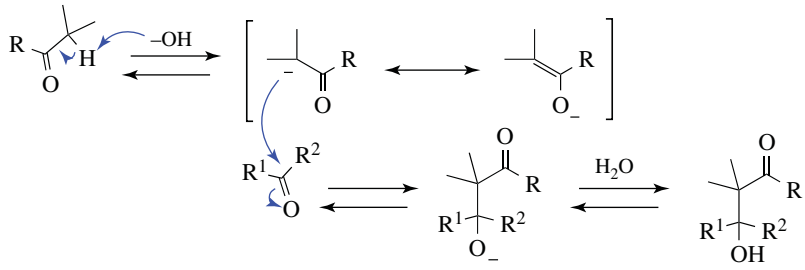
[1220] Markert, M.; Mulzer, M.; Schetter, B.; Mahrwald, R. *J. Am. Chem. Soc.* ***2007***, *129*, 7258. See Erkkilä, A.; Pihko, P.M. *J. Org. Chem.* ***2006***, *71*, 2538.

[1221] Murphy, S.K.; Petrone, D.A.; Coulter, M.M.; Dong, Vy.M. *Org. Lett.* ***2011***, *13*, 6216; Horino, Y.; Sugata, M.; Sugita, T.; Aimono, A.; Abe, H. *Tetrahedron Lett.* ***2017***, *58*, 2131.

[1222] For a review, see Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* ***2011***, *111*, 3076. Symkenberg, G.; Kalesse, M. *Org. Lett.* ***2012***, *14*, 1608; Bastida, D.; Liu, Y.; Tian, X.; Escudero-Adán, E.; Melchiorre, P. *Org. Lett.* ***2013***, *15*, 220; Jing, Z.; Bai, X.; Chen, W.; Zhang, G.; Zhu, B.; Jiang, Z. *Org. Lett.* ***2016***, *18*, 260; Qin, Z.; Ma, R.; Xu, S.; He, Z. *Tetrahedron* ***2013***, *69*, 10424; Ratjen, L.; García-García, P.; Lay, F.; Beck, M.E.; List, B. *Angew. Chem. Int. Ed.* ***2011***, *50*, 754; Pansare, S.V.; Paul, E.K. *Chem. Commun.* ***2011***, *47*, 1027.

[1223] Miura, T.; Nakamuro, T.; Miyakawa, S.; Murakami, M. *Angew. Chem. Int. Ed.* ***2016***, *55*, 8732; See Houghton, M.J.; Huck, C.J.; Wright, S.W.; Collum, D.B. *J. Am. Chem. Soc.* ***2016***, *138*, 10276.

enolate and the equilibrium lies more to the right.[1224] A variety of amide bases can be used to deprotonate the ketone or aldehyde. In the case of an unsymmetrical ketone, removal of the more acidic proton leads to the kinetic enolate anion.[1225] Note that a polymer-bound amide base has been used[1226] and solid-phase chiral lithium amides are known.[1227] The aldol reaction has been done in ionic liquids.[1228]



The product of an aldol condensation is a β-hydroxy aldehyde (called an *aldol*) or a β-hydroxy ketone, which is often dehydrated during the course of the reaction if the resulting C═C unit is conjugated. Indeed, *the aldol product is relatively easy to isolate* when the reaction is done in aprotic solvents with a mild workup procedure, *unless the substrate is an aromatic aldehyde or ketone*.[1229] A retro-aldol condensation has been exploited for crossed-aldol reactions.[1230] Enzyme-mediated aldol reactions have been reported using two aldehydes, including formaldehyde.[1231] A vinylogous (Sec. 6.B) aldol reaction is known,[1232] as is a "double" aldol.[1233] Under the principle of vinylogy (Sec. 6.B), the active hydrogen can be one in the γ position of an α,β-unsaturated carbonyl compound.

The scope of the aldol reaction may be discussed under five headings.

1. *Reaction between two molecules of the same aldehyde*, which is called *homocoupling*. Hydroxide or alkoxide bases are typically used in protic solvents,[1234] and the reaction is quite feasible. Nowadays, the use of dialkylamide bases in aprotic solvents such as ether or THF is more common. Many aldehydes have been converted to aldols and/or their dehydration products in this manner. The most effective

[1224] See Cainelli, G.; Galletti, P.; Giacomini, D.; Orioli, P. *Tetrahedron Lett.* ***2001***, *42*, 7383.
[1225] See Zhao, P.; Condo, A.; Keresztes, I.; Collum, D.B. *J. Am. Chem. Soc.* ***2004***, *126*, 3113; Ichibakase, T.; Nakajima, M. *Org. Lett.* ***2011***, *13*, 1579.
[1226] Seki, A.; Ishiwata, F.; Takizawa, Y.; Asami, M. *Tetrahedron* ***2004***, *60*, 5001. See Flowers II, R.A.; Xu, X.; Timmons, C.; Li, G. *Eur. J. Org. Chem.* ***2004***, 2988.
[1227] Johansson, A.; Abrahamsson, P.; Davidsson, Ö. *Tetrahedron: Asymmetry* ***2003***, *14*, 1261.
[1228] Zheng, X.; Zhang, Y. *Synth. Commun.* ***2003***, 161.
[1229] Also see Kourouli, T.; Kefalas, P.; Ragoussis, N.; Ragoussis, V. *J. Org. Chem.* ***2002***, *67*, 4615.
[1230] See Zhang, S.-L.; Yu, Z.-L. *J. Org. Chem.* ***2016***, *81*, 57; Enders, D.; Nguyen, T.V. *Tetrahedron Lett.* ***2012***, *53*, 2091; Schmidt, J.; Ehasz, C.; Epperson, M.; Klas, K.; Wyatt, J.; Hennig, M.; Forcni, M. *Org. Biomol. Chem.* ***2013***, *11*, 8429.
[1231] Demir, A.S.; Ayhan, P.; Igdir, A.C.; Duygu, A.N. *Tetrahedron* ***2004***, *60*, 6509.
[1232] See Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* ***2000***, *100*, 1929; Casiraghi, G.; Zanardi, F.; Rassu, G. *Pure Appl. Chem.* ***2000***, *72*, 1645; Denmark, S.E.; Heemstra Jr., J.R.; Beutner, G.L. *Angew. Chem. Int. Ed.* ***2005***, *44*, 4782.
[1233] See Abiko, A.; Inoue, T.; Masamune, S. *J. Am. Chem. Soc.* ***2002***, *124*, 10759.
[1234] For discussions of equilibrium constants in aldol reactions, see Guthrie, J.P.; Wang, X. *Can. J. Chem.* ***1991***, *69*, 339; Guthrie, J.P. *J. Am. Chem. Soc.* ***1991***, *113*, 7249, and references cited therein.

catalysts are basic ion-exchange resins. Of course, the aldehyde must possess an α hydrogen.

2. *Reaction between two molecules of the same ketone. homo-coupling*. With hydroxide or alkoxide bases in protic solvents the equilibrium lies well to the left,[1235] and the reaction is most feasible if the equilibrium can be shifted. Such an equilibrium shift can often be done by allowing the reaction to proceed in a Soxhlet extractor (e.g., see *OS* **I**, 199). As with aldehydes, the use of dialkylamide bases such as LDA or lithium hexamethyldisilazide (Sec. 8.F, category 7) in aprotic solvents such as ether or THF are more common. Unsymmetrical ketones condense on the least substituted side (more acidic H) with dialkylamide bases in aprotic solvents, but on the more substituted side (less acidic H) with alkoxide bases in alcohol solvents.
3. *Reaction between two different aldehydes: cross-coupling*. In protic solvents with an alkoxide base this will produce a mixture of four products (eight, if the alkenes are counted). However, if one aldehyde does not have an α hydrogen, only two aldols are possible, and in many cases the crossed product is the main one. The crossed aldol reaction is often called the *Claisen-Schmidt reaction*.[1236] Nowadays, the crossed aldol reaction is readily accomplished using amide bases in an aprotic solvent. For example, the first aldehyde is treated with LDA in THF at −78 °C to form the enolate anion and since the solvent is not acidic the equilibrium lies to the right, and there is a reasonable concentration of the enolate anion. Subsequent treatment with a second aldehyde allows the initially formed enolate anion to react via acyl addition to give the mixed aldol product. Note that the crossed aldol of two aldehydes has been done using potassium *tert*-butoxide and $Ti(OBu)_4$.[1237]
4. *Reaction between two different ketones: cross-coupling*. When hydroxide or alkoxide bases are used, the more acidic hydrogen is removed from the less-substituted α carbon and the conjugate acid is an alcohol. As this is more acidic than the ketone the equilibrium lies to the right. This situation allows the α hydrogen from the more-substituted carbon to be removed (it is only 1–2 pK_a units less acidic after all) to form the more-substituted enolate anion. Since the alcohol conjugate acid also reacts with this enolate anion, this is also a reversible reaction and a dynamic equilibrium is established with both enolate anions and the initial carbonyl. The equilibrium shifts toward the thermodynamically more stable enolate anion, which is the more-substituted enolate anion, and this then reacts with the second added ketone to give the major product. Note that the less-substituted enolate anion (the kinetic enolate) also reacts, so there is a mixture of products that favors the product of the reaction with the more substituted (thermodynamic) enolate anion. If this reaction is done with amide bases in aprotic solvents, the kinetic enolate anion is formed first and the equilibrium is to the right, so the major contributor to the acid–base equilibrium is the kinetic enolate anion. It is this enolate anion that reacts with the second ketone to give the alkoxide product.
5. *Reaction between an aldehyde and a ketone*. This coupling is usually feasible with hydroxide or alkoxides bases in protic solvents when the aldehyde has no α

[1235] The equilibrium concentration of the product from acetone in pure acetone was determined to be 0.01%: Maple, S.R.; Allerhand, A. *J. Am. Chem. Soc.* ***1987***, *109*, 6609.
[1236] In aqueous media: see Buonora, P.T.; Rosauer, K.G.; Dai, L. *Tetrahedron Lett.* ***1995***, *36*, 4009.
[1237] Han, Z.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* ***2000***, *41*, 4415.

hydrogen, since there is no competition from ketone condensing with itself.[1238] This is also called the *Claisen-Schmidt reaction*. Even when the aldehyde has an α hydrogen, it is generally the α carbon of the ketone that adds to the carbonyl of the aldehyde, not the other way around. Mixtures are usually produced, however. The kinetic–thermodynamic enolate anion conditions in point 4 (above) also apply to this reaction. If the ketone or the aldehyde is treated with an amide base in aprotic solvents, a second aldehyde or ketone can be added to give the aldolate with high regioselectivity.

A computational study gave the gas-phase activation energies for lithium enolate anions in an aldol-type reaction.[1239] There is a computational study of the mechanism for an aldol reaction in pure water.[1240] A computational study of the aldol reaction between benzaldehyde and acetone to determine the origin of the enhanced rates and enantioselectivities derived from an enamine-based catalytic antibody 33F12 and a chiral organocatalyst.[1241]

Base-induced formation of the enolate anion generally leads to a mixture of (*E*)- and (*Z*)-isomers, and dialkyl amide bases are used in most cases. The (*E/Z*) stereoselectivity depends on the structure of the lithium dialkylamide base, with the highest (*E/Z*) ratios obtained with LiTMP/butyllithium mixed aggregates in THF.[1242] The use of LiHMDS resulted in a reversal of the (*E/Z*) selectivity. In general, metallic (*Z*)-enolates give the *syn* (or *erythro*) pair, and this reaction is highly useful for the diastereoselective synthesis of these products.[1243] The (*E*)-isomers generally react nonstereoselectively. However, *anti* stereoselectivity has been achieved in a number of cases, with Ti enolates,[1244] with Mg enolates,[1245] and with certain enol borinates.[1246] Enolization and reprotonation accounts for *syn-anti* isomerization of aldols.[1247] In another variation, a β-keto *Weinreb amide* (see **16-29**) reacted with $TiCl_4$ and *Hünig's base* (i-Pr_2NEt) and then an aldehyde to give the β-hydroxy ketone.[1248]

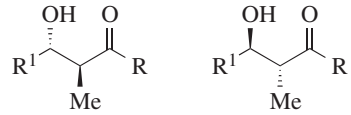
The aldol reaction can be made regioselective by preparing an enol derivative of the ketone separately[1249] under kinetic conditions and then adding this to the aldehyde (or ketone). Other types of preformed derivatives that react with aldehydes and ketones are enamines (with a Lewis acid catalyst),[1250] and enol borinates $R'CH{=}CR^2{-}OBR_2$[1251]

[1238] See Kad, G.L.; Kaur, K.P.; Singh, V.; Singh, J. *Synth. Commun.* ***1999***, *29*, 2583.
[1239] Pratt, L.M.; Nguên, N.V.; Ramachandran, B. *J. Org. Chem.* ***2005***, *70*, 4279.
[1240] Zhang, X.; Houk, K.N. *J. Org. Chem.* ***2005***, *70*, 9712.
[1241] Armacost, K.; Acevedo, O. *J. Am. Chem. Soc.* ***2014***, *136*, 147.
[1242] Pratt, L.M.; Newman, A.; Cyr, J.S.; Johnson, H.; Miles, B.; Lattier, A.; Austin, E.; Henderson, S.; Hershey, B.; Lin, M.; Balamraju, Y.; Sammonds, L.; Cheramie, J.; Karnes, J.; Hymel, E.; Woodford, B.; Carter, C. *J. Org. Chem.* ***2003***, *68*, 6387.
[1243] See Paddon-Row, M.N.; Houk, K.N. *J. Org. Chem.* ***1990***, *55*, 481; Denmark, S.E.; Henke, B.R. *J. Am. Chem. Soc.* ***1991***, *113*, 2177.
[1244] See Nerz-Stormes, M.; Thornton, E.R. *J. Org. Chem.* ***1991***, *56*, 2489.
[1245] Swiss, K.A.; Choi, W.; Liotta, D.; Abdel-Magid, A.F.; Maryanoff, C.A. *J. Org. Chem.* ***1991***, *56*, 5978.
[1246] Danda, H.; Hansen, M.M.; Heathcock, C.H. *J. Org. Chem.* ***1990***, *55*, 173. See also, Corey, E.J.; Kim, S.S. *Tetrahedron Lett.* ***1990***, *31*, 3715.
[1247] Ward, D.E.; Sales, M.; Sasmal, P.K. *J. Org. Chem.* ***2004***, *69*, 4808.
[1248] Calter, M.A.; Guo, X.; Liao, W. *Org. Lett.* ***2001***, *3*, 1499.
[1249] See Mukaiyama, T. *Isr. J. Chem.* ***1984***, *24*, 162; Caine, D. in Augustine, R.L. *Carbon-Carbon Bond Formation*, Vol. 1, Marcel Dekker, NY, ***1979***, pp. 264–276.
[1250] Takazawa, O.; Kogami, K.; Hayashi, K. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 2427.
[1251] See Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* ***1988***, *29*, 1041. For a review, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 324–333. For an *ab initio* study see Murga, J.; Falomir, E.; Carda, M.; Marco, J.A. *Tetrahedron* ***2001***, *57*, 6239.

(which can be synthesized by reaction **15-23** or directly from an aldehyde or ketone).[1252] Metallic enolates can be used for aldol reactions, either preformed or generated *in situ*, with a catalytic amount of a metal compound: Mg,[1253] Ti,[1254] Zn,[1255] Zr,[1256] Pd,[1257] In,[1258] Sn,[1259] La,[1260] and Sm.[1261] Such reactions give products with moderate to excellent diastereoselectivity[1262] and regioselectivity.

The reactions with preformed enol derivatives provide a way to control the stereoselectivity of the aldol reaction.[1263] As with the Michael reaction (**15-20**), the aldol reaction creates two new stereogenic centers, and, in the most general case, there are four stereoisomers of the aldol product (two racemic diastereomers), which can be represented as the *syn* and *anti* diastereomers shown.

Syn (here erythro) (±) pair



Anti (here threo) (±) pair

The reaction may be diastereoselective, however, if one is preferred over the other. The Zimmerman-Traxler model has been used to predict the major diastereomer.[1264]

Among the preformed enol derivatives used for diastereoselective aldol condensations have been enolates of Li,[1265] Mg, Ti,[1266] and Sn,[1267] silyl enol ethers,[1268] enol borinates,[1269]

[1252] See Brown, H.C.; Ganesan, K. *Tetrahedron Lett.* ***1992***, *33*, 3421.

[1253] Wei, H.-X.; Jasoni, R.L.; Shao, H.; Hu, J.; Paré, P.W. *Tetrahedron* ***2004***, *60*, 11829.

[1254] See Alcoberro, S.; Gómez-Palomino, A.; Solà, R.; Romea, P.; Urpí, F.; Font-Bardia, M. *Org. Lett.* ***2014***, *16*, 584.

[1255] Pieczonka, A.M.; Jarzyński, S.; Wujkowska, Z.; Leśniak, S.; Rachwalski, M. *Tetrahedron Lett.* ***2015***, *56*, 6506. See Mulzer, J.; Brüntrup, G.; Finke, J.; Zippel, M. *J. Am. Chem. Soc.* ***1979***, *101*, 7723.

[1256] See Evans, D.A.; McGee, L.R. *J. Am. Chem. Soc.* ***1981***, *103*, 2876.

[1257] Nokami, J.; Mandai, T.; Watanabe, H.; Ohyama, H.; Tsuji, J. *J. Am. Chem. Soc.* ***1989***, *111*, 4126.

[1258] See Loh, T.-P.; Feng, L.-C.; Wei, L.-L. *Tetrahedron* ***2001***, *57*, 4231.

[1259] Yanagisawa, A.; Kimura, K.; Nakatsuka, Y.; Yamamoto, H. *Synlett* ***1998***, 958.

[1260] Kobayashi, S.; Hachiya, I.; Takahori, T. *Synthesis* ***1993***, 371.

[1261] See Yokoyama, Y.; Mochida, K. *Synlett* ***1996***, 445. Also see, Bao, W.; Zhang, Y.; Wang, J. *Synth. Commun.* ***1996***, *26*, 3025.

[1262] For a review, see Mahrwald, R. *Chem. Rev.* ***1999***, *99*, 1095.

[1263] Heathcock, C.H. *Aldrichimica Acta* ***1990***, *23*, 99; *Science* ***1981***, *214*, 395; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 193–220; Heathcock, C.H. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1984***, pp. 111–212; Evans, D.A.; Nelson, J.V.; Taber, T.R. *Top. Stereochem.* ***1982***, *13*, 1; Braun, M.; Sacha, H.; Galle, D.; Baskaran, S. *Pure Appl. Chem.* ***1996***, *68*, 561; Kitamura, M.; Nakano, K.; Miki, T.; Okada, M.; Noyori, R. *J. Am. Chem. Soc.* ***2001***, *123*, 8939.

[1264] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 709–712.

[1265] Ertas, M.; Seebach, D. *Helv. Chim. Acta* ***1985***, *68*, 961.

[1266] Schetter, B.; Ziemer, B.; Schnakenburg, G.; Mahrwald, R. *J. Org. Chem.* ***2008***, *73*, 813. See Zambrana, J.; Romea, P.; Urpí, F.; Luján, C. *J. Org. Chem.* ***2011***, *76*, 8575.

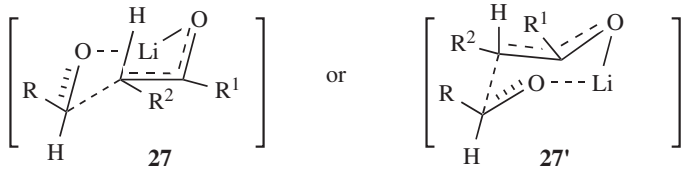
[1267] See Yura, T.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* ***1986***, 187. See also, Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* ***1983***, *24*, 3347.

[1268] See Hagiwara, H.; Kimura, K.; Uda, H. *J. Chem. Soc., Chem. Commun.* ***1986***, 860.

[1269] Walker, M.A.; Heathcock, C.H. *J. Org. Chem.* ***1991***, *56*, 5747. For reviews, see Paterson, I. *Chem. Ind. (London)* ***1988***, 390; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, p. 324.

and enol borates $R'CH{=}CR^2{-}OB(OR)_2$.[1270] The nucleophilicity of silyl enol ethers has been examined.[1271]

There are discussions that relate to the transition state of the aldol condensation.[1272] There is experimental evidence for chair-like transition states in the aldol reactions of methyl ketone lithium enolate anions.[1273] The most popular transition state is the closed or chelated transition state, similar to that proposed by Zimmerman and Traxler[1274] for the *Ivanov condensation*[1275] of phenylacetic acid and benzaldehyde. Subsequent reaction with a carbonyl compound (benzaldehyde) led to an aldol-like product (3-hydroxy-2,3-diphenylpropanoic acid).[1274] When applied to the aldol condensation, with a lithium counterion, cyclic models **27** or **27′** give the stereoisomeric products. These models are used to predict stereochemistry in the aldol condensation, and are referred to as the *Zimmerman-Traxler model*.[1274]



Aldol reactions are enantioselective under the proper conditions[1276] (in which case only one of the four isomers predominates)[1277] by using chiral enol derivatives,[1278] chiral aldehydes or ketones,[1279] or both.[1280] Chiral amine bases,[1281] such as

[1270] Hoffmann, R.W.; Ditrich, K.; Fröch, S. *Liebigs Ann. Chem.* ***1987***, 977.

[1271] Patz, M.; Mayr, H. *Tetrahedron Lett.* ***1993***, *34*, 3393.

[1272] See Perrin, C.L.; Chang, K.-L. *J. Org. Chem.* ***2016***, *81*, 5631.

[1273] Liu, C.M.; Smith III, W.J.; Gustin, D.J.; Roush, W.R. *J. Am. Chem. Soc.* ***2005***, *127*, 5770.

[1274] Heathcock, C.H. in *Asymmetric Synthesis*, Vol. 3, Morrison, J.D. (Ed.), Academic Press, NY, ***1983***, p. 154; Zimmerman, H.E.; Traxler, M.D. *J. Am. Chem. Soc.* ***1957***, *79*, 1920; Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 709–712.

[1275] Ivanoff, D.; Spassoff, A. *Bull. Chim. Soc. Fr.* ***1931***, *49*, 19; Ivanoff, D.; Nicoloff, N.I. *Bull. Chim. Soc. Fr.* ***1932***, *51*, 1325, 1331; *The Merck Index*, 14th ed., Merck & Co., Inc., Whitehouse Station, NJ, ***2006***, p. ONR-47; Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis*, 2nd ed., Wiley-Interscience, NJ, ***2005***, pp. 342–343.

[1276] *Modern Methods in Stereoselective Aldol Reactions*, Mahrwald, R. (Ed.), Wiley-VCH, Weinheim, ***2013***. Allemann, C.; Gordillo, R.; Clemente, F.R.; Cheong, P.H.-Y.; Houk, K.N. *Acc. Chem. Res.* ***2004***, *37*, 558; Saito, S.; Yamamoto, H. *Acc. Chem. Res.* ***2004***, *37*, 570; Zhang, Q.; Cui, X.; Zhang, L.; Luo, S.; Wang, H.; Wu, Y. *Angew. Chem. Int. Ed.* ***2015***, *54*, 5210; Gurka, A.A.; London, G. *Org. Prep. Proceed. Int.* ***2017***, *49*, 415. For a discussion of chelation versus nonchelation control, see Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C.; Huang, T.-Y. *J. Am. Chem. Soc.* ***1993***, *115*, 2613. See Majewski, M.; Lazny, R.; Nowak, P. *Tetrahedron Lett.* ***1995***, *36*, 5465; Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 707–725. For a model for acyclic stereocontrol, see Evans, D.A.; Cee, V.J.; Siska, S.J. *J. Am. Chem. Soc.* ***2006***, *128*, 9433.

[1277] For anti-selective aldol reactions, see Oppolzer, W.; Lienard, P. *Tetrahedron Lett.* ***1993***, *34*, 4321. For a "non-Evans" *syn*-aldol, see Yan, T.-H.; Lee, H.-C.; Tan, C.-W. *Tetrahedron Lett.* ***1993***, *34*, 3559.

[1278] Klein, J. in Patai, S. *The Chemistry of Double-Bonded Functional Groups, Supplement A*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 567–677; Braun, M. *Angew. Chem. Int. Ed.* ***1987***, *26*, 24; Faunce, J.A.; Grisso, B.A.; Mackenzie, P.B. *J. Am. Chem. Soc.* ***1991***, *113*, 3418.

[1279] See Reetz, M.T.; Kesseler, K.; Jung, A. *Tetrahedron* ***1984***, *40*, 4327.

[1280] See Short, R.P.; Masamune, S. *Tetrahedron Lett.* ***1987***, *28*, 2841.

[1281] Notz, W.; Tanaka, F.; Barbas III, C.F. *Acc. Chem. Res.* ***2004***, *37*, 580; Simon, A.; Lam, Y.-h.; Houk, K.N. *J. Am. Chem. Soc.* ***2016***, *138*, 503; Agarwal, J.; Peddinti, R.K. *J. Org. Chem.* ***2011***, *76*, 3502; Popik, O.; Pasternak-Suder,

proline,[1282] proline derivatives,[1283] *Cinchona* amines,[1284] or chiral additives can be used in conjunction with an organobase.[1285] When both new stereogenic centers are formed enantioselectively, the process is called *double asymmetric synthesis*.[1286] Biocatalytic aldol condensation reactions are known.[1287] The anion of an ionic liquid has been used to catalyze an asymmetric aldol reaction,[1288] and ionic liquids have been developed for use in asymmetric aldol condensation reactions.[1289] New chiral organocatalysts are developed on a regular basis,[1290] including those that can be used in aqueous media,[1291] in deep eutectic

M.; Leśniak, K.; Jawiczuk, M.; Górecki, M.; Frelek, J.; Mlynarski, J. *J. Org. Chem.* ***2014***, *79*, 5728; Li, L.; Gou, S.; Liu, F. *Tetrahedron Lett.* ***2013***, *54*, 6358; Gut, B.; Mlynarski, J. *Eur. J. Org. Chem.* ***2015***, 5075. For a discussion of the role of additives, see Sutar, R.L.; Joshi, N.N. *Synth. Commun.* ***2014***, *44*, 352. For a microwave-promoted reaction, see Liao, F.X.; Wang, Y.; Zhu, Q. *Synth. Commun.* ***2014***, *44*, 161.

[1282] See Zhao, Q.; Lam, Y.-h.; Kheirabadi, M.; Xu, C.; Houk, K.N.; Schafmeister, C.E. *J. Org. Chem.* ***2012***, *77*, 4784; Martínez-Castañeda, Á.; Rodríguez-Solla, H.; Concellón, C.; del Amo, V. *J. Org. Chem.* ***2012***, *77*, 10375; Obregón-Zúñiga, A.; Milán, M.; Juaristi, E. *Org. Lett.* ***2017***, *19*, 1108; Cho, E.; Kim, T.H. *Tetrahedron Lett.* ***2014***, *55*, 6470; Qin, L.; Zhang, L.; Jin, Q.; Zhang, J.; Han, B.; Liu, M. *Angew. Chem. Int. Ed.* ***2013***, *52*, 7761; Martínez, A.; van Gemmeren, M.; List, B. *Synlett* ***2014***, *25*, 961. For a ball-mill procedure, see Hernández, J.G.; Juaristi, E. *Tetrahedron* ***2011***, *67*, 6953.

[1283] Yu, N.; Han, S.; Yu, H. *Tetrahedron* ***2015***, *71*, 4665. For a reaction done using flow conditions (Sec. 7.D), see Massi, A.; Cavazzini, A.; Del Zoppo, L.; Pandoli, O.; Costa, V.; Pasti, L.; Giovannini, P.P. *Tetrahedron Lett.* ***2011***, *52*, 619; Han, X.; Wang, Y.; Gai, X.; Zeng, X. *Synlett* ***2015***, *26*, 2858. See Sutar, R.L.; Joshi, N.N. *Tetrahedron: Asymmetry* ***2013***, *24*, 43; Kumar, T.P.; Shekhar, R.C.; Sunder, K.S.; Vadaparthi, R. *Tetrahedron: Asymmetry* ***2015***, *26*, 543; Xu, N.; Xue, D.; Liu, L.; Liu, Z.-T.; Lu, J.; Liu, Z.-W. *Synth. Commun.* ***2012***, *42*, 1559.

[1284] For a sudy of the origins of stereoselectivity in intramolecular aldol reactions, see Lam, Y.-h.; Houk, K.N. *J. Am. Chem. Soc.* ***2015***, *137*, 2116.

[1285] See Mahrwald, R. *Org. Lett.* ***2000***, *2*, 4011; Zhou, Y.; Shan, Z. *J. Org. Chem.* ***2006***, *71*, 9510.

[1286] For a review, see Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. *Angew. Chem. Int. Ed.* ***1985***, *24*, 1.

[1287] Xie, Z.-B.; Wang, N.; Jiang, G.-F.; Yu, X.-Q. *Tetrahedron Lett.* ***2013***, *54*, 945; Xie, B.-H.; Li, W.; Liu, Y.; Li, H.H.; Guan, Z.; He, Y.-H. *Tetrahedron* ***2012***, *68*, 3160; Benedetti, F.; Berti, F.; Biodoggtia, S. *Org. Biomol. Chem.* ***2011***, *9*, 4417; Guan, Z.; Fu, J.-P.; He, Y.-H. *Tetrahedron Lett.* ***2012***, *53*, 4959.

[1288] Gauchot, V.; Schmitzer, A.R. *J. Org. Chem.* ***2012***, *77*, 4917.

[1289] Larionova, N.A.; Kucherenko, A.S.; Siyutkin, D.E.; Zlotin, S.G. *Tetrahedron* ***2011***, *67*, 1948.

[1290] For reviews, see Bisai, V.; Bisai, A.; Singh, V.K. *Tetrahedron* ***2012***, *68*, 4541; Bhanushali, M.; Zhao, C.-G. *Synthesis* ***2011***, *43*, 1815; Heravi, M.M.; Asadi, S. *Tetrahedron: Asymmetry* ***2012***, *23*, 1431. Konda, S.; Guo, Q.-S.; Abe, M.; Huang, H.; Arman, H.; Zhao, J.-C.-G. *J. Org. Chem.* ***2015***, *80*, 806; Pearson, A.J.; Panda, S. *Org. Lett.* ***2011***, *13*, 5548; Knight, J.D.; Coltart, D.M. *Tetrahedron Lett.* ***2013***, *54*, 5470. See Mase, N.; Ando, T.; Shibagaki, F.; Sugita, A.; Narumi, T.; Toda, M.; Watanabe, N.; Tanaka, F. *Tetrahedron Lett.* ***2014***, *55*, 1946; Nakashima, K.; Hirashima, S.-i.; Akutsu, H.; Koseki, Y.; Tada, N.; Itoh, A.; Miura, T. *Tetrahedron Lett.* ***2015***, *56*, 558; Yolacan, C.; Mavis, M.E.; Aydogan, F. *Tetrahedron* ***2014***, *70*, 3707; Maycock, C.D.; Ventura, M.R. *Tetrahedron: Asymmetry* ***2012***, *23*, 1262; Cabrera, H.R.; Huelgas, G.; Pérez, J.M.H.; Walsh, P.J.; Somanathan, R.; de Parrodi, C.A. *Tetrahedron: Asymmetry* ***2015***, *26*, 163. Also see Nakashima, E.; Yamamoto, H. *Chem. Asian J.* ***2017***, *12*, 41; Obregón-Zúñiga, A.; Juaristi, E. *Tetrahedron* ***2017***, *73*, 5373; Akutsu, H.; Nakashima, K.; Yanai, H.; Kotani, A.; Hirashima, S.-i.; Yamamoto, T.; Takahashi, R.; Yoshida, A.; Koseki, Y.; Hakamata, H.; Matsumoto, T.; Miura, T. *Synlett.* ***2017***, *28*, 1363.

[1291] Qiao, Y.; Chen, Q.; Lin, S.; Ni, B.; Headley, A.D. *J. Org. Chem.* ***2013***, *78*, 2693; Shen, H.-M.; Ji, H.-B. *Tetrahedron Lett.* ***2012***, *53*, 3541; Liu, K.; Zhang, G. *Tetrahedron Lett.* ***2015***, *56*, 243; Doyagüez, E.G.; Fernández-Mayoralas, A. *Tetrahedron* ***2012***, *68*, 7345; Pedrosa, R.; Andrés, J.M.; Gamarra, A.; Manzano, R.; Pérez-López, C. *Tetrahedron* ***2013***, *69*, 10811; Uyanik, A.; Bayrakci, M.; Eymur, S.; Yilmaz, M. *Tetrahedron* ***2014***, *70*, 9307; Miura, T.; Ina, M.; Imai, K.; Nakashima, K.; Yasaku, Y.; Koyata, N.; Murakami, Y.; Imai, N.; Tada, N.; Itoh, A. *Tetrahedron: Asymmetry* ***2011***, *22*, 1028; Tian, H.; Gao, J.-L.; Xu, H.; Zheng, L.-Y.; Huang,W.-B.; Liu, Q.-W.; Zhang, S.-Q. *Tetrahedron: Asymmetry* ***2011***, *22*, 1074; Wu, C.; Long, X.; Li, S.; Fu, X. *Tetrahedron: Asymmetry* ***2012***, *23*, 315; Bhowmick, S.; Kunte, S.S.; Bhowmick, K.C. *Tetrahedron: Asymmetry* ***2014***, *25*, 1292; Gurka, A.A.; Szőri, K.; Bartók, M.; London, G. *Tetrahedron: Asymmetry* ***2016***, *27*, 936; Wu, C.; Fu, X.; Li, S. *Eur. J. Org. Chem.* ***2011***, 1291.

solvents,[1292] and under solvent-free conditions.[1293] Chiral auxiliaries[1294] have been developed that can be used in conjunction with the aldol condensation, and chiral ligands[1295] that can be used in catalytic reactions. An α-hydroxy ketone was condensed with an aldehyde using a chiral Zn catalyst to give the aldol (an α,β-dihydroxy ketone) with good *syn* selectivity and good enantioselectivity.[1296] Chiral vinylogous (Sec. 6.B) aldol reactions have been reported.[1297] The magnesium enolate anion formed from a chiral amide adds to aldehydes to give the alcohol enantioselectively.[1298] Diamine protonic acids have been used for catalytic asymmetric aldol reactions.[1299]

It is possible to make the α carbon of the aldehyde add to the carbonyl carbon of the ketone by using an imine instead of an aldehyde and by using $LiN(i\text{-}Pr)_2$ as the base to form an α-lithio imine.[1300] This is known as a *directed aldol reaction*. Similar reactions have been performed with α-lithiated dimethylhydrazones of aldehydes or ketones[1301] and with α-lithiated aldoximes.[1302]

The aldol reaction can also be performed with acid catalysts, as mentioned above, in which case dehydration usually follows. Here there is initial protonation of the carbonyl group to form an oxocarbenium ion, and this is attacked by the α carbon of the *enol* form of the other molecule.[1303] Loss of a proton generates the aldol product. Loss of water under the acidic conditions leads to the conjugated product. With respect to the enol, this mechanism is similar to that of halogenation (**12-4**). A side reaction that is sometimes troublesome is further condensation, since the product of an aldol reaction is still an aldehyde or ketone.

The intramolecular aldol condensation is well known, and aldol reactions are often used to close five- and six-membered rings. Because of the favorable entropy (Sec. 6.D), such ring closures generally take place with ease[1304] when using hydroxide or alkoxide bases in protic solvents. In aprotic solvents with amide bases, formation of the enolate anion occurs by deprotonation of the more acidic site, followed by cyclization to the second carbonyl. The acid-catalyzed intramolecular aldol condensation is known, and the mechanism has been studied.[1305] An asymmetric intramolecular aldol reaction was catalyzed by a

[1292] González-Martínez, D.; Gotor, V.; Gotor-Fernández, V. *Eur. J. Org. Chem.* ***2016***, 1513.

[1293] Zhang, F.; Li, C.; Qi, C. *Tetrahedron: Asymmetry* ***2013***, *24*, 380; Kumar, T.P.; Vavle, N.C.; Patro, V.; Haribabu, K. *Tetrahedron: Asymmetry* ***2014***, *25*, 457.

[1294] Hein, J.E.; Hultin, P.G. *Synlett* ***2003***, 635.

[1295] Trost, B.M.; Ito, H. *J. Am. Chem. Soc.* ***2000***, *122*, 12003; Zhao, H.-W.; Li, H.-L.; Yue, Y.-Y.; Qin, X.; Sheng, Z.-H.; Cui, J.; Su, S.; Song, X.-Q.; Yan, H.; Zhong, R.-G. *Synlett* ***2012***, *23*, 1990.

[1296] Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshma, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* ***2001***, *123*, 2466; Trost, B.M.; Ito, H.; Silcoff, E.R. *J. Am. Chem. Soc.* ***2001***, *123*, 3367. See Trost, B.M.; Shin, S.; Sclafani, J.A. *J. Am. Chem. Soc.* ***2005***, *127*, 8602.

[1297] Takikawa, H.; Ishihara, K.; Saito, S.; Yamamoto, H. *Synlett* ***2004***, 732; Denmark, S.E.; Heemstra Jr., J.R. *Synlett* ***2004***, 2411.

[1298] Evans, D.A.; Tedrow, J.S.; Shaw, J.T.; Downey, C.W. *J. Am. Chem. Soc.* ***2002***, *124*, 392.

[1299] Trost, B.M.; Fettes, A.; Shireman, B.T. *J. Am. Chem. Soc.* ***2004***, *126*, 2660.

[1300] For reviews, see Mukaiyama, T. *Org. React.* ***1982***, *28*, 203; Wittig, G. *Top. Curr. Chem.* ***1976***, *67*, 1; Wittig, G.; Reiff, H. *Angew. Chem. Int. Ed.* ***1968***, *7*, 7; Reiff, H. *Newer Methods Prep. Org. Chem.* ***1971***, *6*, 48.

[1301] Corey, E.J.; Enders, D. *Tetrahedron Lett.* ***1976***, 11. See also, Depezay, J.; Le Merrer, Y. *Bull. Soc. Chim. Fr.* ***1981***, II-306.

[1302] Hassner, A.; Näumann, F. *Chem. Ber.* ***1988***, *121*, 1823.

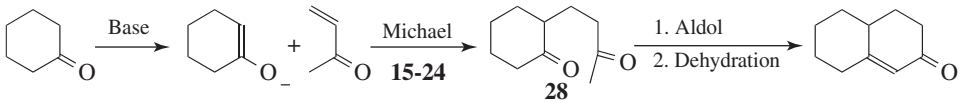
[1303] See Baigrie, L.M.; Cox, R.A.; Slebocka-Tilk, H.; Tencer, M.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1985***, *107*, 3640.

[1304] See Guthrie, J.P.; Guo, J. *J. Am. Chem. Soc.* ***1996***, *118*, 11472; Eberle, M.K. *J. Org. Chem.* ***1996***, *61*, 3844.

[1305] Bouillon, J.-P.; Portella, C.; Bouquant, J.; Humbel, S. *J. Org. Chem.* ***2000***, *65*, 5823.

chiral amine.[1306] Chiral ligands, in conjugation with Cu compounds,[1307] led to asymmetric intramolecular aldol condensation reactions. The regioselectivity of an intramolecular aldol condensation of unsaturated 1,5-diketones is strongly influenced by the presence or absence of a trialkylphosphine.[1308] The Tf_2NH-mediated intermolecular/intramolecular sequential aldol reaction of disilyl enol ethers gave five-, six-, and seven-membered ring products.[1309]

An important extension of the intramolecular aldol condensation is the *Robinson annulation* reaction,[1310] which has often been used in the synthesis of steroids and terpenes. In original versions of this reaction a cyclic ketone is converted to another cyclic ketone under equilibrium conditions using hydroxide or alkoxide bases in a protic solvent (thermodynamic or equilibrium conditions), forming one additional six-membered ring containing a double bond. The reaction can be done in a stepwise manner using amide bases in aprotic solvents. In the reaction with hydroxide or alkoxide bases in alcohol or water solvents, the substrate is treated with methyl vinyl ketone (or a simple derivative of methyl vinyl ketone) and a base.[1311] The enolate ion of the substrate adds to the methyl vinyl ketone in a *Michael reaction* (**15-20**) to give a diketone (**28**) that undergoes or is made to undergo an internal aldol reaction. Subsequent dehydration gave the bicyclic product.[1312]



The Robinson annulation can be combined with alkylation.[1313] An organocatalyst-mediated aldol-Robinson cascade reaction has ben reported.[1314] Enantioselective Robinson annulation techniques have been developed, including a proline-catalyzed reaction.[1315] The Robinson annulation has been done in ionic liquids[1316] and a solvent-free version of the reaction is known.[1317]

Because methyl vinyl ketone has a tendency to polymerize, surrogates are often used instead. Such surrogates are compounds that will give methyl vinyl ketone when treated with a base. One common example, $MeCOCH_2CH_2NEt_2Me^+ I^-$ (see **17-7**), is easily prepared by quaternization of $MeCOCH_2CH_2NEt_2$, which itself is prepared by a *Mannich reaction* (**16-17**) involving acetone, formaldehyde, and diethylamine. α-Silylated vinyl

[1306] Zhou, J.; Wakchaure, V.; Kraft, P.; List, B. *Angew. Chem. Int. Ed.* ***2008***, *47*, 7656. See Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem. Int. Ed.* ***2003***, *42*, 2785.
[1307] Lipshutz, B.H.; Amorelli, B.; Unger, J.B. *J. Am. Chem. Soc.* ***2008***, *130*, 14378.
[1308] Thalji, R.K.; Roush, W.R. *J. Am. Chem. Soc.* ***2005***, *127*, 16778.
[1309] Izumiseki, A.; Yamamoto, H. *J. Am. Chem. Soc.* ***2014***, *136*, 1308.
[1310] Gawley, R.E. *Synthesis* ***1976***, 777; Jung, M.E. *Tetrahedron* ***1976***, *32*, 1. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1356–1358.
[1311] See Heathcock, C.H.; Ellis, J.E.; McMurry, J.E.; Coppolino, A. *Tetrahedron Lett.* ***1971***, 4995.
[1312] For improved procedures, see Sato, T.; Wakahara, Y.; Otera, J.; Nozaki, H. *Tetrahedron Lett.* ***1990***, *31*, 1581, and references cited therein.
[1313] Tai, C.-L.; Ly, T.W.; Wu, J.-D.; Shia, K.-S.; Liu, H.-J. *Synlett* ***2001***, 214.
[1314] Wang, L.; Gong, Q.-P.; Liu, X.-J.; Li, Y.-H.; Huang, P.; Wang, B.-Q.; Zhao, K.-Q. *Chem. Lett.* ***2011***, *40*, 138.
[1315] Rajagopal, D.; Narayanan, R.; Swaminathan, S. *Tetrahedron Lett.* ***2001***, *42*, 4887.
[1316] Morrison, D.W.; Forbes, D.C.; Davis Jr., J.H. *Tetrahedron Lett.* ***2001***, *42*, 6053.
[1317] Miyamoto, H.; Kanetaka, S.; Tanaka, K.; Yoshizawa, K.; Toyota, S.; Toda, F. *Chem. Lett.* ***2000***, 888.

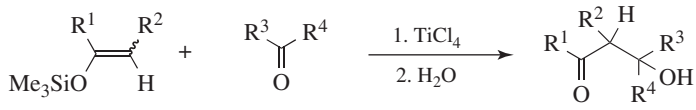
ketones, $RCOC(SiMe_3)=CH_2$, have also been used successfully in annulation reactions[1318] because the $SiMe_3$ group is easily removed.

When the ring closure of a 1,5-diketone is catalyzed by the amino acid (*S*)-proline, the product is optically active with high enantiomeric excess.[1319]

Examples of nitroso aldol reactions have been reported.[1320]

OS **I**, 77, 78, 81, 199, 283, 341; **II**, 167, 214; **III**, 317, 353, 367, 747, 806, 829; **V**, 486, 869; **VI**, 496, 666, 692, 781, 901; **VII**, 185, 190, 332, 363, 368, 473; **VIII**, 87, 208, 241, 323, 339, 620; **IX**, 432, 610; **X**, 339.

16-35 Mukaiyama Aldol and Related Reactions[1321]



An important variation of the aldol condensation involves treatment of an aldehyde or ketone with a ketene silyl acetal $R_2C=C(OSiMe_3)OR'$[1322] or a silyl enol ether, in the presence of $TiCl_4$[1323], to give the β-hydroxyl carbonyl. This variation is known as the *Mukaiyama aldol reaction* or, simply, the *Mukaiyama reaction*.[1324] Note that esters have been used rather than aldehydes in this reaction.[1325] The ketene silyl acetal can be considered a preformed enolate that gives aldol product with $TiCl_4$ in aqueous solution, or with no catalyst at all.[1326] Reaction at the carbonyl of saturated carbonyl compounds is significantly faster than 1,2-addition to unsaturated carbonyl compounds.[1327] The mechanism of this reaction has been explored.[1328] An *ab initio* study of the uncatalyzed Mukaiyama aldol reaction showed that the nucleophilicity of the silyl enol ether and the electrophilicity of the aldehyde are important in promoting the reactivity.[1329] Other

[1318] Stork, G.; Singh, J. *J. Am. Chem. Soc.* ***1974***, *96*, 6181; Boeckman Jr., R.K. *J. Am. Chem. Soc.* ***1974***, *96*, 6179.

[1319] Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* ***1971***, *10*, 496; Hajos, Z.G.; Parrish, D.R. *J. Org. Chem.* ***1974***, *39*, 1615. See Agami, C. *Bull. Soc. Chim. Fr.* ***1988***, 499.

[1320] Merino, P.; Tejero, T.; Delso, I.; Matute, R. *Synthesis* ***2016***, *48*, 653.

[1321] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 697–700.

[1322] For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1745–1752. Also see Revis, A.; Hilty, T.K. *Tetrahedron Lett.* ***1987***, *28*, 4809, and references cited therein.

[1323] Mukaiyama, T. *Pure Appl. Chem.* ***1983***, *55*, 1749; Kohler, B.A.B. *Synth. Commun.* ***1985***, *15*, 39; Mukaiyama, T.; Narasaka, K. *Org. Synth.* ***65***, 6. See Gennari, C.; Colombo, L.; Bertolini, G.; Schimperna, G. *J. Org. Chem.* ***1987***, *52*, 2754. See also, Reetz, M.T. *Organotitanium Reagents in Organic Synthesis*, Springer, NY, ***1986***.

[1324] Matsuo, J.-i.; Murakami, M. *Angew. Chem. Int. Ed.* ***2013***, *52*, 9109.

[1325] Inamoto, Y.; Nishimoto, Y.; Yasuda, M.; Baba, A. *Org. Lett.* ***2012***, *14*, 1168.

[1326] Miura, K.; Sato, H.; Tamaki, K.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* ***1998***, *39*, 2585. For a high pressure, uncatalyzed reaction, see Bellassoued, M.; Reboul, E.; Dumas, F. *Tetrahedron Lett.* ***1997***, *38*, 5631.

[1327] Shirakawa, S.; Maruoka, K. *Tetrahedron Lett.* ***2002***, *43*, 1469.

[1328] Hollis, T.K.; Bosnich, B. *J. Am. Chem. Soc.* ***1995***, *117*, 4570. For the transition state geometry, see Denmark, S.E.; Lee, W. *J. Org. Chem.* ***1994***, *59*, 707.

[1329] Wong, C.T.; Wong, M.W. *J. Org. Chem.* ***2005***, *70*, 124.

catalysts have been used for this reaction, including $InCl_3$,[1330] SmI_2,[1331] Sc,[1332] HgI_2,[1333] $Yb(OTf)_3$,[1334] $Cu(OTf)_2$,[1335] $LiClO_4$,[1336] $VOCl_3$,[1337] $ZnCl_2$,[1338] Fe,[1339] Ti,[1340] aluminosilicates,[1341] Ru,[1342] and $Bi(OTf)_3$.[1343] Brønsted acids have also been used for environmentally friendly Mukaiyama aldol reactions.[1344] The Lewis base catalysis of the Mukaiyama aldol reaction has been reviewed.[1345] Lithium perchlorate in acetonitrile (5 M) can be used for the reaction of an aldehyde and a silyl enol ether.[1346] Silyl enol ethers react with aqueous formaldehyde in the presence of TBAF to give the aldol product.[1347] A catalytic amount of Me_3SiCl facilitates the Ti-mediated reaction.[1348] Homologous Mukaiyama reactions were reported by trapping a Nazarov intermediate with silyloxyalkenes.[1349]

Silyl enol ethers[1350] derived from esters (ketene silyl acetals) react with aldehydes in the presence of various catalysts to give β-hydroxy esters. Water accelerates the reaction of an aldehyde and a ketene silyl acetal with no other additives.[1351] The reaction was done without a catalyst in an ionic liquid.[1352] A vinylogous reaction (Sec. 6.B) is known that gives δ-hydroxy-α,β-unsaturated esters.[1353] Under different conditions, ketene silyl acetals of conjugated esters react with aldehydes to give conjugated lactones.[1354] Propargylic acetals react with silyl enol ethers and a Sc catalyst to give β-alkoxy ketones.[1355] α-Silyl silyl enol ethers, $RCH{=}CH(OTMS)SiMe_3$, react with acetals in the presence of $SnCl_4$ to give β-alkoxy silyl ketones.[1356] Ketene silyl acetals also undergo conjugate addition in reactions with conjugated ketones.[1357]

[1330] Muñoz-Muñiz, O.; Quintanar-Audelo, M.; Juaristi, E. *J. Org. Chem.* ***2003***, *68*, 1622.
[1331] van de Weghe, P.; Collin, J. *Tetrahedron Lett.* ***1993***, *34*, 3881.
[1332] Manabe, K.; Kobayashi, S. *Tetrahedron Lett.* ***1999***, *40*, 3773. See Komoto, I.; Kobayashi, S. *J. Org. Chem.* ***2004***, *69*, 680.
[1333] Dicker, I.B. *J. Org. Chem.* ***1993***, *58*, 2324.
[1334] This catalyst is tolerated in water. See Kobayashi, S.; Hachiya, I. *J. Org. Chem.* ***1994***, *59*, 3590.
[1335] Kobayashi, S.; Nagayama, S.; Busujima, T. *Chem. Lett.* ***1997***, 959.
[1336] Reetz, M.T.; Fox, D.N.A. *Tetrahedron Lett.* ***1993***, *34*, 1119.
[1337] Kurihara, M.; Hayshi, T.; Miyata, N. *Chem. Lett.* ***2001***, 1324.
[1338] Zhao, C.; Mitchell, T.A.; Vallakati, R.; Pérez, L.M.; Romo, D. *J. Am. Chem. Soc.* ***2012***, *134*, 3084.
[1339] See Rodríguez-Gimeno, A.; Cuenca, A.B.; Gil-Tomás, J.; Medio-Simón, M.; Olmos, A.; Asensio, G. *J. Org. Chem.* ***2014***, *79*, 8263.
[1340] Wang, W.; Chen, Q.-Y.; Guo, Y. *Synlett* ***2011***, *22*, 2705.
[1341] Ito, S.; Tanuma, K.; Matsuda, K.; Hayashi, A.; Komai, H.; Kubota, Y.; Asami, M. *Tetrahedron* ***2014***, *70*, 8498.
[1342] Curvey, N.; Widaman, A.K.; Rath, N.P.; Bauer, E.B. *Tetrahedron Lett.* ***2014***, *55*, 3033.
[1343] See Ollevier, T.; Li, Z. *Eur. J. Org. Chem.* ***2007***, 5665.
[1344] Barbero, M.; Bazzi, S.; Cadamuro, S.; Dughera, S.;Magistris, C.; Smarra, A.; Venturello, P. *Org. Biomol. Chem.* ***2011***, *9*, 2192.
[1345] Beutner, G.L.; Denmark, S.E. *Angew. Chem. Int. Ed.* ***2013***, *52*, 9086. See Sutar, R.L.; Joshi, N.N. *Tetrahedron: Asymmetry* ***2013***, *24*, 1345.
[1346] Sudha, R.; Sankararaman, S. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 383.
[1347] Ozasa, N.; Wadamoto, M.; Ishihara, K.; Yamamoto, H. *Synlett* ***2003***, 2219.
[1348] Yoshida, Y.; Matsumoto, N.; Hamasaki, R.; Tanabe, Y. *Tetrahedron Lett.* ***1999***, *40*, 4227.
[1349] Wu, Y.-K.; McDonald, R.; West, F.G. *Org. Lett.* ***2011***, *13*, 3584.
[1350] See Carswell, E.L.; Hayes, D.; Henderson, K.W.; Kerr, W.J.; Russell, C.J. *Synlett* ***2003***, 1017.
[1351] Loh, T.-P.; Feng, L.-C.; Wei, L.-L. *Tetrahedron* ***2000***, *56*, 7309.
[1352] Chen, S.-L.; Ji, S.-J.; Loh, T.-P. *Tetrahedron Lett.* ***2004***, *45*, 375.
[1353] Bluet, G.; Campagne, J.-M. *J. Org. Chem.* ***2001***, *66*, 4293; Christmann, M.; Kalesse, M. *Tetrahedron Lett.* ***2001***, *42*, 1269.
[1354] Bluet, G.; Bazán-Tejeda, B.; Campagne, J.-M. *Org. Lett.* ***2001***, *3*, 3807.
[1355] Yoshimatsu, M.; Kuribayashi, M.; Koike, T. *Synlett* ***2001***, 1799.
[1356] Honda, M.; Oguchi, W.; Segi, M.; Nakajima, T. *Tetrahedron* ***2002***, *58*, 6815.
[1357] Harada, T.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubu, M.; Oku, A. *Org. Lett.* ***2001***, *3*, 2101.

Asymmetric Mukaiyama aldol reactions and reactions of ketene silyl acetals have been reported,[1358] usually using chiral additives[1359] although chiral auxiliaries have also been used.[1360] Chiral catalysts, usually transition metal complexes using chiral ligands, are quite effective,[1361] and lanthanide catalysts[1362] have been used. Chiral Brønsted acid catalysts have been used,[1363] and chiral organocatalysts[1364] are important. Vinylogous (Sec. 6.B) silyl ketene acetals with Ti,[1365] Cu,[1366] In,[1367] Fe,[1368] or Zn[1369] catalysts or an organocatalyst[1370] give the product with good enantioselectivity.[1371] Silyl enol ethers react with aldehydes in the presence of chiral boranes[1372] or other additives[1373] to give aldols with good asymmetric induction. Chiral boron enolates have been used.[1374] The reaction is catalyzed by triphenylphosphine[1375] and also by $SiCl_4$ with a chiral bis(phosphoramide) catalyst.[1376]

Imines react with ketene silyl acetals in the presence of SmI_3 to give β-amino esters.[1377] Imines react with silyl enol ethers in the presence of $BF_3{\bullet}OEt_2$ to give β-amino ketones.[1378]

[1358] Bach, T. *Angew. Chem. Int. Ed.* ***1994***, *33*, 417. For a discussion of stereocontrol, see Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P.G.; Consolandi, E. *J. Org. Chem.* ***1992***, *57*, 456.

[1359] See Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* ***1994***, *116*, 4077; Kiyooka, S.; Kido, Y.; Kaneko, Y. *Tetrahedron Lett.* ***1994***, *35*, 5243.

[1360] See Vasconcellos, M.L.; Desmaële, D.; Costa, P.R.R.; d'Angelo, J. *Tetrahedron Lett.* ***1992***, *33*, 4921.

[1361] See Roiban, G.-D.; Ilie, A.; Reetz, M.T. *Chem. Lett.* ***2014***, *43*, 2. **Ag**: Wadamoto, M.; Ozasa, N.; Yanigisawa, A.; Yamamoto, H. *J. Org. Chem.* ***2003***, *68*, 5593. **Ce**: Kobayashi, S.; Hamada, T.; Nagayama, S.; Manabe, K. *Org. Lett.* ***2001***, *3*, 165. **Cu**: Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron* ***1999***, *55*, 8739. **Fe**: Ollevier, T.; Plancq, B. *Chem. Commun.* ***2012***, *48*, 2289. **Ga**: Plancq, B.; Justafort, L.C.; Lafantaisie, M.; Ollevier, T. *Eur. J. Org. Chem.* ***2013***, 6525. **Ni**: Zhao, J.; Zheng, K.; Yang, Y.; Shi, J.; Lin, L.; Liu, X.; Feng, X.: *Synlett* ***2011***, *22*, 903. **Pb**: Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc* ***2000***, *122*, 11531. **Sc**: Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* ***2004***, *126*, 12236. **Ti**: Imashiro, R.; Kuroda, T. *J. Org. Chem.* ***2003***, *68*, 974. **Zr**: Kobayashi, S.; Ishitani, H.; Yamashita, Y.; Ueno, M.; Shimizu, H. *Tetrahedron* ***2001***, *57*, 861.

[1362] Mei, Y.; Averill, D.J.; Allen, M.J. *J. Org. Chem.* ***2012***, *77*, 5624.

[1363] Sai, M.; Yamamoto, H. *J. Am. Chem. Soc.* ***2015***, *137*, 7091.

[1364] Denmark, S.E.; Beutner, G.L.; Wynn, T.; Eastgate, M.D. *J. Am. Chem. Soc.* ***2005***, *127*, 3774; Denmark, S.E.; Bui, T. *J. Org. Chem.* ***2005***, *70*, 10190; Adachi, S.; Harada, T. *Org. Lett.* ***2008***, *10*, 4999; Senapati, B.K.; Gao, L.; Lee, S.I.; Hwang, G.-S.; Ryu, D.H. *Org. Lett.* ***2010***, *12*, 5088.

[1365] Shirokawa, S.-i.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* ***2004***, *126*, 13604.

[1366] See Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2006***, *128*, 7164.

[1367] Fu, F.; Teo, Y.-C.; Loh, T.-P. *Tetrahedron Lett.* ***2006***, *47*, 4267.

[1368] Jankowska, J.; Paradowska, J.; Mlynarski, J. *Tetrahedron Lett.* ***2006***, *47*, 5281.

[1369] Jankowska, J.; Mlynarski, J. *J. Org. Chem.* ***2006***, *71*, 1317.

[1370] Denmark, S.E.; Heemstra Jr., J.R. *J. Am. Chem. Soc.* ***2006***, *128*, 1038; Jang, H.-Y.; Hong, J.-B.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2007***, *129*, 7004; Gupta, V.; Sudhir, V.S.; Mandal, T.; Schneider, C. *Angew. Chem. Int. Ed.* ***2012***, *51*, 12609.

[1371] See Gieseler, M.T.; Kalesse, M. *Org. Lett.* ***2011***, *13*, 2430.

[1372] Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* ***1993***, *66*, 3483.

[1373] Corey, E.J.; Cywin, C.L.; Roper, T.D. *Tetrahedron Lett.* ***1992***, *33*, 6907.

[1374] See Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* ***2003***, *68*, 1901.

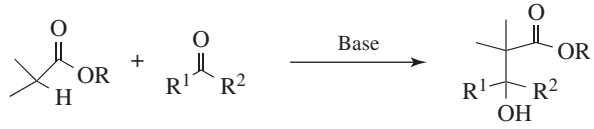
[1375] Matsukawa, S.; Okano, N.; Imamoto, T. *Tetrahedron Lett.* ***2000***, *41*, 103.

[1376] Denmark, S.E.; Heemstra Jr., J.R. *Org. Lett.* ***2003***, *5*, 2303; Denmark, S.E.; Wynn, T.; Beutner, G.L. *J. Am. Chem. Soc.* ***2002***, *124*, 13405.

[1377] Hayakawa, R.; Shimizu, M. *Chem. Lett.* ***1999***, 591.

[1378] Akiyama, T.; Takaya, J.; Kagoshima, H. *Chem. Lett.* ***1999***, 947.

16-36 Condensation Reactions between Carboxylic Acid Derivatives and Aldehydes or Ketones



In the presence of a strong base, removal of a proton from the α carbon of a carboxylic ester or other acid derivative generates an enolate anion that can condense with the carbonyl carbon of an aldehyde or ketone to give a β-hydroxy ester,[1379] amide, and so on. Dehydration of such products will give the α,β-unsaturated derivative. This enolate reaction is called the *Claisen condensation*.[1380] This reaction has been called the *Claisen reaction*, which is unfortunate since that name is more firmly connected to **16-81**. Early reactions used hydroxide or an alkoxide base in water or alcohol solvents, where self-condensation was the major process. Under such conditions, the aldehyde or ketone was usually chosen for its lack of an α proton. Much better control of the reaction was achieved when dialkylamide bases[1381] in aprotic solvents, such as ether or THF, were used to give the enolate anion.[1382] Additives play an important role in the LDA-mediated enolization of esters.[1383]

Transition metal-mediated condensation of esters with aldehydes is known. The enolate anion reaction of acetate derivatives using metal enolates has been reviewed.[1384] The reaction of a thioester and an aryl aldehyde with $TiCl_4/NBu_3$, for example, gave a β-hydroxy thioester with good *syn* selectivity.[1385] The reaction of an α,β-unsaturated ester and benzaldehyde with a chiral Rh catalyst gave a β-hydroxy ester with good diastereoselectivity and good enantioselectivity.[1386] Besides ordinary esters (containing an α hydrogen), the reaction can also be carried out with lactones and, as in **16-34**, with the γ position of α,β-unsaturated esters (vinylogy; Sec. 6.B). The enolate anion of an amide can be condensed with an aldehyde.[1387] Thioesters undergo aldol-type condensations.[1388]

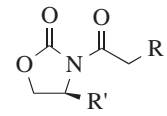
For most esters, a much stronger base is needed than for aldol reactions; $(i\text{-Pr})_2NLi$ (LDA, Sec. 8.F, category 7), Ph_3CNa, and $LiNH_2$ are among those employed. However, esters of malonic acid and succinic acid react more easily and such strong bases are not needed. For example, diethyl succinate and its derivatives condense with aldehydes and ketones in the presence of bases such as NaOEt, NaH, or $KOCMe_3$. This reaction is called the *Stobbe condensation*.[1389] One of the ester groups (sometimes both) is hydrolyzed in the

[1379] See Solladié, G. *Chimia* ***1984***, *38*, 233.
[1380] Because it was discovered by Claisen, L. *Ber.* ***1890***, *23*, 977.
[1381] Huerta, F.F.; Bäckvall, J.-E. *Org. Lett.* ***2001***, *3*, 1209.
[1382] Rathke, M.W.; Sullivan, D.F. *J. Am. Chem. Soc.* ***1973***, *95*, 3050.
[1383] Ramirez, A.; Sun, X.; Collum, D.B. *J. Am. Chem. Soc.* ***2006***, *128*, 10326.
[1384] Ariza, X.; Garcia, J.; Romea, P.; Urpí, F. *Synthesis* ***2011***, *43*, 2175.
[1385] Tanabe, Y.; Matsumoto, N.; Funakoshi, S.; Manta, N. *Synlett* ***2001***, 1959.
[1386] Nishiyama, H.; Shiomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc.* ***2005***, *127*, 6972.
[1387] See Shang, X.; Liu, H.-J. *Synth. Commun.* ***1994***, *24*, 2485.
[1388] Yost, J.M.; Zhou, G.; Coltart, D.M. *Org. Lett.* ***2006***, *8*, 1503.
[1389] See Johnson, W.S.; Daub, G.H. *Org. React.* ***1951***, *6*, 1.

course of the reaction. The Stobbe condensation has been extended to di-*tert*-butyl esters of glutaric acid.[1390] The boron-mediated reaction is known.[1391]

The intramolecular reaction of an aldehyde/carboxylic acid in the presence of triethylamine and a pyridinium salt led to the ring-forming condensation reaction, followed by formation of a β-lactone.[1392]

Chiral additives such as diazaborolidines can be added to an ester, and subsequent treatment with a base and then an aldehyde leads to a chiral β-hydroxy ester.[1393] A variety of chiral amide or oxazolidinone derivatives have been used to form amide linkages to carboxylic acid derivatives. These chiral auxiliaries lead to chirality transfer from the enolate anion of such derivatives, in both alkylation reactions and acyl substitution reactions with aldehydes and ketones. The so-called *Evans auxiliaries* (see **29**) are commonly used and give good enantioselectivity.[1394]



29

A variation is the magnesium halide-catalyzed anti-aldol reaction of chiral *N*-acylthiazolidinethiones.[1395] The use of chiral *N*-acyloxazolidinthiones with $TiCl_4$ and sparteine also gave good selectivity in the acyl addition.[1396] Chiral diazaboron derivatives have also been used to facilitate the condensation of a α-phenylthio ester with an aldehyde.[1397]

Amides participate in this condensation reaction, reacting with aldehydes in the presence of a Ba catalyst to give a β-hydroxy amide derivative.[1398] The reaction of an amide with LDA in the presence of an acyl silane, followed by reaction with an alkyl halide, leads to the β-hydroxy amide with the additional alkyl group at the β carbon.[1399] The enolate condensation of amides was reported using phosphazene-based catalysts.[1400] Thioamides reacted with copper complexes and LiOAr to form the enolate anion, which reacted with aldehydes to give the β-hydroxythioamide with good enantioselectivity.[1401]

The condensation of an ester enolate and a ketone[1402] can be used as part of a *Robinson annulation*-like sequence (see **16-34**). The aldol-like reaction of enol borates and methyl

[1390] Puterbaugh, W.H. *J. Org. Chem.* ***1962***, *27*, 4010. See also, El-Newaihy, M.F.; Salem, M.R.; Enayat, E.I.; El-Bassiouny, F.A. *J. Prakt. Chem.* ***1982***, *324*, 379.
[1391] See Abiko, A. *Acc. Chem. Res.* ***2004***, *37*, 387.
[1392] Oh, S.H.; Cortez, G.S.; Romo, D. *J. Org. Chem.* ***2005***, *70*, 2835.
[1393] Corey, E.J.; Choi, S. *Tetrahedron Lett.* ***2000***, *41*, 2769.
[1394] See Evans, D.A.; Chapman, K.T.; Bisaha, J. *Tetrahedron Lett.* ***1984***, *25*, 4071.
[1395] Evans, D.A.; Downey, C.W.; Shaw, J.T.; Tedrow, J.S. *Org. Lett.* ***2002***, *4*, 1127.
[1396] Crimmins, M.T.; McDougall, P.J. *Org. Lett.* ***2003***, *5*, 591.
[1397] Corey, E.J.; Choi, S. *Tetrahedron Lett.* ***2000***, *41*, 2769.
[1398] Saito, S.; Kobayashi, S. *J. Am. Chem. Soc.* ***2006***, *128*, 8704.
[1399] Lettan II, R.B.; Reynolds, T.E.; Galliford, C.V.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2006***, *128*, 15566.
[1400] Foo, S.W.; Oishi, S.; Saito, S. *Tetrahedron Lett.* ***2012***, *53*, 5445; Echave, H.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* ***2016***, *55*, 3364.
[1401] Sureshkumar, D.; Kawato, Y.; Iwata, M.; Kumagai, N.; Shibasaki, M. *Org. Lett.* ***2012***, *14*, 3108.
[1402] Posner, G.H.; Webb, K.S.; Asirvatham, E.; Jew, S.; Degl'Innocenti, A. *J. Am. Chem. Soc.* ***1988***, *110*, 4754.

phenylacetate gave β-hydroxy esters and it was shown that choice of either the solvent or temperature determines the diastereoselectivity of the reaction.[1403]

OS **I**, 252; **III**, 132; **V**, 80, 564; **70**, 256; **X**, 437; **81**, 157. Also see, OS **IV**, 278, 478; **V**, 251.

16-37 Condensation of Nitro Compounds: the Henry Reaction[1404]

$$CH_3NO_2 + HCHO \xrightarrow{^-OH} HOCH_2CH_2NO_2$$

The condensation of an aliphatic nitro compound with an aldehyde or ketone is usually called the *Henry reaction*[1405] or the *Kamlet reaction*, and is essentially a nitro aldol reaction. An investigation of solvent effects and how they influence the rate and the stereoselectivity of the Henry reaction has been reported.[1406]

A variety of conditions have been reported, including the use of a recoverable polymer catalyst,[1407] a silica catalyst,[1408] a tetraalkylammonium hydroxide,[1409] proazaphosphatranes,[1410] a mesoporous nickel hydroxyapatite nanocomposite,[1411] and In,[1412] and it has been done in aqueous media[1413] or an ionic liquid.[1414] A solvent-free Henry reaction was reported in which a nitroalkane and an aldehyde were reacted on KOH powder,[1415] and a solvent-free microwave-assisted reaction was reported.[1416] Potassium phosphate has been used with nitromethane and aryl aldehydes A gel-entrapped base has been used to catalyze this reaction.[1417]

[1403] Ramachandran, P.V.; Chanda, P.B. *Org. Lett.* ***2012***, *14*, 4346.

[1404] Baer, H.H.; Urbas, L. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Wiley, NY, ***1970***, pp. 76–117. See also, Rosini, G.; Ballini, R.; Sorrenti, P. *Synthesis* ***1983***, 1014; Matsumoto, K. *Angew. Chem. Int. Ed.* ***1984***, *23*, 617; Eyer, M.; Seebach, D. *J. Am. Chem. Soc.* ***1985***, *107*, 3601. For reviews of the nitroalkenes that are the products of this reaction, see Barrett, A.G.M.; Graboski, G.G. *Chem. Rev.* ***1986***, *86*, 751; Kabalka, G.W.; Varma, R.S. *Org. Prep. Proced. Int.* ***1987***, *19*, 283.

[1405] Henry, L. *Compt. Rend.* ***1895***, *120*, 1265; Kamlet, J. *U.S. Patent* 2,151,171 ***1939*** (*Chem. Abstr.* ***1939***, *33*, 50039); Hass, H.B.; Riley, E.F. *Chem. Rev.* ***1943***, *32*, 373 (see p. 406); Lichtenthaler, F.W. *Angew. Chem. Int. Ed.* ***1964***, *3*, 211. For a review, see Luzzio, F.A. *Tetrahedron* ***2001***, *57*, 915.

[1406] Kostal, J.; Voutchkova, A.M.; Jorgensen, W.L. *Org. Lett.* ***2012***, *14*, 260.

[1407] Yan, S.; Gao, Y.; Xing, R.; Shen, Y.; Liu, Y.; Wu, P.; Wu, H. *Tetrahedron* ***2008***, *64*, 6294.

[1408] Hagiwara, H.; Sekifuji, M.; Tsubokawa, N.; Hoshi, T.; Suzuki, T. *Chem. Lett.* ***2009***, *38*, 790.

[1409] Bulbule, V.J.; Jnaneshwara, G.K.; Deshmukh, R.R.; Borate, H.B.; Deshpande, V.H. *Synth. Commun.* ***2001***, *31*, 3623.

[1410] Kisanga, P.B.; Verkade, J.G. *J. Org. Chem.* ***1999***, *64*, 4298.

[1411] Neelakandeswari, N.; Sangami, G.; Emayavaramban, P.; Karvembu, R.; Dharmaraj, N.; Kim, H.Y. *Tetrahedron Lett.* ***2012***, *53*, 2980.

[1412] Soengas, R.G.; Silva, A.M.S. *Synlett* ***2012***, *23*, 873.

[1413] Bora, P.P.; Bez, G. *Eur. J. Org. Chem.* ***2013***, 2922. See Thorat, P.B.; Goswami, S.V.; Jadhav, W.N.; Bhusare, S.R. *Aust. J. Chem.* ***2013***, *66*, 661.

[1414] Jiang, T.; Gao, H.; Han, B.; Zhao, G.; Chang, Y.; Wu, W.; Gao, L.; Yang, G. *Tetrahedron Lett.* ***2004***, *45*, 2699.

[1415] Ballini, R.; Bosica, G.; Parrini, M. *Chem. Lett.* ***1999***, 1105.

[1416] Gan, C.; Chen, X.; Lai, G.; Wang, Z. *Synlett* ***2006***, 387.

[1417] Bandgar, B.P.; Uppalla, L.S. *Synth. Commun.* ***2000***, *30*, 2071.

Catalytic enantioselective Henry reactions are known,[1418] and include the use of Cu,[1419] Zn,[1420] Nd,[1421] Ni,[1422] Cr,[1423] or Ti catalysts.[1424] A heterobimetalic Cu/Sm catalyst has been used.[1425] The Henry reaction of nitromethane and a chiral aldehyde under high pressure gives the β-nitro alcohol with excellent enantioselectivity.[1426] Enantioselective nitroaldol reactions are catalyzed by organocatalysts such as *Cinchona* alkaloids[1427] or other organocatalysts[1428] and biocatalysts.[1429] Biocatalysts have been used.[1430] An *anti*-selective Henry reaction used an urea/transition metal cooperative catalyst.[1431] The development of new chiral ligands is of ongoing importance.[1432] An asymmetric Henry reaction has been reported using flow conditions (Sec. 7.D).[1433]

Aza-Henry reactions[1434] condense nitroalkanes with imine derivatives, and the resulting amino nitro compounds are formed with good enantioselectivity in the presence of organocatalysts[1435] or Brønsted acid catalysts.[1436] Samarium or sodium iodide salts have been used with the aza-Henry reaction.[1437] Aza-Henry products are also formed by the reaction of amines with activated unsaturated compounds.[1438]

[1418] For reviews, see Boruwa, J.; Gogoi, N.; Saikia, P.P.; Barua, N.C. *Tetrahedron: Asymmetry* ***2006***, *17*, 3315; Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* ***2007***, 2561.

[1419] Gualandi, A.; Cerisoli, L.; Stoeckli-Evans, H.; Savoia, D. *J. Org. Chem.* ***2011***, *76*, 3399; Mei, H.; Xiao, X.; Zhao, X.; Fang, B.; Liu, X.; Lin, L.; Feng, X. *J. Org. Chem.* ***2015***, *80*, 2272; Ni, B.; He, J. *Tetrahedron Lett.* ***2013***, *54*, 462; Arai, T.; Kawasaki, N.; Kanoh, H. *Synlett* ***2012***, *23*, 1549; Dhahagani, K.; Rajesh, J.; Kannan, R.; Rajagopal, G. *Tetrahedron: Asymmetry* ***2011***, *22*, 857; Bhosale, D.S.; Drabina, P.; Kincl, M.; Vlček, M.; Sedlák, M. *Tetrahedron: Asymmetry* ***2015***, *26*, 1300; Ji, Y.Q.; Qi, G.; Judeh, Z.M.A. *Eur. J. Org. Chem.* ***2011***, 4892; Zhou, Y.; Gong, Y. *Eur. J. Org. Chem.* ***2011***, 6092; Lu, G.; Zheng, F.; Wang, L.; Guo, Y.; Li, X.; Cao, X.; Wang, C.; Chi, H.; Dong, Y.; Zhang, Z. *Tetrahedron: Asymmetry* ***2017***, *27*, 732.

[1420] Bulut, A.; Aslan, A.; Dogan, Ö. *J. Org. Chem.* ***2008***, *73*, 7373.

[1421] See Nonoyama, A.; Hashimoto, K.; Saito, A.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* ***2016***, *57*, 1815.

[1422] Liu, Y.; Deng, P.; Li, X.; Xiong, Y.; Zhou, H. *Synlett* ***2014***, *25*, 1735.

[1423] Ouyang, G.-H.; He, Y.-M.; Fan, Q.-H. *Chem. Eur. J.* ***2014***, *20*, 16454.

[1424] Tur, F.; Saá, J.M. *Org. Lett.* ***2007***, *9*, 5079.

[1425] Li, Y.; Deng, P.; Zeng, Y.; Xiong, Y.; Zhou, H. *Org. Lett.* ***2016***, *18*, 1578.

[1426] Misumi, Y.; Matsumoto, K. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1031.

[1427] Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* ***2006***, *128*, 732; Liu, M.; Ma, S.; Tian, Z.; Wu, H.; Wu, L.; Xu, X.; Huang, Y.; Wang, Y. *Tetrahedron: Asymmetry* ***2013***, *24*, 736.

[1428] Breugst, M.; Houk, K.N. *J. Org. Chem.* ***2014***, *79*, 6302; Wang, H.-Y.; Chai, Z.; Zhao, G. *Tetrahedron* ***2013***, *69*, 5104; Nakayama, Y.; Hidaka, Y.; Ito, K. *Synlett* ***2013***, *24*, 883; Ganesan, S.S.; Ganesan, A.; Kothandapani, J. *Synlett* ***2014***, *25*, 1847; Balaraman, K.; Vasanthan, R.; Kesavan, V. *Synthesis* ***2012***, *44*, 2455; Androvič, L.; Drabina, P.; Panov, I.; Frumarová, B.; Kalendová, A.; Sedlák, M. *Tetrahedron: Asymmetry* ***2014***, *25*, 775. See Ran, D.-q.; Shen, X.-h.; Zhou, X.-c.; Li, J.-q.; Cui, F.-n.; Ma, C.-a.; Song, Q.-b. *Russ. J. Org. Chem.* ***2013***, *49*, 849.

[1429] Milner, S.E.; Moody, T.S.; Maguire, A.R. *Eur. J. Org. Chem.* ***2012***, 3059.

[1430] Matsumoto, K.; Asakura, S. *Tetrahedron Lett.* ***2014***, *55*, 6919; Surneni, N.; Barua, N.C.; Saikia, B. *Tetrahedron Lett.* ***2016***, *57*, 2814.

[1431] Lang, K.; Park, J.; Hong, S. *Angew. Chem. Int. Ed.* ***2012***, *51*, 1620.

[1432] Huang, H.; Zong, H.; Bian, G.; Yue, H.; Song, L. *J. Org. Chem.* ***2014***, *79*, 9455; White, J.D.; Shaw, S. *Org. Lett.* ***2012***, *14*, 6270; Wolińska, E. *Tetrahedron* ***2013***, *69*, 7269; Zhang, L.; Wu, H.; Yang, Z.; Xu, X.; Zhao, H.; Huang, Y.; Wang, Y. *Tetrahedron* ***2013***, *69*, 10644; Arai, T.; Joko, A.; Sato, K. *Synlett* ***2015***, *26*, 209; Khong, D.T.; Judeh, Z.M.A. *Synthesis* ***2016***, *48*, 2271; Aydin, A.E.; Yuksekdanaci, S. *Tetrahedron: Asymmetry* ***2013***, *24*, 14.

[1433] Hashimoto, K.; Kumagai, N.; Shibasaki, M. *Org. Lett.* ***2014***, *16*, 3496. See Kitagaki, S.; Ueda, T.; Mukai, C. *Chem. Commun.* ***2013***, *49*, 4030.

[1434] See Oyaiza, K.; Uraguchi, D.; Ooi, T. *Chem. Commun.* ***2015***, *51*, 4437.

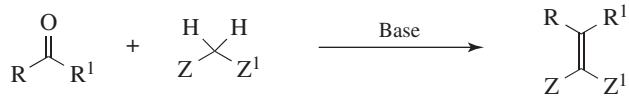
[1435] See Singh, A.; Johnston, J.N. *J. Am. Chem. Soc.* ***2008***, *130*, 5866. For reactions in DMSO, see Isobe, T.; Kato, A.; Oriyama, T. *Chem. Lett.* ***2015***, *44*, 483.

[1436] Rueping, M.; Antonchick, A.P. *Org. Lett.* ***2008***, *10*, 1731.

[1437] Rodríguez-Solla, H.; Concellón, C.; Alvaredo, N.; Soengas, R.G. *Tetrahedron* ***2012***, *68*, 1736.

[1438] Ziyaei-Halimehjani, A.; Saidi, M.R. *Tetrahedron Lett.* ***2008***, *49*, 1244.

16-38 The Knoevenagel Reaction



The condensation of aldehydes or ketones, traditionally not containing an α hydrogen, with compounds of the form $Z{-}CH_2{-}Z'$ or $Z{-}CHR{-}Z'$ is called the *Knoevenagel reaction*.[1439] Both Z and Z′ may be CHO, COR, CO_2H, CO_2R, CN, NO_2, SOR, SO_2R, SO_2OR, or similar electron-withdrawing groups. The presence of two electron-withdrawing groups makes this α proton much more acidic (Table 8.1 in Sec. 8.A.i), and such compounds have a significantly higher enol content.[1440] When $Z = CO_2H$, decarboxylation of the product often takes place *in situ*.[1441] Nitroalkanes[1404] as well as β-keto sulfoxides[1442] undergo the reaction.

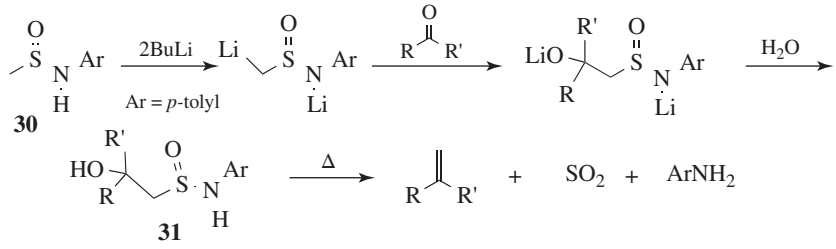
As with **16-34**, these reactions have sometimes been mediated by an acid catalyst.[1443] Ionic liquid solvents have been used,[1444] and heating on quaternary ammonium salts without solvent has been used for a Knoevenagel reaction.[1445] Other solvent-free reactions are known.[1446] Ultrasound has been used to promote the reaction,[1447] and it has also been done using microwave irradiation.[1448] High pressure conditions have been used.[1449] Transition metal compounds of Pd,[1450] Sm,[1451] Ce,[1452] In,[1453] Cu,[1454] Ti,[1455] or Bi[1456] have been used to promote the Knoevenagel reaction.[1457] Organocatalysts have been developed.[1458] Domino reactions based on Knoevenagel condensation for the synthesis of heterocyclic compounds have been reviewed.[1459]

[1439] For reviews, see Jones, G. *Org. React.* ***1967***, *15*, 204; Wilk, B.K. *Tetrahedron* ***1997***, *53*, 7097.
[1440] Rochlin, E.; Rappoport, Z. *J. Org. Chem.* ***2003***, *68*, 1715.
[1441] See Tanaka, M.; Oota, O.; Hiramatsu, H.; Fujiwara, K. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 2473.
[1442] Kuwajima, I.; Iwasawa, H. *Tetrahedron Lett.* ***1974***, 107. See also, Huckin, S.N.; Weiler, L. *Can. J. Chem.* ***1974***, *52*, 2157.
[1443] See Bartoli, G.; Beleggia, R.; Giuli, S.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Paoletti, M. *Tetrahedron Lett.* ***2006***, *47*, 6501.
[1444] Harjani, J.R.; Nara, S.J.; Salunkhe, M.M. *Tetrahedron Lett.* ***2002***, *43*, 1127. See Su, C.; Chen, Z.-C.; Zheng, Q.G. *Synthesis* ***2003***, 555.
[1445] Bose, D.S.; Narsaiah, A.V. *J. Chem. Res. (S)* ***2001***, 36.
[1446] See Pillai, M.K.; Singh, S.; Jonnalagadda, S.B. *Synth. Commun.* ***2010***, *40*, 3710.
[1447] Li, J.-T.; Zang, H.-J.; Feng, Y.-Y.; Li, L.-J.; Li, T.-S. *Synth. Commun.* ***2001***, *31*, 653.
[1448] Yadav, J.S.; Reddy, B.V.S.; Basak, A.K.; Visali, B.; Narsaiah, A.V.; Nagaiah, K. *Eur. J. Org. Chem.* ***2004***, 546.
[1449] Jenner, G. *Tetrahedron Lett.* ***2001***, *42*, 243.
[1450] You, J.; Verkade, J.G. *J. Org. Chem.* ***2003***, *68*, 8003.
[1451] Chandrasekhar, S.; Yu, J.; Falck, J.R.; Mioskowski, C. *Tetrahedron Lett.* ***1994***, *35*, 5441.
[1452] Bartoli, G.; Beleggia, R.; Giuli, S.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Paoletti, M. *Tetrahedron Lett.* ***2006***, *47*, 6501.
[1453] Ogiwara, Y.; Takahashi, K.; Kitazawa, T.; Sakai, N. *J. Org. Chem.* ***2015***, *80*, 3101.
[1454] Schneider, E.M.; Zeltner, M.; Kränzlin, N.; Grass, R.N.; Stark, W.J. *Chem. Commun.* ***2015***, *51*, 10695.
[1455] Yamashita, K.; Tanaka, T.; Haya, M. *Tetrahedron* ***2005***, *61*, 7981.
[1456] A solvent-free reaction: see Prajapati, D.; Sandhu, J.S. *Chem. Lett.* ***1992***, 1945.
[1457] See Lee, A.; Michrowska, A.; Sulzer-Mosse, S.; List, B. *Angew. Chem. Int. Ed.* ***2011***, *50*, 1707.
[1458] Mase, N.; Horibe, T. *Org. Lett.* ***2013***, *15*, 1854; Benzekri, Z.; El Mejdoubi, K.; Boukhris, S.; Sallek, B.; Lakjrissi, B.; Souizi, A. *Synth. Commun.* ***2016***, *46*, 442. See Liu, Q.; Ai, H.-M. *Synth. Commun.* ***2012***, *42*, 3004.
[1459] Voskressensky, L.G.; Festa, A.A.; Varlamov, A.V. *Tetrahedron* ***2014***, *70*, 551.

With most of these reagents, dehydration to the conjugated system can occur,[1460] but with a careful workup the alcohol is the major product. With suitable reactants, the Knoevenagel reaction, like the aldol condensation (**16-34**), has been carried out diastereoselectively[1461] and enantioselectively.[1462] When the reactant is of the form ZCH_2Z', aldehydes react much better than ketones. In reactions with ZCH_2Z', the catalyst is most often a secondary amine (piperidine is common), but many other catalysts have been used, including alkoxides. When the catalyst is pyridine (to which piperidine may or may not be added) the reaction is known as the *Doebner modification* of the Knoevenagel reaction and dehydration and decarboxylation occur after condensation with the aldehyde to give a conjugated acid. Microwave-induced Doebner condensation reactions are known.[1463]

A number of special applications of the Knoevenagel reaction follow.

1. The dilithio derivative of *N*-methanesulfinyl-*p*-toluidine[1464] (**30**) adds to aldehydes and ketones to give, after hydrolysis, the hydroxysulfinamides **31**. Subsequent heating leads to a stereospecific *syn* elimination to give an alkene.[1465] The reaction is thus a method for achieving the conversion $RR'CO \rightarrow RR'C{=}CH_2$ and represents an alternative to the *Wittig reaction*.[1466]



2. The reaction of ketones with tosylmethylisocyanide ($TsCH_2{}^+N{\equiv}C^-$) gives different products,[1467] depending on the reaction conditions. When potassium *tert*-butoxide in THF is used at −5 °C, one obtains (after hydrolysis) the normal Knoevenagel product [$R_2C{=}C(Ts)NHCHO$], except that the isocyano group has been hydrated (**16-91**).[1468] With the same base but with 1,2-dimethoxyethane (DME) as solvent the product is the nitrile ($R_2CHC{\equiv}N$).[1469]. The conversions to $RCHR'COOH$ and to $RCHR'CN$[1470] have also been carried out with certain aldehydes ($R' = H$).

[1460] For lists of reagents with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 317–325, 341–350. For those that give the alcohol product, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1178–1179, 1540–1541, 1717–1724, 1727, 1732–1736, 1778–1780, 1801–1805.

[1461] See Barrett, A.G.M.; Robyr, C.; Spilling, C.D. *J. Org. Chem.* ***1989***, *54*, 1233; Pyne, S.G.; Boche, G. *J. Org. Chem.* ***1989***, *54*, 2663.

[1462] See Togni, A.; Pastor, S.D. *J. Org. Chem.* ***1990***, *55*, 1649; Sakuraba, H.; Ushiki, S. *Tetrahedron Lett.* ***1990***, *31*, 5349; Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* ***1990***, 937.

[1463] Pellón, R.F.; Mamposo, T.; González, E.; Calderón, O. *Synth. Commun.* ***2000***, *30*, 3769.

[1464] See Bowlus, S.B.; Katzenellenbogen, J.A. *Synth. Commun.* ***1974***, *4*, 137.

[1465] Corey, E.J.; Durst, T. *J. Am. Chem. Soc.* ***1968***, *90*, 5548, 5553.

[1466] See Arenz, T.; Vostell, M.; Frauenrath, H. *Synlett* ***1991***, 23.

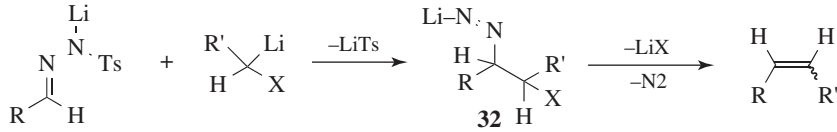
[1467] See Schöllkopf, U. *Pure Appl. Chem.* ***1979***, *51*, 1347; Hoppe, D. *Angew. Chem. Int. Ed.* ***1974***, *13*, 789.

[1468] Schöllkopf, U.; Schröder, U. *Angew. Chem. Int. Ed.* ***1972***, *11*, 311.

[1469] Oldenziel, O.H.; van Leusen, D.; van Leusen, A.M. *J. Org. Chem.* ***1977***, *42*, 3114.

[1470] van Leusen, A.M.; Oomkes, P.G. *Synth. Commun.* ***1980***, *10*, 399.

3. Aldehydes and ketones, RCOR′, react with α-methoxyvinyllithium, CH_2=C(Li)OMe, to give hydroxy enol ethers, RR′C(OH)C(OMe)=CH_2, which are easily hydrolyzed to acyloins, RR′C(OH)COMe.[1471] In this reaction, the CH_2=C(Li)OMe is a synthon for the unavailable $H_3C-{}^{-}C{=}O$,[1472] and is termed an *acyl anion equivalent*. The reagent also reacts with esters, RCOOR′, to give RC(OH)(COMe=CH_2)$_2$. A synthon for the Ph–C=O ion is PhC(CN)OSiMe_3, which adds to aldehydes and ketones, RCOR′, to give, after hydrolysis, the α-hydroxy ketones, RR′C(OH)COPh.[1473]
4. Lithiated allylic carbamates react with aldehydes or ketones (RCOR) in a reaction accompanied by an allylic rearrangement to give (after hydrolysis) γ-hydroxy aldehydes or ketones.[1474] The reaction is called *the homoaldol reaction*, since the product is a homolog of the product of **16-34**. The reaction has been performed enantioselectively.[1475]
5. The lithium salt of an active hydrogen compound adds to the lithium salt of the tosylhydrazone of an aldehyde to give product **32**.



If X = CN, SPh, or SO_2R, **32** spontaneously loses N_2 and LiX to give the alkene. The entire process is done in one reaction vessel. The active hydrogen compound is mixed with the tosylhydrazone and the mixture is treated with (*i*-Pr)$_2$NLi to form both salts at once.[1476] This process is another alternative to the *Wittig reaction* for forming double bonds.

OS **I**, 181, 290, 413; **II**, 202; **III**, 39, 165, 317, 320, 377, 385, 399, 416, 425, 456, 479, 513, 586, 591, 597, 715, 783; **IV**, 93, 210, 221, 234, 293, 327, 387, 392, 408, 441, 463, 471, 549, 573, 730, 731, 777; **V**, 130, 381, 572, 585, 627, 833, 1088, 1128; **VI**, 41, 95, 442, 598, 683; **VII**, 50, 108, 142, 276, 381, 386, 456; **VIII**, 258, 265, 309, 353, 391, 420; **X**, 271. Also see, OS **III**, 395; **V**, 450.

16-39 The Perkin Reaction

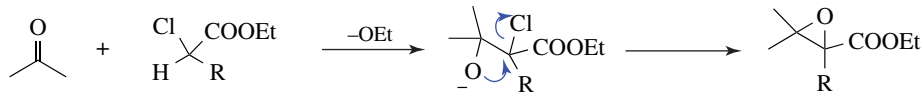
The condensation of aromatic aldehydes with anhydrides is called the *Perkin reaction*.[1477] When the anhydride has two α hydrogen atoms (as shown), dehydration almost always

[1471] Baldwin, J.E.; Höfle, G.A.; Lever Jr., O.W. *J. Am. Chem. Soc.* ***1974***, *96*, 7125. For a similar reaction, see Tanaka, K.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* ***1978***, 4809.
[1472] Also see Reetz, M.T.; Heimbach, H.; Schwellnus, K. *Tetrahedron Lett.* ***1984***, *25*, 511.
[1473] Hünig, S.; Wehner, G. *Synthesis* ***1975***, 391.
[1474] For a review, see Hoppe, D. *Angew. Chem. Int. Ed.* ***1984***, *23*, 932.
[1475] Krämer, T.; Hoppe, D. *Tetrahedron Lett.* ***1987***, *28*, 5149.
[1476] Vedejs, E.; Dolphin, J.M.; Stolle, W.T. *J. Am. Chem. Soc.* ***1979***, *101*, 249.
[1477] See Johnson, J.R. *Org. React.* ***1942***, *1*, 210; Edwards, M.; Rourk, P.M.; Riby, P.G.; Mendham, A.P. *Tetrahedron* ***2014***, *70*, 7245.

occurs; the β-hydroxy acid salt is rarely isolated. In some cases, anhydrides of the form $(R_2CHCO)_2O$ have been used, and then the hydroxy compound is the product since dehydration cannot take place. The base in the Perkin reaction is nearly always the salt of the acid corresponding to the anhydride. Although the Na and K salts have been most frequently used, higher yields and shorter reaction times have been reported for the Cs salt.[1478] Besides aromatic aldehydes, their vinylogs ArCH═CHCHO also give the reaction (Sec. 6.B). Otherwise, the reaction does not work for aliphatic aldehydes.[1479]

OS **I**, 398; **II**, 61, 229; **III**, 426.

16-40 Darzens Glycidic Ester Condensation



Aldehydes and ketones condense with α-halo esters in the presence of bases to give α,β-epoxy esters, called *glycidic esters*. This is called *the Darzens condensation*.[1480] The reaction consists of an initial Knoevenagel-type reaction (**16-38**), followed by an internal S_N2 reaction (**10-9**).[1481] Although the intermediate halo alkoxide is generally not isolated,[1482] it has been with α-chloro esters and also with α-fluoro esters (fluorine is generally a poor leaving group in nucleophilic substitutions).[1483] This is only one of several types of evidence that rule out a carbene intermediate.[1484] Sodium ethoxide is often used as the base but other bases, including sodium amide, are sometimes used. Aromatic aldehydes and ketones give good yields. Simple aliphatic aldehydes as well as aromatic aldehydes and ketones also give good yields by treatment of the α-halo ester with the base lithium bis(trimethylsilyl)amide, $LiN(SiMe_3)_2$, in THF at − 78 °C (to form the conjugate base of the ester) and addition of the aldehyde or ketone to this solution.[1485] If a preformed dianion of an α-halo carboxylic acid $^-CR(Cl)CO_2^-$ is used instead, α,β-epoxy acids are produced directly.[1486] The Darzens reaction has also been carried out on α-halo ketones, α-halo nitriles,[1487] α-halo sulfoxides[1488] and sulfones,[1489] α-halo *N*,*N*-disubstituted amides,[1490] α-halo ketimines,[1491] and even on

[1478] Koepp, E.; Vögtle, F. *Synthesis* ***1987***, 177.
[1479] Crawford, M.; Little, W.T. *J. Chem. Soc.* ***1959***, 722.
[1480] See Berti, G. *Top. Stereochem.* ***1973***, *7*, 93 (pp. 210–218). Also see, Bakó, P.; Szöllõsy, Á; Bombicz, P.; Töke, L. *Synlett* ***1997***, 291.
[1481] See Bansal, R.K.; Sethi, K. *Bull. Chem. Soc. Jpn.* ***1980***, *53*, 1197.
[1482] See Yliniemelä, A.; Brunow, G.; Flügge, J.; Teleman, O. *J. Org. Chem.* ***1996***, *61*, 6723.
[1483] Ballester, M.; Pérez-Blanco, D. *J. Org. Chem.* ***1958***, *23*, 652; Elkik, E.; Francesch, C. *Bull. Soc. Chim. Fr.* ***1973***, 1277, 1281.
[1484] See also, Zimmerman, H.E.; Ahramjian, L. *J. Am. Chem. Soc.* ***1960***, *82*, 5459.
[1485] Borch, R.F. *Tetrahedron Lett.* ***1972***, 3761.
[1486] Johnson, C.R.; Bade, T.R. *J. Org. Chem.* ***1982***, *47*, 1205.
[1487] See White, D.R.; Wu, D.K. *J. Chem. Soc., Chem. Commun.* ***1974***, 988.
[1488] Satoh, T.; Sugimoto, A.; Itoh, M.; Yamakawa, K. *Tetrahedron Lett.* ***1989***, *30*, 1083.
[1489] Arai, S.; Ishida, T.; Shioiri, T. *Tetrahedron Lett.* ***1998***, *39*, 8299.
[1490] Tung, C.C.; Speziale, A.J.; Frazier, H.W. *J. Org. Chem.* ***1963***, *28*, 1514.
[1491] Mauzé, B. *J. Organomet. Chem.* ***1979***, *170*, 265.

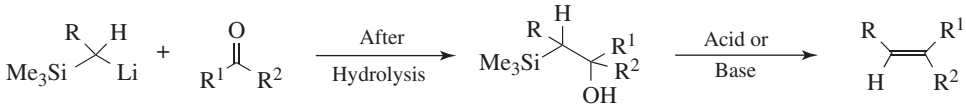
allylic[1492] and benzylic halides. Phase-transfer catalysis has been used.[1493] Note that the reaction of a β-bromo-α-oxo ester and a Grignard reagent leads to the glycidic ester.[1494] Acid-catalyzed Darzens reactions have also been reported.[1495] (see also **16-46**).

Diastereoselective Darzens condensations are possible.[1496] The Darzens reaction has been performed with good enantioselectivity,[1497] and chiral additives have proven to be effective.[1498] Chiral phase-transfer agents have been used to give epoxy ketones with modest enantioselectivity.[1499]

The reaction has been extended to the formation of analogous aziridines by treatment of an imine with an α-halo ester or an α-halo *N*,*N*-disubstituted amide and *t*-BuOK in the solvent 1,2-dimethoxyethane.[1500] However, yields were not high. Aza-Darzens aziridine synthesis has been reported via diazoalkane azomethine reactions.[1501] Catalytic aza-Darzens reactions have been reported.[1502]

OS **III**, 727; **IV**, 459, 649.

16-41 The Peterson Alkenylation Reaction



In the *Peterson alkenylation reaction*[1503], the lithio (or sometimes magnesio) derivative of a trialkylsilane adds to an aldehyde or ketone to give a β-hydroxysilane, which spontaneously eliminates water, or can be made to do so by treatment with acid or base, to produce an alkene. This reaction is still another alternative to the *Wittig reaction* (**16-44**), and is sometimes called the *silyl-Wittig reaction*.[1504] The R group can also be a COOR group, in which

[1492] Sulmon, P.; De Kimpe, N.; Schamp, N.; Declercq, J.; Tinant, B. *J. Org. Chem.* ***1988***, *53*, 4457.

[1493] See Arai, S.; Suzuki, Y.; Tokumaru, K.; Shioiri, T. *Tetrahedron Lett.* ***2002***, *43*, 833. See Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***, pp. 197–198.

[1494] Jung, M.E.; Mengel, W.; Newton, T.W. *Synth. Commun.* ***1999***, *29*, 3659.

[1495] Sipos, G.; Schöbel, G.; Sirokmán, F. *J. Chem. Soc., Perkin Trans. 2* ***1975***, 805.

[1496] See Tanaka III, K.T.; Kobayashi, K.; Takatori, K.; Kogen, H. *Tetrahedron* ***2017***, *73*, 2062.

[1497] See Chai, G.-L.; Han, J.-W.; Wong, H.N.C. *Synthesis* ***2017***, *49*, 181; Liu, G.; Zhang, D.; Li, J.; Xu, G.; Sun, J. *Org. Biomol. Chem.* ***2013***, *11*, 900. For a review, see Ohkata, K.; Kimura, J.; Shinohara, Y.; Takagi, R.; Hiraga, Y. *Chem. Commun.* ***1996***, 2411.

[1498] Aggarwal, V.K.; Hynd, G.; Picoul, W.; Vasse, J.-L. *J. Am. Chem. Soc.* ***2002***, *124*, 9964.

[1499] Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* ***1999***, *55*, 6375.

[1500] Deyrup, J.A. *J. Org. Chem.* ***1969***, *34*, 2724.

[1501] Troyer, T.L.; Muchalski, H.; Hong, K.B.; Johnston, J.N. *Org. Lett.* ***2011***, *13*, 1790. See Moragas, T.; Churcher, I.; Lewis, W.; Stockman, R.A. *Org. Lett.* ***2014***, *16*, 6290; Trost, B.M.; Saget, T.; Hung, C.-I. *Angew. Chem. Int. Ed.* ***2017***, *56*, 2440.

[1502] Larson, S.E.; Li, G.; Rowland, G.B.; Junge, D.; Huang, R.; Woodcock, H.L.; Antilla, J.C. *Org. Lett.* ***2011***, *13*, 2188.

[1503] Peterson, D.J. *J. Org. Chem.* ***1968***, *33*, 780. See Ager, D.J. *Org. React.* ***1990***, *38*, 1; Colvin, E.W. *Silicon Reagents in Organic Synthesis*, Academic Press, NY, ***1988***, pp. 63–75; Weber, W.P. *Silicon Reagents for Organic Synthesis*, Springer, NY, ***1983***, pp. 58–78; Magnus, P. *Aldrichimica Acta* ***1980***, *13*, 43; Chan, T. *Acc. Chem. Res.* ***1977***, *10*, 442. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 337–341.

[1504] See Hudrlik, P.F.; Agwaramgbo, E.L.O.; Hudrlik, A.M. *J. Org. Chem.* ***1989***, *54*, 5613.

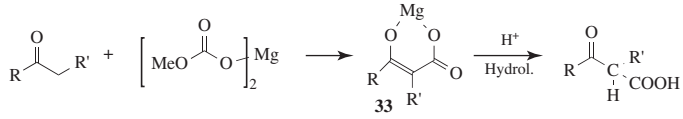
case the product is an α,β-unsaturated ester,[1505] or the R group can be an SO_2Ph group, in which case the product is a vinylic sulfone.[1506] The stereochemistry of the product can often be controlled by whether an acid or a base is used to achieve elimination. The role of Si—O interactions has also been examined.[1507] Use of a base generally gives *syn* elimination (E^i mechanism, Sec. 17.C.i), while an acid usually results in *anti* elimination (E2 mechanism, Sec. 17.A.i).[1508] Samarium(II) iodide in HMPA has also been used for elimination of the hydroxy sulfone.[1509]

When aldehydes or ketones are treated with reagents such as $Me_3SiCMe(Cl)Li$, the product is an epoxy silane (**16-46**) that can be hydrolyzed to a methyl ketone.[1510] For aldehydes, this is a method for converting RCHO to a methyl ketone RCH_2COMe. The reagents $Me_3SiCHRM$ (M = Li or Mg) are often prepared from $Me_3SiCHRCl$[1511] (by **12-37** or **12-38**), but they have also been made by **12-22** and by other procedures.[1512] Lithio alkenylsilanes have been used for this reaction.[1513]

An aza-Peterson reaction has been reported, using bis(trimethylsilane) reagents and sulfonyl imines.[1514] A Peterson-like synthesis of alkenyl nitriles has been reported using catalytic conditions.[1515] A new version of the reaction has been developed, reacting $Me_3SiCH_2CO_2Et$ with an aldehyde and a catalytic amount of CsF in DMSO.[1516] A selenoamide derivative has been used in a similar manner.[1517]

See OS **VIII**, 602, for a related reaction.

16-42 The Reaction of Active Hydrogen Compounds With Metal Carbonates, CO_2, or CS_2



Ketones of the form $RCOCH_3$ and $RCOCH_2R'$ can be carboxylated indirectly by treatment with magnesium methyl carbonate.[1518] Because formation of the chelate **33** provides the driving force of the reaction, carboxylation cannot be achieved at a disubstituted α position.

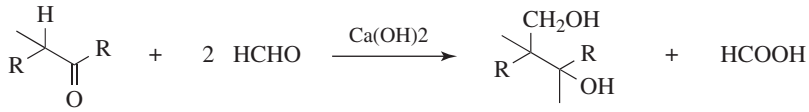
[1505] See Strekowski, L.; Visnick, M.; Battiste, M.A. *Tetrahedron Lett.* ***1984***, *25*, 5603.
[1506] Craig, D.; Ley, S.V.; Simpkins, N.S.; Whitham, G.H.; Prior, M.J. *J. Chem. Soc., Perkin Trans. 1* ***1985***, 1949.
[1507] Bassindale, A.R.; Ellis, R.J.; Taylor, P.G. *J. Chem. Res. (S)* ***1996***, 34.
[1508] See Colvin, E.W. *Silicon Reagents in Organic Synthesis*, Academic Press, NY, ***1988***, pp. 65–69.
[1509] Markò, I.E.; Murphy, F.; Kumps, L.; Ates, A.; Touillaux, R.; Craig, D.; Carballares, S.; Dolan, S. *Tetrahedron* ***2001***, *57*, 2609.
[1510] Cooke, F.; Roy, G.; Magnus, P. *Organometallics* ***1982***, *1*, 893.
[1511] For a review of these reagents, see Anderson, R. *Synthesis* ***1985***, 717.
[1512] See Barrett, A.G.M.; Flygare, J.A. *J. Org. Chem.* ***1991***, *56*, 638.
[1513] Tsubouchi, A.; Kira, T.; Takeda, T. *Synlett* ***2006***, 2577.
[1514] Das, M.; O'Shea, D.F. *Org. Lett.* ***2016***, *18*, 336.
[1515] Lanari, D.; Alonzi, M.; Ferlin, F.; Santoro, S.; Vaccaro, L. *Org. Lett.* ***2016***, *18*, 2680.
[1516] Bellassoued, M.; Ozanne, N. *J. Org. Chem.* ***1995***, *60*, 6582.
[1517] Murai, T.; Fujishima, A.; Iwamoto, C.; Kato, S. *J. Org. Chem.* ***2003***, *68*, 7979.
[1518] Stiles, M. *J. Am. Chem. Soc.* ***1959***, *81*, 2598; *Ann. N.Y. Acad. Sci.* ***1960***, *88*, 332; Crombie, L.; Hemesley, P.; Pattenden, G. *Tetrahedron Lett.* ***1968***, 3021.

Direct carboxylation has been reported in a number of instances. Ketones have been carboxylated in the α position to give β-keto acids[1519] using lithium 4-methyl-2,6-di-*tert*-butyl phenoxide.

The reaction of benzylic positions of *o*-alkylphenyl ketones with CO_2 gave the carboxylic acid by irradiation with UV light or solar light.[1520] Ketones $RCOCH_2R'$ (as well as other active hydrogen compounds) undergo base-catalyzed addition to CS_2[1521] to give a dianion intermediate $RCOC^-R'CSS^{2-}$, which can be dialkylated with a halide R^2X to produce α-dithiomethylene ketones $RCOCR'{=}C(SR^2)_2$.[1522] Compounds of the form ZCH_2Z' also react with bases and CS_2 to give analogous dianions.[1523]

OS **VII**, 476. See also, OS **VIII**, 578.

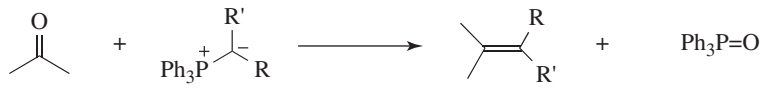
16-43 Tollens′ Reaction



In the *Tollens' reaction* an aldehyde or ketone containing an α hydrogen is treated with formaldehyde in the presence of $Ca(OH)_2$ or a similar base. The first step is formation of an enolate anion and a mixed aldol reaction (**16-34**). The reaction can be stopped at this point, but more often a second equivalent of formaldehyde is permitted to reduce the newly formed aldol to a 1,3-diol, in a *crossed Cannizzaro reaction* (**19-85**). If the aldehyde or ketone has several α hydrogen atoms, they can all be replaced. An important use of the reaction is to prepare pentaerythritol [$C(CH_2OH)_4$] by reaction of acetaldehyde with 4 or more equivalents of formaldehyde.

OS **I**, 425; **IV**, 907; **V**, 833.

16-44 The Wittig Reaction[1524]



In the *Wittig reaction* an aldehyde or ketone is treated with a *phosphorus ylid* (a *phosphorane*; also spelled ylide) to give an alkene.[1525] The conversion of a carbonyl compound to

[1519] Tirpak, R.E.; Olsen, R.S.; Rathke, M.W. *J. Org. Chem.* ***1985***, *50*, 4877. For an enantioselective version, see Hogeveen, H.; Menge, W.M.P.B. *Tetrahedron Lett.* ***1986***, *27*, 2767.

[1520] Masuda, Y.; Ishida, N.; Murakami, M. *J. Am. Chem. Soc.* ***2015***, *137*, 14063.

[1521] See Dunn, A.D.; Rudorf, W. *Carbon Disulphide in Organic Chemistry*, Ellis Horwood, Chichester, ***1989***, pp. 120–225; Yokoyama, M.; Imamoto, T. *Synthesis* ***1984***, 797, pp. 797–804.

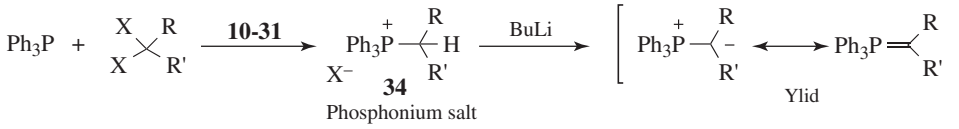
[1522] See Corey, E.J.; Chen, R.H.K. *Tetrahedron Lett.* ***1973***, 3817.

[1523] See Konen, D.A.; Pfeffer, P.E.; Silbert, L.S. *Tetrahedron* ***1976***, *32*, 2507, and references cited therein.

[1524] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 629–641.

[1525] See Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***; Johnson, A.W. *Ylid Chemistry*, Academic Press, NY, ***1966***. For reviews, see Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* ***1989***, *89*, 863; Bestmann, H.J.; Vostrowsky, O. *Top. Curr. Chem.* ***1983***, *109*, 85; Pommer, H.; Thieme, P.C. *Top. Curr. Chem.* ***1983***, *109*, 165; Maercker, A. *Org. React.* ***1965***, *14*, 270. For related reviews, see Zbiral, E. *Synthesis* ***1974***,

an alkene with a phosphorus ylid is called the *Wittig reaction*. Phosphorus ylids are usually prepared by treatment of a phosphonium salt with a base,[1526] and phosphonium salts (**34**) are usually prepared from a triarylphosphine, or a phosphine that does not have an α hydrogen, and an alkyl halide (**10-30**).



The reaction of triphenylphosphine and an alkyl halide is facilitated by the use of microwave irradiation.[1527] Indeed, the Wittig reaction itself is assisted by microwave irradiation.[1528] Phosphonium salts are also prepared by addition of phosphines to *Michael alkenes* (like **15-8**) and in other ways.[1529]

If an alkyl halide is viewed as the starting material in the reaction

alkyl halide phosphonium salt → phosphorus ylid → alkene

then the halogen-bearing carbon of an alkyl halide must contain at least one hydrogen, for deprotonation at the phosphonium salt stage.

The phosphonium salts are most often converted to the ylids by treatment with a strong base such as butyllithium, sodium amide,[1530] sodium hydride, or a sodium alkoxide, though weaker bases can be used if the salt is acidic enough. In some cases an excess of fluoride ion is sufficient.[1531] For $(Ph_3P^+)_2CH_2$, sodium carbonate is a strong-enough base.[1532] When the base used does not contain lithium, the ylid is said to be prepared under "salt-free" conditions[1533] because the lithium halide (where the halide counterion comes from the phosphonium salt) is absent. Wittig reactions can be done in aqueous media in the presence of surfactants.[1534]

When the phosphorus ylid reacts with the aldehyde or ketone to form an alkene, a phosphine oxide is also formed. When triphenylphosphine is used to give $Ph_3P{=}CRR'$, for example, the by-product is triphenylphosphine oxide, Ph_3PO, which is sometimes difficult

775; Bestmann, H.J. *Angew. Chem. Int. Ed.* ***1965***, *4*, 583 (pp. 645–660, 830–838); *Newer Methods Prep. Org. Chem.* ***1968***, *5*, 1; Horner, L. *Fortschr. Chem. Forsch.* ***1966***, *7*, 1. For a historical background, see Wittig, G. *Pure Appl. Chem.* ***1964***, *9*, 245. For a list of reagents and references for the Wittig and related reactions, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 327–337.

[1526] Amberlite resin has been used as a base, see Valkute, T.R.; Aratikatla, E.K.; Bhattacharya, A.K. *Synth. Commun.* ***2017***, *47*, 581. When phosphonium *fluorides* are used, no base is necessary, as these react directly with the substrate to give the alkene: Schiemenz, G.P.; Becker, J.; Stöckigt, J. *Chem. Ber.* ***1970***, *103*, 2077.

[1527] Kiddle, J.J. *Tetrahedron Lett.* ***2000***, *41*, 1339.

[1528] Wu, J.; Wu, H.; Wei, S.; Dai, W.-M. *Tetrahedron Lett.* ***2004***, *45*, 4401.

[1529] Shimojuh, N.; Imura, Y.; Moriyama, K.; Togo, H. *Tetrahedron* ***2011***, *67*, 951; Xia, X.; Toy, P.H. *Synlett* ***2015***, *26*, 1737; Lebel, H.; Davi, M.; Roy, M.-N.; Zeghida, W.; Charette, A.B. *Synthesis* ***2011***, *43*, 2275.

[1530] See Schlosser, M.; Schaub, B. *Chimia* ***1982***, *36*, 396.

[1531] Kobayashi, T.; Eda, T.; Tamura, O.; Ishibashi, H. *J. Org. Chem.* ***2002***, *67*, 3156.

[1532] Ramirez, F.; Pilot, J.F.; Desai, N.B.; Smith, C.P.; Hansen, B.; McKelvie, N. *J. Am. Chem. Soc.* ***1967***, *89*, 6273.

[1533] Bestmann, H.J. *Angew. Chem. Int. Ed.* ***1965***, *4*, 586.

[1534] Orsini, F.; Sello, G.; Fumagalli, T. *Synlett* ***2006***, 1717.

to separate from the other reaction products. Other triarylphosphines[1535] and trialkylphosphines[1536] have been used, but phosphines that have an α hydrogen should be avoided, so that reaction with the chosen alkyl halide will lead to a phosphonium salt (**34**) with the α proton at the desired position. This limitation is essential if a specific ylid is to be formed from the alkyl halide precursor. The Wittig reaction has been carried out with polymer-supported ylids.[1537] It has also been done on silica gel.[1538] Polymer-bound aryldiphenylphosphino compounds[1539] have been used in reactions with alkyl halides to complete a Wittig reaction.

The reaction is very general.[1540] The aldehyde or ketone may be aliphatic, alicyclic, or aromatic (including diaryl ketones). Wittig reactions are known in which the ylid and/or the carbonyl substrate contain double or triple bonds. Various functional groups may be present, such as OH, OR, NR_2, aromatic nitro or halo, acetal, amide,[1541] or even ester groups.[1542] An important advantage of the Wittig reaction is that the *position* of the new double bond is always certain, in contrast to the result in most of the base-catalyzed condensations (**16-34** to **16-43**).

β-Lactams have been converted to alkenyl azetidine derivatives using phosphorus ylids.[1543] Double or triple bonds *conjugated* with the carbonyl also do not interfere, the attack being at the C=O carbon.

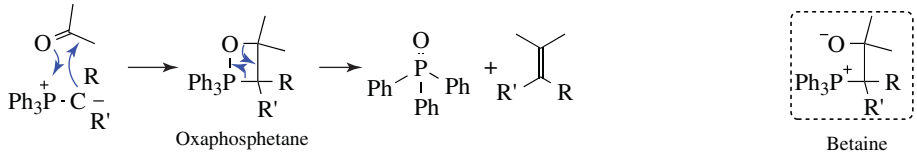
As noted above, the phosphorus ylid may also contain double or triple bonds and certain functional groups. Simple ylids (R, R′ = hydrogen or alkyl) are highly reactive, reacting with oxygen, water, hydrohalic acids, and alcohols, as well as carbonyl compounds and carboxylic esters, so the reaction must be run under conditions where these materials are absent. When an electron-withdrawing group, for example, COR, CN, CO_2R, CHO, is present in the α position, the ylids are much more stable, because the charge on the carbon is delocalized by resonance. Such ylids react readily with aldehydes, but slowly or not at all with ketones.[1544] In extreme cases (e.g., where the carbanion unit is part of the aromatic cyclopentadienyl anion), the ylid does not react with ketones *or* aldehydes. Besides these groups, the ylid may contain one or two α halogens[1545] or an α OR or OAr group. In the latter case, the product of the reaction with an aldehyde or ketone is an enol ether, which can be hydrolyzed (**10-6**) to an aldehyde,[1546] so that this reaction is a means of achieving the conversion RCOR′ → RR′CHCHO.[1547] However, the ylid may not contain an α nitro group. If the phosphonium salt contains a potential leaving group, such as Br or OMe, in

[1535] Schiemenz, G.P.; Thobe, J. *Chem. Ber.* ***1966***, *99*, 2663.
[1536] See Bestmann, H.J.; Kratzer, O. *Chem. Ber.* ***1962***, *95*, 1894.
[1537] Bernard, M.; Ford, W.T.; Nelson, E.C. *J. Org. Chem.* ***1983***, *48*, 3164.
[1538] Patil, V.J.; Mävers, U. *Tetrahedron Lett.* ***1996***, *37*, 1281.
[1539] Betancort, J.M.; Barbas III, C.F. *Org. Lett.* ***2001***, *3*, 3737.
[1540] See Dunne, E.C.; Coyne, É.J.; Crowley, P.B.; Gilheany, D.G. *Tetrahedron Lett.* ***2002***, *43*, 2449.
[1541] Smith, M.B.; Kwon, T.W. *Synth. Commun.* ***1992***, *22*, 2865. Also see Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2004***, *126*, 7559.
[1542] See Harcken, C.; Martin, S.F. *Org. Lett.* ***2001***, *3*, 3591; Yu, X.; Huang, X. *Synlett* ***2002***, 1895.
[1543] Baldwin, J.E.; Edwards, A.J.; Farthing, C.N.; Russell, A.T. *Synlett* ***1993***, 49.
[1544] See Isaacs, N.S.; El-Din, G.N. *Tetrahedron Lett.* ***1987***, *28*, 2191. See also, Dauben, W.G.; Takasugi, J.J. *Tetrahedron Lett.* ***1987***, *28*, 4377.
[1545] See Stork, G.; Zhao, K. *Tetrahedron Lett.* ***1989***, *30*, 2173.
[1546] See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1441–1444, 1457–1458.
[1547] See Ceruti, M.; Degani, I.; Fochi, R. *Synthesis* ***1987***, 79; Moskal, J.; van Leusen, A.M. *Recl. Trav. Chim. Pays-Bas* ***1987***, *106*, 137; Doad, G.J.S. *J. Chem. Res. (S)* ***1987***, 370.

the β position, treatment with a base gives elimination and the product is the vinyl phosphonium salt rather than the ylid. However, a β COO^- group may be present, and the product is a β,γ-unsaturated acid.[1548] This approach is the only convenient way to make these compounds, since elimination by any other route gives the thermodynamically more stable α,β-unsaturated isomers, which is an illustration of the utility of the Wittig method for the specific location of a double bond. Another illustration is the conversion of cyclohexanones to alkenes containing exocyclic double bonds (e.g., cyclohexanone to methylenecyclohexane).[1549] Still another example is the formation of *anti-Bredt* bicycloalkenones[1550] (Sec. 4.Q.iii).

As indicated above, α,α′-dihalophosphoranes can be used to prepare 1,1-dihaloalkenes. Another way to prepare haloalkenes[1551] is to treat the carbonyl compound with a mixture of CX_4 (X = Cl, Br, or I) and triphenylphosphine, either with or without the addition of zinc dust (which allows less Ph_3P to be used).[1552] Aryl aldehydes react with these dihalophosphoranes to give aryl alkynes after treatment of the initially formed vinyl halide with potassium *tert*-butoxide.[1553] Functionalized styrenes including terminal 1,3-dienes have been prepared from benzylic and allylic alcohols by initial reaction with Et_3P•HBr under microwave conditions, followed by reaction with aqueous formalin and K_2CO_3 under microwave conditions.[1554] A photochemical Wittig reaction has been reported.[1555]

The generally accepted mechanism[1556] of the key step of the Wittig reaction is as shown.[1557]



The energetics of ylid formation and their reaction is solution has been studied.[1558] For many years it was assumed that a diionic compound, called a *betaine*,[1559] is an intermediate on the pathway from the starting compounds to the oxaphosphetane, but it has been

[1548] Corey, E.J.; McCormick, J.R.D.; Swensen, W.E. *J. Am. Chem. Soc.* ***1964***, *86*, 1884.
[1549] Wittig, G.; Schöllkopf, U. *Chem. Ber.* ***1954***, *87*, 1318.
[1550] Bestmann, H.J.; Schade, G. *Tetrahedron Lett.* ***1982***, *23*, 3543.
[1551] For a list of references to the preparation of haloalkenes by Wittig reactions, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 725–727.
[1552] See Li, P.; Alper, H. *J. Org. Chem.* ***1986***, *51*, 4354.
[1553] Michel, P.; Gennet, D.; Rassat, A. *Tetrahedron Lett.* ***1999***, *40*, 8575. See Michael, P.; Rassat, A. *Tetrahedron Lett.* ***1999***, *40*, 8579.
[1554] Das, P.; McLeod, D.; McNulty, J. *Tetrahedron Lett.* ***2011***, *52*, 199.
[1555] Ghosh, S.; Das, J. *Tetrahedron Lett.* ***2011***, *52*, 1112.
[1556] See Cockerill, A.F.; Harrison, R.G. in Patai, S. *The Chemistry of Functional Groups: Supplement A*, pt. 1, Wiley, NY, ***1977***, pp. 232–240; Vedejs, E.; Marth, C.F. *J. Am. Chem. Soc.* ***1988***, *110*, 3948.
[1557] For a discussion of the second step, see López, J.G.; Ramallal, A.-M.; González, J.; Roces, L.; García-Granda, S.; Iglesias, M.J.; Oña-Burgos, P.; Ortiz, F.L. *J. Am. Chem. Soc.* ***2012***, *134*, 19504. It has been contended that another mechanism, involving single electron transfer, may be taking place in some cases: Olah, G.A.; Krishnamurthy, V.V. *J. Am. Chem. Soc.* ***1982***, *104*, 3987; Yamataka, H.; Nagareda, K.; Hanafusa, T.; Nagase, S. *Tetrahedron Lett.* ***1989***, *30*, 7187. A diradical mechanism has also been proposed for certain cases: Ward Jr., W.J.; McEwen, W.E. *J. Org. Chem.* ***1990***, *55*, 493.
[1558] Arnett, E.M.; Wernett, P.C. *J. Org. Chem.* ***1993***, *58*, 301.
[1559] See Schmidt, A.; Guan, Z. *Synthesis* ***2012***, *44*, 3251.

argued that there is little evidence for it.[1560] However, "betaine" precipitates have been isolated in certain Wittig reactions,[1561] although these are betaine/lithium halide adducts, and might just as well have been formed from the oxaphosphetane as from a true betaine.[1562] There is one report of a betaine lithium salt that was formed during the course of a Wittig reaction.[1563]

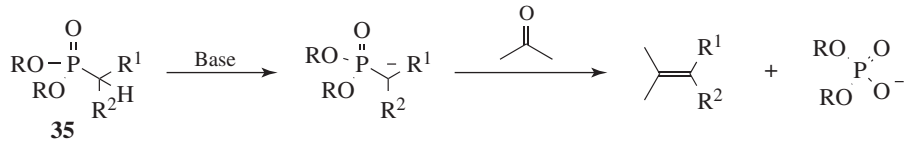
An X-ray structure was determined for a *gauche* betaine from a thio-Wittig reaction.[1564] In contrast, there is much evidence for the presence of the oxaphosphetane intermediates, at least with unstable ylids. For example, ^{31}P NMR spectra taken of the reaction mixtures at low temperatures[1565] are compatible with an oxaphosphetane structure that persists for some time but not with a tetra-coordinated phosphorus species. Since a betaine, an ylid, and a phosphine oxide all have tetracoordinated phosphorus, these species could not be causing the spectra, leading to the conclusion that an oxaphosphetane intermediate is present in the solution. In certain cases oxaphosphetanes have been isolated.[1566] It has been possible to detect *cis* and *trans* isomers of the intermediate oxaphosphetanes by NMR spectroscopy.[1567] According to this mechanism, an optically active phosphonium salt $RR^1R^2P^+CHR^2$ should retain its configuration all the way through the reaction, and it should be preserved in the phosphine oxide RR^1R^2PO. Such retention has been shown to be the case.[1568]

It is noted that the proposed betaine intermediates can be formed, in a completely different manner, by nucleophilic substitution by a phosphine on an epoxide (**10-34**). Betaines formed in this way can then be converted to the alkene, and this is one reason why betaine intermediates were long accepted in the Wittig reaction. It is also noteworthy that stable phosphonium enolate zwitterions have been formed by the reaction of an aryl aldehyde, a phosphine, and a propargylic ester.[1569]

Vinylogous Wittig reaction have been reported, using PBu_3 to mediate the reaction.[1570] Vinyl ethers were formed followed by hydrogenation using continuous flow techniques (Sec. 7.D).[1571] Phosphorus is not the only key element used to produce useful ylids. Triphenylarsine[1572] has been used. Tellurium ylids have been prepared *in situ* from α-halo esters and $BrTeBu_2OTeBu_2Br$ and react with aldehydes to give conjugated esters.[1573]

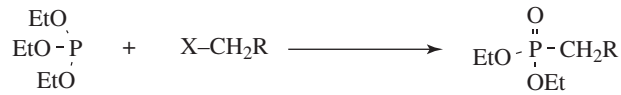
[1560] See Vedejs, E.; Marth, C.F. *J. Am. Chem. Soc.* ***1990***, *112*, 3905.
[1561] See Schlosser, M.; Christmann, K.F. *Liebigs Ann. Chem.* ***1967***, *708*, 1.
[1562] Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* ***1989***, *89*, 863 (see p. 865).
[1563] Neumann, R.A.; Berger, S. *Eur. J. Org. Chem.* ***1998***, 1085.
[1564] Puke, C.; Erker, G.; Wibbeling, B.; Fröhlich, R. *Eur. J. Org. Chem.* ***1999***, 1831.
[1565] Vedejs, E.; Meier, G.P.; Snoble, K.A.J. *J. Am. Chem. Soc.* ***1981***, *103*, 2823. See also, Nesmayanov, N.A.; Binshtok, E.V.; Reutov, O.A. *Dokl. Chem.* ***1973***, *210*, 499.
[1566] Mazhar-Ul-Haque; Caughlan, C.N.; Ramirez, F.; Pilot, J.F.; Smith, C.P. *J. Am. Chem. Soc.* ***1971***, *93*, 5229.
[1567] Maryanoff, B.E.; Reitz, A.B.; Mutter, M.S.; Inners, R.R.; Almond Jr., H.R.; Whittle, R.R.; Olofson, R.A. *J. Am. Chem. Soc.* ***1986***, *108*, 7664. See also, Pískala, A.; Rehan, A.H.; Schlosser, M. *Coll. Czech. Chem. Commun.* ***1983***, *48*, 3539.
[1568] McEwen, W.E.; Kumli, K.F.; Bladé-Font, A.; Zanger, M.; VanderWerf, C.A. *J. Am. Chem. Soc.* ***1964***, *86*, 2378.
[1569] Zhu, X.-F.; Henry, C.E.; Kwon, O. *J. Am. Chem. Soc.* ***2007***, *129*, 6722.
[1570] Xu, S.; Chen, R.; He, Z. *J. Org. Chem.* ***2011***, *76*, 7528.
[1571] Balti, M.; Efrit, M.L.; Leadbeater, N.E. *Tetrahedron Lett.* ***2016***, *57*, 1804.
[1572] Li, L.; Stimac, J.C.; Geary, L.M. *Tetrahedron Lett.* ***2017***, *58*, 1379; Lau, K.C.Y.; Chiu, P. *Tetrahedron* ***2011***, *67*, 8769; Wang, P.; Liu, C.-R.; Sun, X.-L.; Chen, S.-S.; Li, J.-F.; Xie, Z.; Tang, Y. *Chem. Commun.* ***2012***, *48*, 290. For a catalytic version, Huang, Z.-Z.; Huang, X.; Huang, Y.-Z. *Tetrahedron Lett.* ***1995***, *36*, 425.
[1573] Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* ***2002***, *67*, 5320.

The Wittig reaction has been carried out with phosphorus ylids other than phosphoranes, the most important being prepared from phosphonate esters such as **35**.[1574]



35

This method, called the *Horner-Emmons*, *Wadsworth-Emmons*, *Wittig-Horner*, or *Horner-Wadsworth-Emmons reaction*,[1575] has several advantages over the use of phosphoranes, including selectivity.[1576] Once formed, these ylids are more reactive than the corresponding phosphoranes, and when R^1 or R^2 is an electron-withdrawing group, these compounds often react with ketones that are inert to phosphoranes. High pressure has been used to facilitate this reaction.[1577] In addition, the phosphorus product is a phosphate ester and hence is soluble in water, unlike Ph_3PO, which makes it easy to separate it from the alkene product. Phosphonates are also cheaper than phosphonium salts and can easily be prepared by the *Arbuzov reaction*, which is the reaction of trialkoxyphosphines (trialkyl phosphite) with alkyl halides:[1578]



Phosphonates have also been prepared from alcohols and $(ArO)_2P(=O)Cl$, NEt_3, and a $TiCl_4$ catalyst.[1579] α-Aryl phosphonoacetates have been prepared and are useful synthetic precursors.[1580] The reaction of $(RO)_2P(=O)H$ and aryl iodides with a CuI catalyst leads to aryl phosphonates.[1581] Polymer-bound phosphonate esters have been used for olefination.[1582] Dienes are produced when allylic phosphonate esters react with aldehydes.[1583] Nucleophilicity parameters have been determined for phosphoryl-stabilized carbanions.[1584]

[1574] Horner, L.; Hoffmann, H.; Wippel, H.G.; Klahre, G. *Chem. Ber.* ***1959***, *92*, 2499; Wadsworth Jr., W.S.; Emmons, W.D. *J. Am. Chem. Soc.* ***1961***, *83*, 1733. See Boduszek, B.; Olszewski, T.K.; Goldeman, W.; Grzegolec, K.; Blazejewska, P. *Tetrahedron* ***2012***, *68*, 1223.

[1575] Wadsworth Jr., W.S. *Org. React.* ***1977***, *25*, 73; Stec, W.J. *Acc. Chem. Res.* ***1983***, *16*, 411; Walker, B.J. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 156–205; Boutagy, J.; Thomas, R. *Chem. Rev.* ***1974***, *74*, 87; Seguineau, P.; Villieras, J. *Tetrahedron Lett.* ***1988***, *29*, 477, and other papers in this series.

[1576] Motoyoshiya, J.; Kasaura, T.; Kokin, K.; Yokoya, S.-i.; Takaguchi, Y.; Narita, S.; Aoyama, H. *Tetrahedron* ***2001***, *57*, 1715.

[1577] Has-Becker, S.; Bodmann, K.; Kreuder, R.; Santoni, G.; Rein, T.; Reiser, O. *Synlett* ***2001***, 1395.

[1578] Also known as the *Michaelis-Arbuzov rearrangement*. For reviews, see Bhattacharya, A.K.; Thyagarajan, G. *Chem. Rev.* ***1981***, *81*, 415. See also Shokol, V.A.; Kozhushko, B.N. *Russ. Chem. Rev.* ***1985***, *53*, 98; Brill, T.B.; Landon, S.J. *Chem. Rev.* ***1984***, *84*, 577. See Rajeshwaran, G.G.; Nandakumar, M.; Sureshbabu, R.; Mohanakrishnan, A.K. *Org. Lett.* ***2011***, *13*, 1270; Yang, G.; Shen, C.; Zhang, L.; Zhang, W. *Tetrahedron Lett.* ***2011***, *52*, 5032.

[1579] Jones, S.; Selitsianos, D. *Org. Lett.* ***2002***, *4*, 3671.

[1580] VanGelder, K.F.; Wang, M.; Kozlowski, M.C. *J. Org. Chem.* ***2015***, *80*, 10288.

[1581] Gelman, D.; Jiang, L.; Buchwald, S.L. *Org. Lett.* ***2003***, *5*, 2315.

[1582] Barrett, A.G.M.; Cramp, S.M.; Roberts, R.S.; Zecri, F.J. *Org. Lett.* ***1999***, *1*, 579.

[1583] Wang, Y.; West, F.G. *Synthesis* ***2002***, 99.

[1584] Appel, R.; Loos, R.; Mayr, H. *J. Am. Chem. Soc.* ***2009***, *131*, 704.

A Zn-promoted reaction is known using diprotic phosphonates.[1585] Wittig reactions of stabilized phosphorus ylids have also been done in water.[1586] The reaction of diethyl 3-diazo-2-oxopropylphosphonate and aldehydes in the presence of a base gave α,β-unsaturated diazo ketones via a Horner-Wadsworth-Emmons reaction.[1587]

Stereoselective alkenylation reactions have been achieved using chiral additives[1588] or auxiliaries.[1589] The stereoselectivity of the reaction has been linked to steric effects.[1590] (*Z*)-selective reagents are known.[1591] The reaction of a functionalized aldehyde (R—CHO) with $(MeO)_2POCHN_2$ leads to an alkyne (R—C≡CH).[1592] Organocatalytic asymmetric Wittig reactions have been reported,[1593] and microwave-assisted catalytic Wittig reactions are known.[1594] The phospholane-catalyzed Wittig reaction is known.[1595] Catalytic intramolecular Wittig reactions have been reported.[1596] An interesting intramolecular version of the Horner-Emmons reaction leads to alkynes.[1597]

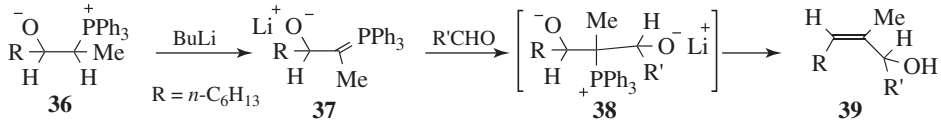
Some Wittig reactions give the (*Z*)-alkene; some the (*E*)-alkene, and others give mixtures, and the question of which factors determine the stereoselectivity has been much studied.[1598] It is generally found that ylids containing stabilizing groups or formed from trialkylphosphines give (*E*)-alkenes. Keto-stabilized ylids reacted with *ortho*-heteroatom-substituted benzaldehdyes to give higher than expected amounts of (*Z*)-alkenes.[1599] The origin of the (*E*)-selectivity in salt-free stabilized ylids may be related to dipole–dipole interactions.[1600] The energy of the elimination transition state must also be taken into account.[1601] It has been shown that ylids formed from triarylphosphines and not containing stabilizing groups often give (*Z*)-alkenes or a mixture of (*Z*)- and (*E*)-alkenes.[1602] One explanation for this[1568] is that the reaction of the ylid with the carbonyl compound is a [2 + 2] cycloaddition,

[1585] Schauer, D.J.; Helquist, P. *Synthesis* ***2006***, 3654.
[1586] Wu, J.; Li, D.; Zhang, D. *Synth. Commun.* ***2005***, *35*, 2543. See also McNulty, J.; Das, P.; McLeod, D. *Chem. Eur. J.* ***2010***, *16*, 6756.
[1587] Pinho, V.D.; Burtoloso, A.C.B. *J. Org. Chem.* ***2011***, *76*, 289.
[1588] Mizuno, M.; Fujii, K.; Tomioka, K. *Angew. Chem. Int. Ed.* ***1998***, *37*, 515. Also see, Arai, S.; Hamaguchi, S.; Shioiri, T. *Tetrahedron Lett.* ***1998***, *39*, 2997. For a review of asymmetric Wittig-type reactions see Rein, T.; Pedersen, T.M. *Synthesis* ***2002***, 579.
[1589] Abiko, A.; Masamune, S. *Tetrahedron Lett.* ***1996***, *37*, 1077.
[1590] Stępień, M. *J. Org. Chem.* ***2013***, *78*, 9512. See Byrne, P.A.; Muldoon, J.; Ortin, Y.; Müller-Bunz, H.; Gilheany, D.G. *Eur. J. Org. Chem.* ***2014***, 86. See Molnár, K.; Takács, L.; Kádár, M.; Faigi, F.; Kardos, Z. *Synth. Commun.* ***2017***, *47*, 1214.
[1591] Ando, K. *Tetrahedron Lett.* ***1995***, *36*, 4105.
[1592] Hauske, J.R.; Dorff, P.; Julin, S.; Martinelli, G.; Bussolari, J. *Tetrahedron Lett.* ***1992***, *33*, 3715.
[1593] Gramigna, L.; Duce, S.; Filippini, G.; Fochi, M.; Franchini, M.C.; Bernardi, L. *Synlett* ***2011***, *22*, 2745. See O'Brien, C.J.; Nixon, Z.S.; Holohan, A.J.; Kunkel, S.R.; Tellez, J.L.; Doonan, B.J.; Coyle, E.E.; Lavigne, F.; Kang, L.J.; Przeworski, K.C. *Chem. Eur. J.* ***2013***, *19*, 15281.
[1594] Hoffmann, M.; Deshmukh, S.; Werner, T. *Eur. J. Org. Chem.* ***2015***, 4532.
[1595] Werner, T.; Hoffmann, M.; Deshmukh, S. *Eur. J. Org. Chem.* ***2015***, 3286.
[1596] Wang, L.; Sun, M.; Ding, M.-W. *Eur. J. Org. Chem.* ***2017***, 2568.
[1597] See Nangia, A.; Prasuna, G.; Rao, P.B. *Tetrahedron Lett.* ***1994***, *35*, 3755.
[1598] See Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* ***1989***, *89*, 863; Gosney, I.; Rowley, A.G. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 17–153; Reucroft, J.; Sammes, P.G. *Q. Rev. Chem. Soc.* ***1971***, *25*, 135 (see pp. 137–148, 169); Schlosser, M. *Top. Stereochem.* ***1970***, *5*, 1. Also see, Takeuchi, K.; Paschal, J.W.; Loncharich, R.J. *J. Org. Chem.* ***1995***, *60*, 156.
[1599] Byrne, P.A.; Higham, L.J.; McGovern, P.; Gilheany, D.G. *Tetrahedron Lett.* ***2012***, *53*, 6701.
[1600] Robiette, R.; Richardson, J.; Aggarwal, V.K.; Harvey, J.N. *J. Am. Chem. Soc.* ***2005***, *127*, 13468.
[1601] Robiette, R.; Richardson, J.; Aggarwal, V.K.; Harvey, J.N. *J. Am. Chem. Soc.* ***2006***, *128*, 2394.
[1602] See Le Bigot, Y.; El Gharbi, R.; Delmas, M.; Gaset, A. *Tetrahedron* ***1986***, *42*, 3813. Also see Schlosser, M.; Schaub, B.; de Oliveira-Neto, J.; Jeganathan, S. *Chimia* ***1986***, *40*, 244.

which in order to be concerted must adopt the $[_{\pi}2_{s} + _{\pi}2_{a}]$ pathway. As discussed in **15-59**, this pathway leads to the formation of the more sterically crowded product, in this case the (*Z*)-alkene. If this explanation is correct, it is not easy to explain the predominant formation of (*E*)-products from stable ylids, but (*E*)-compounds are of course generally thermodynamically more stable than the (*Z*)-isomers, and the stereochemistry seems to depend on many factors.

The (*E*/*Z*) ratio of the product can often be changed by a change in solvent or by the addition of salts.[1603] Another way of controlling the stereochemistry of the product is by use of the aforementioned phosphonic acid bisamides. In this case, the betaine does form and, when treated with water, gives the β-hydroxyphosphonic acid bisamides, which can be crystallized and then cleaved to $R^1R^2C{=}CR^3R^4$ by refluxing in benzene or toluene in the presence of silica gel.[1604] β-Hydroxy products are generally formed as mixtures of diastereomers, and these mixtures can be separated by recrystallization. Each diastereomer will give one of the two isomeric alkenes. Optically active phosphonic acid bis(amides) have been used to give optically active alkenes.[1605] Another method of controlling the stereochemistry of the alkene [to obtain either the (*Z*)- or (*E*)-isomer] starting with a phosphine oxide (Ph_2POCH_2R), has been reported.[1606]

In reactions where the betaine/lithium halide intermediate is present, it is possible to extend the chain further if a hydrogen is present α to the phosphorus. For example, reaction of ethylidenetriphenylphosphorane with heptanal at −78 °C gave **36**, and subsequent treatment with butyllithium gave the ylid, **37**. Treatment of **37** with an aldehyde R′CHO gave the intermediate **38** that gave, after workup, **39**[1607] stereoselectively.



36 **37** **38** **39**

Alkoxide **37** also reacts with other electrophiles. For example, treatment of **37** with NCS or $PhICl_2$ gave the vinylic chloride RCH=CMeCl stereoselectively: NCS gave the *cis* and $PhICl_2$ the *trans* isomer.[1608] The use of Br_2 and $FClO_3$ (note that several explosions have been observed with this reagent[1609]) gives the corresponding bromide or fluoride, respectively.[1610] Reactions of **37** with electrophiles have been called *scoopy reactions* (α substitution plus carbonyl alkenylation via β-oxido phosphorus ylids).[1611]

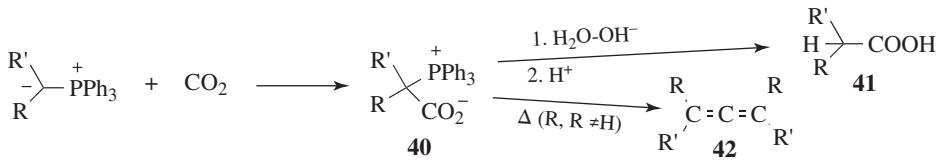
The reaction of a phosphonate ester, DBU, NaI, and HMPA with an aldehyde leads to a conjugated ester with excellent (*Z*)-selectivity.[1612] A (*Z*)-selective reaction was reported using a trifluoroethyl phosphonate in a reaction with an aldehyde and potassium *tert*-butoxide.[1613]

[1603] See Reitz, A.B.; Nortey, S.O.; Jordan Jr., A.D.; Mutter, M.S.; Maryanoff, B.E. *J. Org. Chem.* ***1986***, *51*, 3302.
[1604] Corey, E.J.; Cane, D.E. *J. Org. Chem.* ***1969***, *34*, 3053.
[1605] See Rein, T.; Reiser, O. *Acta Chem. Scand. B* ***1996***, *50*, 369. For a review of asymmetric ylid reactions, see Li, A.-H.; Dai, L.-X.; Aggarwal, V.K. *Chem. Rev.* ***1997***, *97*, 2341.
[1606] Ayrey, P.M.; Warren, S. *Tetrahedron Lett.* ***1989***, *30*, 4581.
[1607] See Schlosser, M.; Tuong, H.B.; Respondek, J.; Schaub, B. *Chimia* ***1983***, *37*, 10.
[1608] See Corey, E.J.; Shulman, J.I.; Yamamoto, H. *Tetrahedron Lett.* ***1970***, 447.
[1609] See Adcock, W.; Khor, T. *J. Organomet. Chem.* ***1975***, *91*, C20.
[1610] Schlosser, M.; Christmann, K.-F. *Synthesis* ***1969***, 38.
[1611] Schlosser, M. *Top. Stereochem.* ***1970***, *5*, 1 (p. 22).
[1612] Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* ***2000***, *65*, 4745.
[1613] Touchard, F.P. *Tetrahedron Lett.* ***2004***, *45*, 5519.

The Wittig reaction has been carried out intramolecularly, to prepare rings containing from 5 to 16 carbons,[1614] both by single ring closure to give cyclic alkenes, or by double ring closure, as in the conversion of 1,2-bis(triphenyphosphinomethyl)benzene to (5*Z*,11*Z*)-dibenzo[*a*,*e*][8]annulene).[1615]

The Wittig reaction has proved very useful in the synthesis of natural products, some of which are quite difficult to prepare in other ways.[1616]

Phosphorus ylids also react in a similar manner with the C═O bonds of ketenes,[1617] isocyanates,[1618] certain anhydrides,[1619] lactones,[1620] and imides,[1621] with the N═O of nitroso groups, and with the C═N of imines.[1622] Phosphorus ylids react with carbon dioxide to give isolable salts such as **40**,[1623] which can be hydrolyzed to the carboxylic acids **41** (thus achieving the conversion RR′CHX → RR′CHCOOH) or (if neither R nor R′ is hydrogen) dimerized to allenes (**42**).

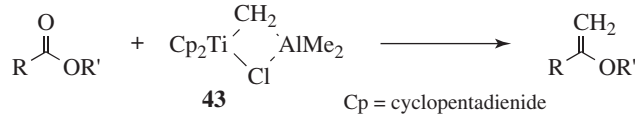


Although phosphorus ylids are most commonly used for alkenylation reactions, nitrogen ylids can occasionally be used.[1624] However, nitrogen ylids are often difficult to form, unstable, and highly reactive. The reaction of *N*-benzyl-*N*-phenylpiperidinium bromide with base to give a *N*-ylid is one example, and it reacted with benzaldehyde to form styrene.[1625] The structure has been determined for an intermediate in an *aza-Wittig reaction*.[1626] An aza-Wittig reaction[1627] has been used to prepare pyrrolines and tetrahydropyridines.[1628] A boron-Wittig reaction with aldehydes gave vinyl boronates.[1629]

OS **V**, 361, 390, 499, 509, 547, 751, 949, 985; **VI**, 358; **VII**, 164, 232; **VIII**, 265, 451; **75**, 139, OS **IX**, 39, 230.

[1614] For a review, see Becker, K.B. *Tetrahedron* ***1980***, *36*, 1717.
[1615] For a review of these double ring closures, see Vollhardt, K.P.C. *Synthesis* ***1975***, 765.
[1616] See Bestmann, H.J.; Vostrowsky, O. *Top. Curr. Chem.* ***1983***, *109*, 85.
[1617] See Aksnes, G.; Frøyen, P. *Acta Chem. Scand.* ***1968***, *22*, 2347.
[1618] See Frøyen, P. *Acta Chem. Scand. Ser. B* ***1974***, *28*, 586.
[1619] See Kayser, M.M.; Breau, L. *Can. J. Chem.* ***1989***, *67*, 1401. For a study of the mechanism, see Abell, A.D.; Clark, B.M.; Robinson, W.T. *Aust. J. Chem.* ***1988***, *41*, 1243.
[1620] With microwave irradiation, see Sabitha, G.; Reddy, M.M.; Srinivas, D.; Yadov, J.S. *Tetrahedron Lett.* ***1999***, *40*, 165.
[1621] Murphy, P.J.; Brennan, J. *Chem. Soc. Rev.* ***1988***, *17*, 1; Flitsch, W.; Schindler, S.R. *Synthesis* ***1975***, 685.
[1622] Bestmann, H.J.; Seng, F. *Tetrahedron* ***1965***, *21*, 1373.
[1623] Bestmann, H.J.; Denzel, T.; Salbaum, H. *Tetrahedron Lett.* ***1974***, 1275.
[1624] For a review, see Jiang, K.; Chen, Y.-C. *Tetrahedron Lett.* ***2014***, *55*, 2049.
[1625] Lawrence, N.J.; Beynek, H. *Synlett* ***1998***, 497.
[1626] Kano, N.; Hua, X.J.; Kawa, S.; Kawashima, T. *Tetrahedron Lett.* ***2000***, *41*, 5237. See Okamoto, K.; Shimbayashi, T.; Tamura, E.; Ohe, K. *Chem. Eur. J.* ***2014***, *20*, 1490.
[1627] For a review, see Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J.M. *Tetrahedron* ***2007***, *63*, 523.
[1628] Singh, P.N.D.; Klima, R.F.; Muthukrishnan, S.; Murthy, R.S.; Sankaranarayanan, J.; Stahlecker, H.M.; Patel, B.; Gudmundsdóttir, A.D. *Tetrahedron Lett.* ***2005***, *46*, 4213.
[1629] Coombs, J.R.; Zhang, L.; Morken, J.P. *Org. Lett.* ***2015***, *17*, 1708.

16-45 Tebbe, Petasis, And Alternative Alkenylations[1630]



43 Cp = cyclopentadienide

A useful alternative to phosphorus ylids are Ti reagents such as **43** prepared from dicyclopentadienyltitanium dichloride and trimethylaluminum.[1631] Treatment of a carbonyl compound with **43** (the *Tebbe reagent*) in toluene/THF containing a small amount of pyridine[1632] leads to the alkene. Dimethyltitanocene (Me_2TiCp_2, the *Petasis reagent*) is a convenient, more stable, easier to prepare, and highly useful alternative to **43**.[1633] The mechanism of Petasis olefination has been examined.[1634] Both the Tebbe reagent and the Petasis reagent give good results with ketones.[1635] An important feature of these new reagents is their reaction with the C=O group of carboxylic esters and lactones[1636] which gave the corresponding enol ethers in good yields. The enol ether can be hydrolyzed to a ketone (**10-6**), so this is also an indirect method for making the conversion $RCO_2R' \rightarrow RCOCH_3$ (see also, **16-29**). Conjugated esters are converted to alkoxy dienes with this reagent.[1637] Lactams, including β-lactams, are converted to alkylidene cycloamines (alkylidene azetidines from β-lactams, which are easily hydrolyzed to β-amino ketones).[1638] Formation of alkenes using Petasis reagent has been done using flow conditions (Sec. 7.D).[1639]

Besides stability and ease of preparation, another advantage of the Petasis reagent is that structural analogs can be prepared, including $Cp_2Ti(C_3H_5)_2$[1640] (C_3H_5 = cyclopropyl), $CpTi(CH_2SiMe_3)_3$,[1641] $Me(i\text{-}PrO)_3Ti$,[1642] and $Cp_2TiMe(CH{=}CH_2)$.[1643] Accelerated Petasis reactions have been reported.[1644] An alternative Ti reagent was prepared using $TiCl_4$, Mg metal, and dichloromethane, reacting with both ketones[1645] and esters[1646] to give alkenes or vinyl ethers, respectively. Other catalysts have been used,[1647] including

[1630] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 644–653.

[1631] For *in situ* generation, see Cannizzo, L.F.; Grubbs, R.H. *J. Org. Chem.* ***1985***, *50*, 2386.

[1632] Tebbe, F.N.; Parshall, G.W.; Reddy, G.S. *J. Am. Chem. Soc.* ***1978***, *100*, 3611; Pine, S.H.; Pettit, R.J.; Geib, G.D.; Cruz, S.G.; Gallego, C.H.; Tijerina, T.; Pine, R.D. *J. Org. Chem.* ***1985***, *50*, 1212. See also, Clawson, L.; Buchwald, S.L.; Grubbs, R.H. *Tetrahedron Lett.* ***1984***, *25*, 5733; Clift, S.M.; Schwartz, J. *J. Am. Chem. Soc.* ***1984***, *106*, 8300.

[1633] Petasis, N.A.; Bzowej, E.I. *J. Am. Chem. Soc.* ***1990***, *112*, 6392. See Zhang, Y.-Q.; Jakoby, V.; Stainer, K.; Schmer, A.; Klare, S.; Bauer, M.; Grimme, S.; Cuerva, J.M.; Gansäuer, A. *Angew. Chem. Int. Ed.* ***2016***, *55*, 1523.

[1634] Meurer, E.C.; Santos, L.S.; Pilli, R.A.; Eberlin, M.N. *Org. Lett.* ***2003***, *5*, 1391.

[1635] Pine, S.H.; Shen, G.S.; Hoang, H. *Synthesis* ***1991***, 165.

[1636] Martínez, I.; Andrews, A.E.; Emch, J.D.; Ndakala, A.J.; Wang, J.; Howell, A.R. *Org. Lett.* ***2003***, *5*, 399.

[1637] Petasis, N.A.; Lu, S.-P. *Tetrahedron Lett.* ***1995***, *36*, 2393.

[1638] Tehrani, K.A.; De Kimpe, N. *Tetrahedron Lett.* ***2000***, *41*, 1975. See Martínez, I.; Howell, A.R. *Tetrahedron Lett.* ***2000***, *41*, 5607.

[1639] Koch, S.; Löwe, H.; Kunz, H. *Synlett* ***2011***, *22*, 1978.

[1640] Petasis, N.A.; Browej, E.I. *Tetrahedron Lett.* ***1993***, *34*, 943. See Rassadin, V.A.; Six, Y. *Tetrahedron* ***2014***, *70*, 787.

[1641] Petasis, N.A.; Akritopoulou, I. *Synlett* ***1992***, 665.

[1642] Veguillas, M.; Solà, R.; Fernández-Ibañez, M.Á.; Maciá, B. *Tetrahedron: Asymmetry* ***2016***, *27*, 643.

[1643] Petasis, N.A.; Hu, Y.-H. *J. Org. Chem.* ***1997***, *62*, 782. Also see, Petasis, N.A.; Browej, E.I. *J. Org. Chem.* ***1992***, *57*, 1327.

[1644] Shi, X.; Hebrault, D.; Humora, M.; Kiesman, W.F.; Peng, H.; Talreja, T.; Wang, Z.; Xin, Z. *J. Org. Chem.* ***2012***, *77*, 1154.

[1645] Yan, T.H.; Tsai, C.-C.; Chien, C.-T.; Cho, C.-C.; Huang, P.-C. *Org. Lett.* ***2004***, *6*, 4961.

[1646] Yan, T.-H.; Chien, C.-T.; Tsai, C.-C.; Lin, K.-W.; Wu, Y.-H. *Org. Lett.* ***2004***, *6*, 4965.

[1647] Muncipinto, G.; Moquist, P.N.; Schreiber, S.L.; Schaus, S.E. *Angew. Chem. Int. Ed.* ***2011***, *50*, 8172.

copper.[1648] Alkenes are generated from ketones and alkyl iodides in the presence of a catalytic amount of $Cp_2Ti[P(OEt)_3]_2$.[1649] 1-Alkenyl bromides have been prepared using a $CHBr_3/TiCl_4/Mg$ system.[1650]

Enantioselective Petasis reactions using BINOL have been reported.[1651] The enantioselective preparation of allenes was reported using a "catalyst-traceless" Petasis reaction.[1652] The catalytic asymmetric Petasis reaction of vinylboranes has been reported.[1653]

Carboxylic esters undergo the conversion C═O → C═CHR (R = primary or secondary alkyl) when treated with $RCHBr_2$, Zn,[1654] and $TiCl_4$ in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.[1655] Metal carbene complexes[1656] $R_2C{=}ML_n$ (L = ligand), where M is a transition metal such as Zr, W, or Ta, have also been used to convert the C═O of carboxylic esters and lactones to CR_2.[1657] It is likely that the complex $Cp_2Ti{=}CH_2$ is an intermediate in the reaction with the Tebbe reagent. Indeed, Ti carbenoids have been used to convert carbonyl groups to the corresponding alkene.[1658]

Alternative alkene-forming reactions have been developed. The *Nysted reagent* (cyclodibromodi-μ-methylene[μ-(tetrahydrofuran)]trizinc)[1659] is commercially available, and it reacts with aldehydes or ketones in the presence of BF_3•etherate to give an alkene.[1660] Reaction with (*S*)-2-phenylpropanal, for example, gave an 82% yield of (*R*)-but-3-en-2-ylbenzene.[1661] Other metal-ylid type reagents have been developed, including a Cr-based reagent. The *Takai reaction*[1662] used an alkyl di-or triiodide in the presence of $CrCl_2$ to react with an aldehyde or ketone to generate an alkene moiety. A methylenation reaction for aldehydes and ketones used a Julia-type[1663] reagent, 1-methyl-2-(methylsulfonyl)benzimidazole.[1664] The Julia-Kocienski reaction[1665] prepared alkenes via reaction of aldehydes with benzothiazol-2-yl sulfones.[1666]

[1648] Morin, M.S.T.; Lu, Y.; Black, D.A.; Arndtsen, B.A. *J. Org. Chem.* ***2012***, *77*, 2013; Frauenlob, R.; García, C.; Bradshaw, G.A.; Burke, H.M.; Bergin, E. *J. Org. Chem.* ***2012***, *77*, 4445.

[1649] Takeda, T.; Shimane, K.; Ito, K.; Saeki, N.; Tsubouchi, A. *Chem. Commun.* ***2002***, 1974.

[1650] Bhorge, Y.R.; Chang, S.-H.; Chang, C.-T.; Yan, T.-H. *Tetrahedron* ***2012***, *68*, 4846.

[1651] Han, W.-Y.; Zuo, J.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* ***2013***, *69*, 537.

[1652] Jiang, Y.; Diagne, A.B.; Thomson, R.J.; Schaus, S.E. *J. Am. Chem. Soc.* ***2017***, *139*, 1998; Periasamy, M.; Sanjeevakumar, N.; Dalai, M.; Gurubrahamam, R.; Reddy, P.O. *Org. Lett.* ***2012***, *14*, 2932.

[1653] Shi, X.; Kiesman, W.F.; Levina, A.; Xin, Z. *J. Org. Chem.* ***2013***, *78*, 9415.

[1654] Ishino, Y.; Mihara, M.; Nishihama, S.; Nishiguchi, I. *Bull. Chem. Soc. Jpn.* ***1998***, *71*, 2669.

[1655] See Matsubra, S.; Ukai, K.; Mizuno, T.; Utimoto, K. *Chem. Lett.* ***1999***, 825.

[1656] For a review, see Aguero, A.; Osborn, J.A. *New J. Chem.* ***1988***, *12*, 111.

[1657] See Hartner Jr., F.W.; Schwartz, J.; Clift, S.M. *J. Am. Chem. Soc.* ***1990***, *105*, 640.

[1658] Hartley, R.C.; Li, J.; Main, C.A.; McKiernan, G.J. *Tetrahedron* ***2007***, *63*, 4825.

[1659] Nysted, L.N. *US Patent* 3,865,848, ***1975*** (*Chem. Abstr.* ***1975***, *83*, 10406q); Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis*, 2nd ed., Wiley-Interscience, NJ, ***2005***, p. 826.

[1660] See Haahr, A.; Rankovic, Z.; Hartley, R.C. *Tetrahedron Lett.* ***2011***, *52*, 3020.

[1661] Matsubara, S.; Sugihara, M.; Utimoto, K. *Synlett* ***1998***, 313.

[1662] Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* ***1986***, *108*, 7408; Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* ***1987***, *109*, 951; Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis*, 2nd ed., Wiley-Interscience, NJ, ***2005***, pp. 640–641.

[1663] For reviews, see: Blakemore, P.R. *J. Chem. Soc., Perkin Trans. 1* ***2002***, 2563; Aiśsa, C. *Eur. J. Org. Chem.* ***2009***, 1831. See Pospíšil, J. *Tetrahedron Lett.* ***2011***, *52*, 2348.

[1664] Ando, K.; Kobayashi, T.; Uchida, N. *Org. Lett.* ***2015***, *17*, 2554. Also see Srimani, D.; Leitus, G.; Ben-David, Y.; Milstein, D. *Angew. Chem. Int. Ed.* ***2014***, *53*, 11092.

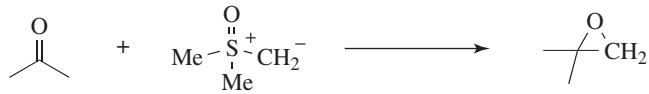
[1665] For a review, see Chatterjee, B.; Bera, S.; Mondal, D. *Tetrahedron: Asymmetry* ***2014***, *25*, 1.

[1666] Julia, M.; Paris, J.-M. *Tetrahedron Lett.* ***1973***, *14*, 4833; Blakemore, P.R. *J. Chem. Soc., Perkin Trans. 1* ***2002***, 2563; Kocienski, P.J.; Lythgoe, B. *J. Chem. Soc., Perkin Trans, 1* ***1980***, 1045; Bellingham, R.; Jarowicki, K.; Kocienski, P.; Martin, V. *Synthesis*, ***1996***, 285. See Pospíšil, J. *Tetrahedron Lett.* ***2011***, *52*, 2348; Ayeni, D.O.; Mandal, S.K.; Zajc, B. *Tetrahedron Lett.* ***2013***, *54*, 6008.

There are a few other methods for converting ketones or aldehydes to alkenes.[1667] Carbonyl compounds react with bis(iodozincio)methane to give alkenes.[1668] When a ketone is treated with CH_3CHBr_2/Sm/SmI_2, with a catalytic amount of $CrCl_3$, the alkene is formed.[1669] α-Halo esters also react with $CrCl_2$ in the presence of a ketone to give vinyl halides.[1670] Organozinc reagents have been used to convert carbonyl compounds to alkenes in the presence of Lewis acids.[1671] α-Diazo esters react with ketones in the presence of an Fe catalyst to give the corresponding alkene.[1672] α-Diazo silylalkanes react similarly in the presence of a Rh catalyst.[1673] Ketone olefination has been accomplished using methyltrioxorhenium.[1674] α-Halosulfones react with aldehydes in the presence of LiHMDS and $MgBr_2$•OEt_2 to give a vinyl chloride.[1675] It is noted that an engineered myoglobin variant catalyzed the reaction of aldehydes and α-diazo esters to give the alkene with excellent (*E*) diastereoselectivity.[1676]

OS **VIII**, 512, **IX**, 404; **X**, 355.

16-46 The Formation of Epoxides from Aldehydes and Ketones



44

Aldehydes and ketones can be converted to epoxides[1677] in good yields with the sulfur ylids[1678] dimethyloxosulfonium methylid (**44**)[1679] and dimethylsulfonium methylid (**45**).[1680] The chemoselectivity, regioselectivity, and diastereoselectivity of reactions of

[1667] See List, B.; Doehring, A.; Fonseca, M.T.H.; Job, A.; Torres, R.R. *Tetrahedron* ***2006***, *62*, 476.

[1668] Sada, M.; Komagawa, S.; Uchiyama, M.; Kobata, M.; Mizuno, T.; Utimoto, K.; Oshima, K.; Matsubara, S. *J. Am. Chem. Soc.* ***2010***, *132*, 17452.

[1669] Matsubara, S.; Horiuchi, M.; Takai, K.; Utimoto, K. *Chem. Lett.* ***1995***, 259. See also, Concellón, J.M.; Concellón, C. *J. Org. Chem.* ***2006***, *71*, 1728.

[1670] Barma, D.K.; Kundu, A.; Zhang, H.; Mioskowski, C.; Falck, J.R. *J. Am. Chem. Soc.* ***2003***, *125*, 3218.

[1671] Peng, Z.-Y.; Ma, F.-F.; Zhu, L.-F.; Xie, X.-M.; Zhang, Z. *J. Org. Chem.* ***2009***, *74*, 6855.

[1672] Chen, Y.; Huang, L.; Zhang, X.P. *Org. Lett.* ***2003***, *5*, 2493; Aggarwal, V.K.; Fulton, J.R.; Sheldon, C.G.; de Vincente, J. *J. Am. Chem. Soc.* ***2003***, *125*, 6034.

[1673] Lebel, H.; Guay, D.; Paquet, V.; Huard, K. *Org. Lett.* ***2004***, *6*, 3047. For a synthesis of dienes from conjugated aldehydes, see Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* ***2004***, *126*, 320.

[1674] Pedro, F.M.; Hirner, S.; Kühn, F.E. *Tetrahedron Lett.* ***2005***, *46*, 7777.

[1675] Lebrun, M.-E.; Le Marquand, P.; Berthelette, C. *J. Org. Chem.* ***2006***, *71*, 2009.

[1676] Tyagi, V.; Fasan, R. *Angew. Chem. Int Ed.* ***2016***, *55*, 2512.

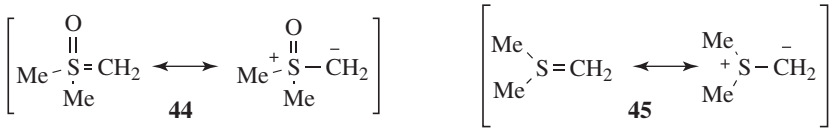
[1677] See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 101–105; Berti, G. *Top. Stereochem.* ***1973***, *7*, 93, pp. 218–232. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 944–951.

[1678] The bond enthalpies for S and Se ylids have been determined. See Stoffregen, S.A.; McCulla, R.D.; Wilson, R.; Cercone, S.; Miller, J.; Jenks, W.S. *J. Org. Chem.* ***2007***, *72*, 8235. See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 641–646.

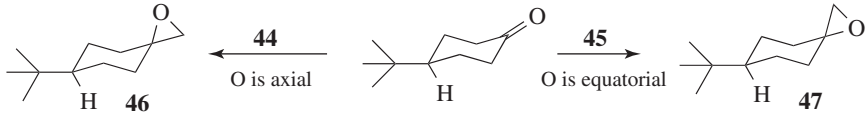
[1679] See Paxton, R.J.; Taylor, R.J.K. *Synlett* ***2007***, 633.

[1680] See Kavanagh, S.A.; Piccinini, A.; Fleming, E.M.; Connon, S.J. *Org. Biomol. Chem.* ***2008***, *6*, 1339. For reviews, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 709–733; Durst, T. *Adv. Org. Chem.* ***1969***, *6*, 285 (see pp. 321–330). For a monograph on sulfur ylids, see Trost, B.M.; Melvin Jr., L.S. *Sulfur Ylids*, Academic Press, NY, ***1975***.

sulfur ylids with enones has been examined.[1681] Ylid **45** is rather unstable and ordinarily must be used as soon as it is formed, while **44** can be stored for several days at room temperature. When diastereomeric epoxides can be formed, **45** usually attacks from the more-hindered side and **44** from the less-hindered side.



Thus, if 4-*tert*-butylcyclohexanone is treated with **44** it gives exclusively **46** with an axial O, while **45** gives mostly **47** with an equatorial O.[1682]

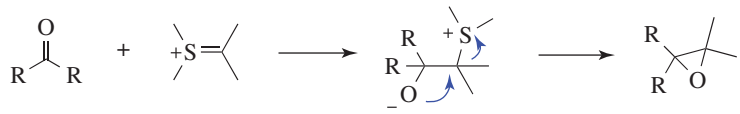


Another difference in behavior between the two reagents is that with α,β-unsaturated ketones, **44** gives only cyclopropanes (reaction **15-60**), while **45** gives oxirane formation. Other sulfur ylids have been used in an analogous manner, to transfer CHR or CR_2.[1683] A solvent-free version of this reaction has been developed using powdered potassium *tert*-butoxide and $Me_3S^+I^-$.[1684] Note that treatment of epoxides with 2 equivalents of $Me_2S{=}CH_2$ leads to allylic alcohols.[1685] Note too that phosphorus ylids do not give this epoxidation reaction, but give **16-44** instead.

Chiral sulfur ylids[1686] have been prepared, giving the epoxide with good asymmetric induction,[1687] and chiral additives have also been used.[1688] Chiral Se ylids have been used in a similar manner.[1689] Cyclic sulfur ylids have been used to prepare epoxy amides.[1690]

The generally accepted mechanism for the reaction between sulfur ylids and aldehydes or ketone is formation of **48**, with displacement of the Me_2S leaving group by the alkoxide.[1691]

[1681] Janardanan, D.; Sunj, R.B. *Org. Biomol. Chem.* ***2011***, *9*, 1642.
[1682] Corey, E.J.; Chaykovsky, M. *J. Am. Chem. Soc.* ***1965***, *87*, 1353.
[1683] Adams, J.; Hoffman Jr., L.; Trost, B.M. *J. Org. Chem.* ***1970***, *35*, 1600; Braun, H.; Huber, G.; Kresze, G. *Tetrahedron Lett.* ***1973***, 4033; Corey, E.J.; Jautelat, M.; Oppolzer, W. *Tetrahedron Lett.* ***1967***, 2325.
[1684] Toda, F.; Kanemoto, K. *Heterocycles* ***1997***, *46*, 185.
[1685] Alcaraz, L.; Harnett, J.J.; Mioskowski, C.; Martel, J.P.; Le Gall, T.; Shin, D.-S.; Falck, J.R. *Tetrahedron Lett.* ***1994***, *35*, 5449. Also see, Alcaraz, L.; Harnett, J.J.; Mioskowski, C.; Martel, J.P.; Le Gall, T.; Shin, D.-S.; Falck, J.R. *Tetrahedron Lett.* ***1994***, *35*, 5453.
[1686] See Aggarwal, V.K.; Angelaud, R.; Bihan, D.; Blackburn, P.; Fieldhouse, R.; Fonguerna, S.J.; Ford, G.D.; Hynd, G.; Jones, E.; Jones, R.V.H.; Jubault, P.; Palmer, M.J.; Ratcliffe, P.D.; Adams, H. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 2604.
[1687] See Sone, T.; Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2008***, *130*, 10078.
[1688] Hansch, M.; Illa, O.; McGarrigle, E.M.; Aggarwal, V.K. *Chem. Asian J.* ***2008***, *3*, 1657.
[1689] See Takada, H.; Metzner, P.; Philouze, C. *Chem. Commun.* ***2001***, 2350.
[1690] Sarabia, F.; Vivar-García, C.; García-Castro, M.; Martín-Ortiz, J. *J. Org. Chem.* ***2011***, *76*, 3139.
[1691] See Aggarwal, V.K.; Harvey, J.N.; Richardson, J. *J. Am. Chem. Soc.* ***2002***, *124*, 5747.



48

This mechanism is similar to that of the reaction of sulfur ylids with C═C double bonds (**15-60**).[1692] The stereochemical difference in the behavior of **44** and **45** has been attributed to formation of the betaine **48** being reversible for **44** but not for the less stable **45** The result is that the more-hindered product is the result of kinetic control and the less-hindered product is the result of thermodynamic control.[1693]

The *Juliá-Colonna epoxidation* is an asymmetric poly(leucine)-catalyzed epoxidation of electron-deficient alkenes.[1694] Supramolecular catalysis of this reaction has been reported.[1695] The stereoselectivity of this reaction has been inverted.[1696]

Aldehydes and ketones can also be converted to epoxides by treatment with a diazoalkane,[1697] most commonly diazomethane, but an important side reaction is the formation of an aldehyde or ketone with one more carbon than the starting compound (reaction **18-9**). The reaction can be carried out with many aldehydes, ketones, and quinones, usually with a Rh catalyst.[1698]

An alternative route to epoxides from ketones uses α-chloro sulfones and potassium *tert*-butoxide to give α,β-epoxy sulfones.[1699] A similar reaction was reported using KOH and 10% of a chiral phase-transfer agent, giving moderate enantioselectivity in the epoxy sulfone product.[1700]

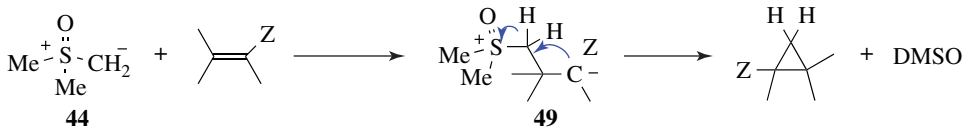
Dihalocarbenes and carbenoids, which readily add to C═C bonds (**15-60**), do not generally add to the C═O bonds of ordinary aldehydes and ketones.[1701] (See also **16-85**.) Carbonyl-stabilized ammonium ylids reacted with aldehydes to give epoxy amides.[1702] Terminal epoxides were prepared with high enantioselectivity using ylid reactions.[1703] There is a report of a strained azetidinium ylid that has been used for epoxidation.[1704]

OS **V**, 358, 755.

Double-bond compounds that undergo the *Michael reaction* (**15-20**) can be converted to cyclopropane derivatives with sulfur ylids.[1705] Among the most common of these is

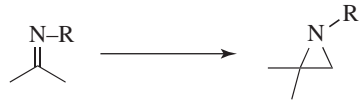
[1692] See Johnson, C.R.; Schroeck, C.W.; Shanklin, J.R. *J. Am. Chem. Soc.* ***1973***, *95*, 7424.
[1693] Johnson, C.R.; Schroeck, C.W.; Shanklin, J.R. *J. Am. Chem. Soc.* ***1973***, *95*, 7424.
[1694] Juliá, S.N.; Masana, J.; Vega, J.C. *Angew. Chem. Int. Ed. Engl.* ***1980***, 19, 929; Juliá, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R.; Molinari, H. *J. Chem. Soc., Perkin Trans. 1* ***1982***, 1317. See Luo, W.; Yu, Z.; Qiu, W.; Yang, F.; Liu, X.; Tang, J. *Tetrahedron* ***2011***, *67*, 289.
[1695] Bérubé, C.; Barbeau, X.; Lagüe, P.; Voyer, N. *Chem. Commun.* ***2017***, *53*, 5099.
[1696] Akagawa, K.; Hirata, T.; Kudo, K. *Synlett* ***2016***, *27*, 1217.
[1697] See Gutsche, C.D. *Org. React.* ***1954***, *8*, 364.
[1698] See Davies, H.M.L.; De Meese, J. *Tetrahedron Lett.* ***2001***, *42*, 6803.
[1699] Mąkosza, M.; Urbańska, N.; Chesnokov, A.A. *Tetrahedron Lett.* ***2003***, *44*, 1473.
[1700] Arai, S.; Shioiri, T. *Tetrahedron* ***2002***, *58*, 1407.
[1701] For exceptions, see Sadhu, K.M.; Matteson, D.S. *Tetrahedron Lett.* ***1986***, *27*, 795; Araki, S.; Butsugan, Y. *J. Chem. Soc., Chem. Commun.* ***1989***, 1286.
[1702] Novacek, J.; Roiser, L.; Zielke, K.; Robiette, R.; Waser, M. *Chem. Eur. J.* ***2016***, *22*, 11322. See Roiser, L.; Robiette, R.; Waser, M. *Synlett* ***2016***, *27*, 1963.
[1703] Piccinini, A.; Kavanagh, S.A.; Connon, S.J. *Chem. Commun.* ***2012***, *48*, 7814.
[1704] Alex, A.; Larmanjat, B.; Marrot, J.; Couty, F.; David, O. *Chem. Commun.* ***2007***, 2500.
[1705] Trost, B.M.; Melvin Jr., L.S. *Sulfur Ylids*, Academic Press, NY, ***1975***. For reviews, see Fava, A. in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, ***1985***, pp. 299–354; Belkin, Yu.V.;

dimethyloxosulfonium methylid **44**,[1706] which reacts with conjugated C═C units to give anion **49**; intramolecular displacement of the DMSO leaving group gave the cyclopropane.



Other sulfur ylids have also been used. A combination of DMSO and KOH in an ionic liquid converts conjugated ketones to α,β-cyclopropyl ketones.[1707] Both CHR and CR_2 can be added in a similar manner with certain nitrogen-containing compounds. Functionalized ylids,[1708] such as $Ph(Me_2N)SO{-}CH_2$, add various groups to activated double bonds.[1709] Sulfur ylids react with allylic alcohols in the presence of MnO_2 and molecular sieve 4 Å to give the cyclopropyl aldehyde.[1710] Similar reactions have been performed with phosphorus ylids[1711] or with pyridinium ylids.[1712] The reactions with ylids such as these of course involve nucleophilic acyl addition. Enantioselective cyclopropanation occurs in the presence of certain organocatalysts[1713] or chiral metal catalysts.[1714] The organocatalytic reaction of β,γ-unsaturated α-keto esters with stabilized sulfur ylids gave 1,2,3-trisubstituted cyclopropane derivatives.[1715]

16-47 The Formation of Aziridines from Imines



Just as sulfur ylids such as **44** react with the carbonyl of an aldehyde or ketone to give an epoxide, *Te ylids react with imines to give an aziridine.* The reaction of an allylic Te salt, $RCH{=}CHCH_2Te^+Bu_2\ Br^-$, with lithium hexamethyldisilazide in HMPA/toluene leads to the Te ylid via deprotonation. In the presence of an imine, the ylid adds to the imine; subsequent displacement of Bu_2Te generates an aziridine with a pendant vinyl group.[1716] Catalytic aziridination of tosylimines was reported, mediated by arsonium ylids.[1717]

Polezhaeva, N.A. *Russ. Chem. Rev.* ***1981***, *50*, 481; Block, E. in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, part 2, Wiley, NY, ***1981***, pp. 680–702; Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 91–127.

[1706] See Gololobov, Yu.G.; Nesmeyanov, A.N.; Lysenko, V.P.; Boldeskul, I.E. *Tetrahedron* ***1987***, *43*, 2609.

[1707] Chandrasekhar, S.; Jagadeshwar, N.V.; Reddy, K.V. *Tetrahedron Lett.* ***2003***, *44*, 3629.

[1708] See Kennewell, P.D.; Taylor, J.B. *Chem. Soc. Rev.* ***1980***, *9*, 477.

[1709] Johnson, C.R. *Aldrichimica Acta* ***1985***, *18*, 1; *Acc. Chem. Res.* ***1973***, *6*, 341; Kennewell, P.D.; Taylor, J.B. *Chem. Soc. Rev.* ***1975***, *4*, 189; Trost, B.M. *Acc. Chem. Res.* ***1974***, *7*, 85.

[1710] Oswald, M.F.; Raw, S.A.; Taylor, R.J.K. *Org. Lett.* ***2004***, *6*, 3997.

[1711] See Grieco, P.A.; Finkelhor, R.S. *Tetrahedron Lett.* ***1972***, 3781.

[1712] Shestopalov, A.M.; Sharanin, Yu.A.; Litvinov, V.P.; Nefedov, O.M. *J. Org. Chem. USSR* ***1989***, *25*, 1000.

[1713] Kunz, R.K.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2005***, *127*, 3240.

[1714] Kakei, H.; Sone, T.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2007***, *129*, 13410.

[1715] Cheng, Y.; An, J.; Lu, L.-Q.; Luo, L.; Wang, Z.-Y.; Chen, J.-R.; Xiao, W.-J. *J. Org. Chem.* ***2011***, *76*, 81.

[1716] Liao, W.-W.; Deng, X.-M.; Tang, Y. *Chem. Commun.* ***2004***, 1516.

[1717] Zhu, S.; Liao, Y.; Zhu, S. *Synlett* ***2005***, 1429.

The enantioselective synthesis of aryl aziridines has been reported.[1718] The asymmetric aziridine-forming reaction of aldehydes with protected amines and α-diazo esters in the presence of a boroxinate catalyst was reported.[1719] The organocatalyzed aziridination of β-dicarbonyl compounds using TMS azide was reported.[1720] Terminal aziridines were prepared by methylene transfer from sulfonium ylids to imines.[1721] Imines reacted with α-keto esters to give aziridine 2-carboxylates using $P(NMe_2)_3$ as a mediator.[1722]

The reaction of tosylaldimines with BnHN—OBz and an optically active phase-transfer catalyst gave optically active diaziridines.[1723] A chiral thiourea organocatalyst was used for a catalytic asymmetric oxaziridination reaction.[1724]

16-48 The Formation of Episulfides and Episulfones[1725]

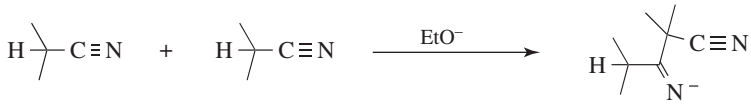
Epoxides can be converted directly to episulfides by treatment with NH_4SCN and ceric ammonium nitrate.[1726] Diazoalkanes, treated with sulfur, give episulfides.[1727] It is likely that $R_2C{=}S$ is an intermediate, which is attacked by another molecule of diazoalkane, in a process similar to that is shown in **16-46**. Thioketones *do* react with diazoalkanes to give episulfides,[1728] and have also been converted to episulfides with sulfur ylids.[1682]

Alkanesulfonyl chlorides give episulfones when treated with diazomethane in the presence of a base (usually a tertiary amine).[1729] The base removes HCl from the sulfonyl halide to produce the highly reactive sulfene ($RCH{=}SO_2$) (see **17-12**), which then adds CH_2. The episulfone can subsequently be heated to give off SO_2 (see **17-18**), making the entire process a method for achieving the conversion $RCH_2SO_2Cl \rightarrow RCH{=}CH_2$.[1730]

OS **V**, 231, 877.

[1718] Huang, M.-T.; Wu, H.-Y.; Chein, R.-J. *Chem. Commun.* ***2014***, *50*, 1101.
[1719] Gupta, A.K.; Mukherjee, M.; Wulff, W.D. *Org. Lett.* ***2011***, *13*, 5866. See Wang, S.-H.; Chein, R.-J. *Tetrahedron* ***2016***, *72*, 2607.
[1720] Yasui, K.; Kojima, K.; Kato, T.; Odagi, M.; Kato, M.; Nagasawa, K. *Tetrahedron* ***2016***, *72*, 5350.
[1721] Kavanagh, S.A.; Piccinini, A.; Connon, S.J. *Org. Biomol. Chem.* ***2013***, *11*, 3535.
[1722] Jiang, J.; Liu, H.; Lu, C.-D.; Xu, Y.-J. *J. Org. Chem.* ***2017***, *82*, 811.
[1723] Lykke, L.; Halskov, K.S.; Carlsen, B.D.; Chen, V.X.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2013***, *135*, 4692. See Beebe, A.W.; Dohmeier, E.F.; Moura-Letts, G. *Chem. Commun.* ***2015***, *51*, 13511.
[1724] Ji, N.; Yuan, J.; Xue, S.; Zhang, J.; He, W. *Tetrahedron* ***2016***, *72*, 512.
[1725] See Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***, pp. 57–86.
[1726] Iranpoor, N.; Kazemi, F. *Synthesis* ***1996***, 821.
[1727] Schönberg, A.; Frese, E. *Chem. Ber.* ***1962***, *95*, 2810.
[1728] See Beiner, J.M.; Lecadet, D.; Paquer, D.; Thuillier, A. *Bull. Soc. Chim. Fr.* ***1973***, 1983.
[1729] Opitz, G.; Fischer, K. *Angew. Chem. Int. Ed.* ***1965***, *4*, 70.
[1730] For a review of this process, see Fischer, N.S. *Synthesis* **1970**, 393.

16-49 The Thorpe Reaction

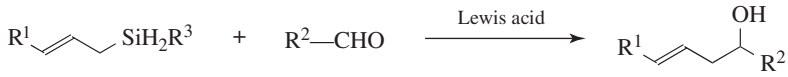


In the *Thorpe reaction*, the α carbon of one nitrile molecule is added to the CN carbon of another, so this reaction has analogies with the aldol reaction (**16-34**). The imine unit is, of course, subject to hydrolysis (**16-2**), so β-keto nitriles can be prepared in this manner. The Thorpe reaction can be done intramolecularly, in which case it is called the *Thorpe-Ziegler reaction*.[1731] As with other cyclization methods, yields are high for five- to eight-membered rings, fall off to about zero for rings of nine to thirteen members, but are high again for fourteen-membered and larger rings, if high-dilution techniques are employed. The product in the Thorpe-Ziegler reaction is not the imine, but the tautomeric enamine, which can be hydrolyzed to an α-cyano ketone (**16-2**) if desired. In turn this product can be hydrolyzed and decarboxylated (**16-4**, **12-39**). Other active-hydrogen compounds can also be added to nitriles.[1732]

OS **VI**, 932.

H. Other Carbon or Silicon Nucleophiles

16-50 The Addition of Silanes



Allylic silanes react with aldehydes, in the presence of Lewis acids, to give a homoallylic alcohol.[1733] In the case of benzylic silanes, this addition reaction has been induced with $Mg(ClO_4)_2$ under photochemical conditions.[1734] Cyclopropylcarbinyl silanes add to acetals in the presence of TMSOTf to give a homoallylic alcohol.[1735] Allyltrichlorosilane adds an allyl group to an aldehyde in the presence of a cyclic urea and AgOTf.[1736] The use of chiral additives leads to the alcohol with good asymmetric induction.[1737]

[1731] Taylor, E.C.; McKillop, A. *The Chemistry of Cyclic Enaminonitriles and ortho-Amino Nitriles*, Wiley, NY, ***1970***; Schaefer, J.P.; Bloomfield, J.J. *Org. React.* ***1967***, *15*, 1.
[1732] See Page, P.C.B.; van Niel, M.B.; Westwood, D. *J. Chem. Soc., Perkin Trans. 1* ***1988***, 269.
[1733] Panek, J.S.; Liu, P. *Tetrahedron Lett.* ***1997***, *38*, 5127.
[1734] Fukuzumi, S.; Okamoto, T.; Otera, J. *J. Am. Chem. Soc.* ***1994***, *116*, 5503.
[1735] Braddock, D.C.; Badine, D.M.; Gottschalk, T. *Synlett* ***2001***, 1909.
[1736] Chataigner, I.; Piarulli, U.; Gennari, C. *Tetrahedron Lett.* ***1999***, *40*, 3633.
[1737] Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* ***1993***, *115*, 11490. See Malkov, A.V.; Liddon, A.J.P.S.; Ramírez-López, P.; Bendová, L.; Haigh, D.; Kočovský, P. *Angew. Chem. Int. Ed.* ***2006***, *45*, 1432.

16-51 The Formation of Cyanohydrins

The addition of HCN to aldehydes or ketones produces cyanohydrins.[1738] This is an equilibrium reaction, and for aldehydes and aliphatic ketones the equilibrium lies to the right so the reaction is quite feasible, except with sterically hindered ketones such as diisopropyl ketone. However, aryl ketones (ArCOR) give poor yields, and the reaction cannot be carried out with diaryl ketones (ArCOAr) since the equilibrium lies too far to the left. With aromatic aldehydes the *benzoin condensation* (**16-54**) competes. With α,β-unsaturated aldehydes and ketones, 1,4-addition competes (**15-34**).

Ketones of low reactivity, such as ArCOR, can be converted to cyanohydrins by treatment with diethylaluminum cyanide (Et_2AlCN) (see OS **VI**, 307) or, indirectly, with cyanotrimethylsilane (Me_3SiCN)[1739] in the presence of a Lewis acid or base,[1740] followed by hydrolysis of the resulting *O*-trimethylsilyl cyanohydrin. Both direct formation of the cyanohydrin (hydrocyanation) and formation of the cyano-*O*-silyl ether have been carried out enantioselectively using chiral catalysts,[1741] including chiral organocatalysts,[1742] or chiral additives.[1743] Biocatalysts have been used.[1744] Hydrogen cyanide adds to aldehydes in the presence of a lyase to give the cyanohydrin with good enantioselectivity.[1745] Cyanohydrins have been formed using a lyase in an ionic liquid.[1746]

Solvent-free conditions have been reported using TMSCN, an aldehyde, and potassium carbonate.[1747] Amine *N*-oxides catalyze the reaction,[1748] as does tetrabutylammonium cyanide.[1749] Lithium perchlorate in ether facilitates this reaction,[1750] and lithium chloride catalyzes the reaction with Me_3SiCN.[1751] *N*-Heterocyclic carbenes catalyze the

[1738] Friedrich, K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1983***, pp. 1345–1390; Friedrich, K.; Wallenfels, K. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 72–77; Uemura, M.; Kurono, N.; Ohkuma, T. *Org. Lett.* ***2012***, *14*, 882; Miyagawa, S.; Yoshimura, K.; Yamazaki, Y.; Takamatsu, N.; Kuraishi, T.; Aiba, S.; Tokunaga, Y.; Kawasaki, T. *Angew. Chem. Int. Ed.* ***2017***, *56*, 1055.

[1739] Rasmussen, J.K.; Heilmann, S.M.; Krepski, L. *Adv. Silicon Chem.* ***1991***, *1*, 65; Sukata, K. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 3820.

[1740] See Kanai, M.; Hamashima, Y.; Shibasaki, M. *Tetrahedron Lett.* ***2000***, *41*, 2405. For a reaction without a Lewis acid, see Manju, K.; Trehan, S. *J. Chem. Soc., Perkin Trans. 1* ***1995***, 2383.

[1741] See Gröger, H.; Capan, E.; Barthuber, A.; Vorlop, K.-D. *Org. Lett.* ***2001***, *3*, 1969, and references cited therein; Shen, K.; Liu, X.; Li, Q.; Feng, X. *Tetrahedron* ***2008***, *64*, 147. See also, North, M.; Omedes-Pujol, M.; Williamson, C. *Chem. Eur. J.* ***2010***, *16*, 11367.

[1742] See Liu, X.; Qin, B.; Zhou, X.; He, B.; Feng, X. *J. Am. Chem. Soc.* ***2005***, *127*, 12224; Kurono, N.; Yoshikawa, T.; Yamasaki, M.; Ohkuma, T. *Org. Lett.* ***2011***, *13*, 1254.

[1743] Lv, C.; Wu, M.; Wang, S.; Xia, C.; Sun, W. *Tetrahedron: Asymmetry* ***2010***, *21*, 1869.

[1744] van Langen, L.M.; Selassa, R.P.; van Rantwijk, F.; Sheldon, R.A. *Org. Lett.* ***2005***, *7*, 327.

[1745] Gerrits, P.J.; Marcus, J.; Birikaki, L.; van der Gen, A. *Tetrahedron: Asymmetry* ***2001***, *12*, 971.

[1746] Gaisberger, R.P.; Fechter, M.H.; Griengl, H. *Tetrahedron: Asymmetry* ***2004***, *15*, 2959.

[1747] He, B.; Li, Y.; Feng, X.; Zhang, G. *Synlett* ***2004***, 1776.

[1748] Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. *Tetrahedron* ***2003***, *59*, 5667. See Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. *Eur. J. Org. Chem.* ***2004***, 129.

[1749] Amurrio, I.; Córdoba, R.; Csákÿ, A.G.; Plumet, J. *Tetrahedron* ***2004***, *60*, 10521.

[1750] Jenner, G. *Tetrahedron Lett.* ***1999***, *40*, 491.

[1751] Kurono, N.; Yamaguchi, M.; Suzuki, K.; Ohkuma, T. *J. Org. Chem.* ***2005***, *70*, 6530.

reaction,[1752] as do certain ionic liquids.[1753] With $MgBr_2$ as a catalyst, the reaction proceeds with good *syn* selectivity.[1754] Other useful catalysts include Pt,[1755] Au,[1756] Ru/Li,[1757] or Ti[1758] compounds, and $InBr_3$.[1759] The reaction of aldehydes and 2 equivalents of TMSCN used a V catalyst to give the cyanohydrin.[1760] Chiral transition metal catalysts have been used to give *O*-trialkylsilyl cyanohydrins with good enantioselectivity.[1761] Titanium catalysts, a Si(IV),[1762] Al,[1763] or Lewis base[1764] were used to give the OTMS cyanohydrin.[1765] The use of chiral additives leads to cyanohydrins with good asymmetric induction.[1766] A V catalyst has been used in an ionic liquid.[1767] Note that the reaction of an aldehyde and TMSCN in the presence of aniline and a $BiCl_3$ catalyst leads to an α-cyano amine.[1768] Enzymatic catalysis has been used for the formation of cyanohydrins.[1769]

Rather than direct reaction with an aldehyde or ketone, the bisulfite addition product is often treated with cyanide. The reaction rate is increased by the addition of base, as demonstrated by Lapworth in 1903; this was one of the first organic mechanisms to be known.[1770] This method is especially useful for aromatic aldehydes, since it avoids competition from the benzoin condensation. If desired, it is possible to hydrolyze the cyanohydrin *in situ* to the corresponding α-hydroxy acid. This reaction is important in the *Kiliani-Fischer* method of extending the carbon chain of a sugar.

A particularly useful variation of this reaction uses a cyanide source rather than HCN. α-Amino nitriles[1771] can be prepared in one step by the treatment of an aldehyde or ketone with NaCN and NH_4Cl. This reaction is called the *Strecker synthesis*;[1772] and it is a special case of the *Mannich reaction* (**16-17**). Since the CN group is easily hydrolyzed to the acid,

[1752] Song, J.J.; Gallou, F.; Reeves, J.T.; Tan, Z.; Yee, N.K.; Senanayake, C.H. *J. Org. Chem.* ***2006***, *71*, 1273; Suzuki, Y.; Abu Bakar, M.D.; Muramatsu, K.; Sato, M. *Tetrahedron* ***2006***, *62*, 4227.

[1753] Shen, Z.-L.; Ji, S.-J.; Loh, T.-P. *Tetrahedron Lett.* ***2005***, *46*, 3137.

[1754] Ward, D.E.; Hrapchak, M.J.; Sales, M. *Org. Lett.* ***2000***, *2*, 57.

[1755] Fossey, J.S.; Richards, C.J. *Tetrahedron Lett.* ***2003***, *44*, 8773.

[1756] Cho, W.K.; Kang, S.M.; Medda, A.K.; Lee, J.K.; Choi, I.S.; Lee, H.-S. *Synthesis* ***2008***, 50.

[1757] Ohkuma, T.; Kurono, N. *Synlett* ***2012***, *23*, 1865.

[1758] He, B.; Chen, F.-X.; Li, Y.; Feng, X.; Zhang, G. *Tetrahedron Lett.* ***2004***, *45*, 5465. See Saá, J.M.; Baeza, A.; Nájera, C.; Sansano, J.M. *Tetrahedron: Asymmetry* ***2011***, *22*, 1292.

[1759] Bandini, M.; Cozzi, P.G.; Melchiorre, P.; Umani-Ronchi, A. *Tetrahedron Lett* ***2001***, *42*, 3041.

[1760] Chu, C.-Y.; Hsu, C.-T.; Lo, P.H.; Uang, B.-J. *Tetrahedron: Asymmetry* ***2011***, *22*, 1981.

[1761] See He, B.; Qin, B.; Feng, X.; Zhang, G. *J. Org. Chem.* ***2004***, *69*, 7910; Chen, F.-X.; Qin, B.; Feng, X.; Zhang, G.; Jiang, Y. *Tetrahedron* ***2004***, *60*, 10449; Uang, B.-J.; Fu, I.-P.; Hwang, C.-D.; Chang, C.-W.; Yang, C.-T.; Hwang, D.-R. *Tetrahedron* ***2004***, *60*, 10479. Also see Karimi, B.; Ma'Mani, L. *Org. Lett.* ***2004***, *6*, 4813.

[1762] Swamy, V.S.V.S.N.; Bisai, M.K.; Das, T.; Sen, S.S. *Chem. Commun.* ***2017***, *53*, 6910.

[1763] Yang, Z.; Yi, Y.; Zhong, M.; De, S.; Mondal, T.; Koley, D.; Ma, X.; Zhang, D.; Roesky, H.W. *Chem. Eur. J.* ***2016***, *22*, 6932.

[1764] North, M.; Omedes-Pujol, M.; Young, C. *Org. Biomol. Chem.* ***2012***, *10*, 4289.

[1765] Serra, M.S.S.; Murtinho, D.; Goth, A. *Tetrahedron: Asymmetry* ***2013***, *24*, 315. See Błocka, E.; Bosiak, M.J.; Wełniak, M.; Ludwiczak, A.; Wojtczak, A. *Tetrahedron: Asymmetry* ***2014***, *25*, 554.

[1766] See Ryu, D.H.; Corey, E.J. *J. Am. Chem. Soc.* ***2004***, *126*, 8106.

[1767] Baleizão, C.; Gigante, B.; Garcia, H.; Corma, A. *Tetrahedron Lett.* ***2003***, *44*, 6813.

[1768] De, S.K.; Gibbs, R.A. *Tetrahedron Lett.* ***2004***, *45*, 7407.

[1769] Zheng, Z.; Zi, Y.; Li, Z.; Zou, X. *Tetrahedron: Asymmetry* ***2013***, *24*, 434.

[1770] Lapworth, A. *J. Chem. Soc.* ***1903***, *83*, 998. See also, Ching, W.; Kallen, R.G. *J. Am. Chem. Soc.* ***1978***, *100*, 6119.

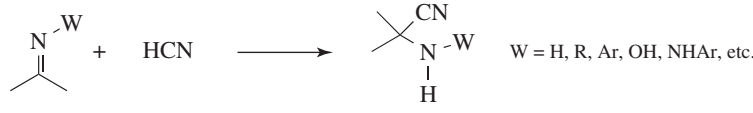
[1771] See Shafran, Yu.M.; Bakulev, V.A.; Mokrushin, V.S. *Russ. Chem. Rev.* ***1989***, *58*, 148.

[1772] See Williams, R.M. *Synthesis of Optically Active* α*-Amino Acids*, Pergamon Press, Elmsford, NY, ***1989***, pp. 208–229; Gröger, H. *Chem. Rev.* ***2003***, *103*, 2795. See Li, P.; Zhang, Y.; Chen, Z.; Zhang, X. *Tetrahedron Lett.* ***2017***, *58*, 1854.

this is a convenient method for the preparation of α-amino acids. The reaction has also been carried out with NH_3 and HCN and with NH_4CN. Salts of primary and secondary amines can be used instead of NH_4^+ to obtain *N*-substituted and *N*,*N*-disubstituted α-amino nitriles. Brønsted acids can also be used.[1773] The Strecker synthesis is useful for aromatic as well as aliphatic ketones. The Me_3SiCN method has been used and the intermediate converted to the product with ammonia or an amine.[1774] The effect of pressure on the Strecker synthesis has been studied.[1775] A catalyst-free multi-component Strecker reaction is known.[1776] There is also an In-mediated Strecker reaction in aqueous media.[1777] Enantioselective Strecker syntheses are possible,[1778] using chiral ammonium salts[1779] and other organocatalysts,[1780] chiral acids,[1781] or chiral metal complexes.[1782] The asymmetric Strecker synthesis of α-arylglycines has been reported[1783] and a decarboxylative Strecker reaction is known.[1784] There is a radical version of the Strecker synthesis.[1785]

OS **I**, 336; **II**, 7, 29, 387; **III**, 436; **IV**, 58, 506; **VI**, 307; **VII**, 20, 381, 517, 521. For the reverse reaction, see OS **III**, 101. For the Strecker synthesis, see OS **I**, 21, 355; **III**, 66, 84, 88, 275; **IV**, 274; **V**, 437; **VI**, 334.

16-52 The Addition of HCN to C═N and C≡N Bonds



In a prototype reaction, HCN adds to imines, Schiff bases, hydrazones, oximes, and similar compounds. Cyanide can be added to iminium ions to give α-cyano amines. As in **16-49**, the addition to imines has been carried out enantioselectively.[1786] Chiral ammonium salts have been used with HCN.[1787] Trimethylsilyl cyanide (TMSCN) reacts with *N*-tosyl

[1773] See Zhang, G.-W.; Zheng, D.-H.; Nie, J.; Wang, T.; Ma, J.-A. *Org. Biomol. Chem.* ***2010***, *8*, 1399. See also, Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* ***2010***, *132*, 5522.

[1774] See Mai, K.; Patil, G. *Synth. Commun.* ***1985***, *15*, 157. See Dekamin, M.G.; Mokhtari, Z. *Tetrahedron* ***2012***, *68*, 922.

[1775] Jenner, G.; Salem, R.B.; Kim, J.C.; Matsumoto, K. *Tetrahedron Lett.* ***2003***, *44*, 447.

[1776] Martínez, R.; Ramón, D.J.; Yus, M. *Tetrahedron Lett.* ***2005***, *46*, 8471.

[1777] Shen, Z.-L.; Ji, S.-J.; Loh, T.-P. *Tetrahedron* ***2008***, *64*, 8159.

[1778] For a review, see Wang, J.; Liu, X.; Feng, X. *Chem. Rev.* ***2011***, *111*, 6947.

[1779] Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Am. Chem. Soc.* ***2006***, *128*, 2548.

[1780] Saravanan, S.; Sadhukhan, A.; Khan, N.-u.H.; Kureshy, R.I.; Abdi, S.H.R.; Bajaj, H.C. *J. Org. Chem.* ***2012***, *77*, 4375; Liu, Y.-L.; Shi, T.-D.; Zhou, F.; Zhao, X.-L.; Wang, X.; Zhou, J. *Org. Lett.* ***2011***, *13*, 3826; Martínez-Muñoz, A.; Monge, D.; Martín-Zamora, E.; Marqués-López, E.; Álvarez, E.; Fernández, R.; Lassaletta, J.M. *Org. Biomol. Chem.* ***2013***, *11*, 8247.

[1781] Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem. Int. Ed.* ***2006***, *45*, 2617.

[1782] Blacker, J.; Clutterbuck, L.A.; Crampton, M.R.; Grosjean, C.; North, M. *Tetrahedron: Asymmetry* ***2006***, *17*, 1449.

[1783] Pérez-Fuertes, Y.; Taylor, J.E.; Tickell, D.A.; Mahon, M.F.; Bull, S.D.; James, T.D. *J. Org. Chem.* ***2011***, *76*, 6038.

[1784] Das, D.; Richers, M.T.; Ma, L.; Seidel, D. *Org. Lett.* ***2011***, *13*, 6584.

[1785] Cannella, R.; Clerici, A.; Panzeri, W.; Pastori, N.; Punta, C.; Porta, O. *J. Am. Chem. Soc.* ***2006***, *128*, 5358.

[1786] Saito, K.; Harada, K. *Tetrahedron Lett.* ***1989***, *30*, 4535.

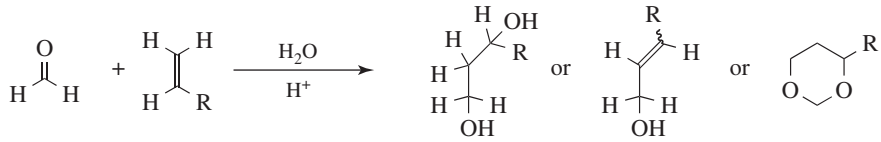
[1787] Huang, J.; Corey, E.J. *Org. Lett.* ***2004***, *6*, 5027.

imines in the presence of BF_3•OEt_2 to give the α-cyano *N*-tosyl amine.[1788] In the presence of a chiral Zr[1789] or Al[1790] catalyst, Bu_3SnCN reacts with imines to give α-cyano amines enantioselectively. The reaction of an imine and TMSCN gives the cyano amine with good enantioselectivity using a chiral Sc catalyst.[1791] Titanium catalysts have been used in the presence of a chiral Schiff base.[1792]

The addition of KCN to triisopropylbenzenesulfonyl hydrazones provides an indirect method for achieving the conversion RR′CO → RR′CHCN.[1793] The reaction is successful for hydrazones of aliphatic aldehydes and ketones. HCN can also be added to the C≡N bond to give iminonitriles or α-aminomalononitriles $[R(H_2N)C(CN)_2]$.[1794] The acylcyanation of imines is known, and enantioselectivity is achieved with a suitable catalyst.[1795]

OS **V**, 344. See also, OS **V**, 269.

16-53 The Prins Reaction



The addition of an alkene to formaldehyde in the presence of an acid catalyst[1796] is called the *Prins reaction*.[1797] Three main products are possible; which one predominates depends on the alkene and the conditions.

When the product is the 1,3-diol or the dioxane,[1798] the reaction involves addition to the C═C as well as to the C═O. The mechanism is one of electrophilic attack on both double bonds. The acid first protonates the C═O, and the resulting oxocarbenium ion is attacked by the C═C unit of the alkene to give HO—C—C—C^+, which can undergo loss of a proton to give the alkene or add water to give the diol.[1799] It has been proposed that the intermediate carbocation is stabilized by neighboring-group attraction with either the oxygen (to give a protonated oxetane)[1800] or a carbon (to give a cyclic oxocarbenium ion)[1801] stabilizing the

[1788] Prasad, B.A.B.; Bisai, A.; Singh, V.K. *Tetrahedron Lett.* ***2004***, *45*, 9565.
[1789] Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* ***2000***, *122*, 762.
[1790] Nakamura, S.; Sato, N.; Sugimoto, M.; Toru, T. *Tetrahedron: Asymmetry* ***2004***, *15*, 1513.
[1791] Chavarot, M.; Byrne, J.J.; Chavant, P.Y.; Vallée, Y. *Tetrahedron: Asymmetry* ***2001***, *12*, 1147.
[1792] Krueger, C.A.; Kuntz, K.W.; Dzierba, C.D.; Wirschun, W.G.; Gleason, J.D.; Snapper, M.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1999***, *121*, 4284.
[1793] Jiricny, J.; Orere, D.M.; Reese, C.B. *J. Chem. Soc., Perkin Trans. 1* ***1980***, 1487. Also see Okimoto, M.; Chiba, T. *J. Org. Chem.* ***1990***, *55*, 1070.
[1794] See Ferris, J.P.; Sanchez, R.A. *Org. Synth.* V, 344.
[1795] Pan, S.C.; Zhou, J.; List, B. *Angew. Chem. Int. Ed.* ***2007***, *46*, 612.
[1796] With basic catalysts: Griengl, H.; Sieber, W. *Monatsh. Chem.* ***1973***, *104*, 1008, 1027.
[1797] See Adams, D.R.; Bhatnagar, S.P. *Synthesis* ***1977***, 661; Isagulyants, V.I.; Khaimova, T.G.; Melikyan, V.R.; Pokrovskaya, S.V. *Russ. Chem. Rev.* ***1968***, *37*, 17. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 248.
[1798] See Safarov, M.G.; Nigmatullin, N.G.; Ibatullin, U.G.; Rafikov, S.R. *Dokl. Chem.* ***1977***, *236*, 507.
[1799] Hellin, M.; Davidson, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* ***1966***, 1890, 3217.
[1800] Blomquist, A.T.; Wolinsky, J. *J. Am. Chem. Soc.* ***1957***, *79*, 6025; Schowen, K.B.; Smissman, E.E.; Schowen, R.L. *J. Org. Chem.* ***1968***, *33*, 1873.
[1801] See Safarov, M.G.; Isagulyants, V.I.; Nigmatullin, N.G. *J. Org. Chem. USSR* ***1974***, *10*, 1378.

charge. This stabilization is postulated to explain the fact that with but-2-enes[1802] and with cyclohexenes the addition is *anti*. A back-side attack of H_2O on the three- or four-membered ring would account for it. Additional evidence for the intermediacy of a protonated oxetane is the finding that oxetanes that are subjected to the reaction conditions give essentially the same product ratios as the corresponding alkenes.[1803] An argument against the intermediacy of the protonated oxetane or a cyclic oxocarbenium ion is that not all alkenes show the *anti* stereoselectivity mentioned above. Indeed, the stereochemical results are often quite complex, with *syn*, *anti*, and nonstereoselective addition reported, depending on the nature of the reactants and the reaction conditions.[1804] Since addition to the C═C bond is electrophilic, the reactivity of the alkene increases with alkyl substitution and *Markovnikov's rule* is followed. The dioxane product may arise from a reaction between the 1,3-diol and formaldehyde[1805] (**16-5**) or between a protonated oxetane and formaldehyde. Racemization may occur in the Prins cyclization reaction by 2-oxonia-Cope rearrangements (see **18-32**) by way of a (*Z*)-oxocarbenium ion intermediate.[1806] A catalytic asymmetric Prins cyclization has been reported.[1807] A catalytic asymmetric vinylogous Prins cyclization has been reported.[1808] The Prins reaction with ketones has been reported.[1809] A solvent-free and metal-free Prins cyclization has been reported as a green chemistry contribution.[1810]

Iodine can promote the Prins reaction.[1811] Lewis acids such as $SnCl_4$ also catalyze the reaction, in which case the species that adds to the alkenes is $H_2C^+ \ ^-O{-}SnCl_4$.[1812] The reaction can also be catalyzed by peroxides, in which case the mechanism is probably a free-radical one. Other transition metal complexes can be used to form homoallylic alcohols. Samarium iodide promotes this addition reaction.[1813] Dienes react with alcohols in the presence of a transition metal compound to give alkenyl alcohols.[1814] Allenes also add to aldehydes[1815] and enynes undergo Prins cyclization with Au catalysts.[1816]

A closely related reaction has been performed with activated aldehydes or ketones; without a catalyst such as chloral and acetoacetic ester, but with heat.[1817] The product in these cases is a β-hydroxy alkene, a homoallylic alcohol, and the mechanism is pericyclic.[1818] This reaction is reversible and suitable β-hydroxy alkenes can be cleaved by heat (**17-30**). There is evidence that the cleavage reaction occurs by a cyclic mechanism (see **17-30**),

[1802] Fremaux, B.; Davidson, M.; Hellin, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* ***1967***, 4250.
[1803] Meresz, O.; Leung, K.P.; Denes, A.S. *Tetrahedron Lett.* ***1972***, 2797.
[1804] See Karpaty, M.; Hellin, M.; Davidson, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* ***1971***, 1736; Coryn, M.; Anteunis, M. *Bull. Soc. Chim. Belg.* ***1974***, *83*, 83.
[1805] Sharf, V.Z.; Kheifets, V.I.; Freidlin, V.I. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1974***, *23*, 1681.
[1806] Jasti, R.; Rychnovsky, S.D. *J. Am. Chem. Soc.* ***2006***, *128*, 13640.
[1807] Liu, L.; Kaib, P.S.J.; Tap, A.; List, B. *J. Am. Chem. Soc.* ***2016***, *138*, 10822.
[1808] Xie, Y.; Cheng, G.-J.; Lee, S.; Kaib, P.S.J.; Thiel, W.; List, B. *J. Am. Chem. Soc.* ***2016***, *138*, 14538.
[1809] Jacolot, M.; Jean, M.; Levoin, N.; van de Weghe, P. *Org. Lett.* ***2012***, *14*, 58.
[1810] Clarisse, D.; Pelotir, B.; Piva, O.; Fache, F. *Chem. Commun.* ***2012***, *48*, 157.
[1811] Yadav, J.S.; Subba Reddy, B.V.; Hara Gopal, A.V.; Narayana Kumar, G.G.K.S.; Madavi, C.; Kunwar, A.C. *Tetrahedron Lett.* ***2008***, *49*, 4420.
[1812] Yang, D.H.; Yang, N.C.; Ross, C.B. *J. Am. Chem. Soc.* ***1959***, *81*, 133.
[1813] Sarkar, T.K.; Nandy, S.K. *Tetrahedron Lett.* ***1996***, *37*, 5195.
[1814] Cho, H.Y.; Morken, J.P. *J. Am. Chem. Soc.* ***2008***, *130*, 16140. See Yang, Y.; Zhu, S.-F.; Duan, H.-F.; Zhou, C.-Y.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* ***2007***, *129*, 2248.
[1815] Song, M.; Montgomery, J. *Tetrahedron* ***2005***, *61*, 11440.
[1816] Jiménez-Núñez, E.; Claverie, C.K.; Nieto-Oberhuber, C.; Echavarren, A.M. *Angew. Chem. Int. Ed.* ***2006***, *45*, 5452.
[1817] See Klimova, E.I.; Antonova, N.D.; Arbuzov, Yu.A. *J. Org. Chem. USSR* ***1969***, *5*, 1312, 1315.
[1818] See Ben Salem, R.; Jenner, G. *Tetrahedron Lett.* ***1986***, *27*, 1575. There is evidence that the mechanism is somewhat more complicated: Kwart, H.; Brechbiel, M. *J. Org. Chem.* ***1982***, *47*, 3353.

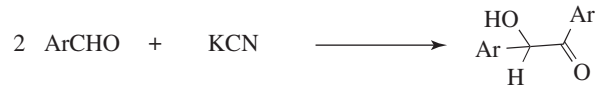
and, by the principle of microscopic reversibility, the addition mechanism should be cyclic too.[1818,1819] Note that this reaction is an oxygen analog of the ene synthesis (**15-19**). This reaction can also be carried out with unactivated aldehydes[1820] and ketones[1821] if Lewis acid catalysts such as dimethylaluminum chloride (Me_2AlCl) or ethylaluminum dichloride ($EtAlCl_2$) are used.[1822] Lewis acid catalysts also increase rates with activated aldehydes.[1823] The use of optically active catalysts has given optically active products with high % ee.[1824]

In a related reaction, alkenes can be added to aldehydes and ketones to give γ-alkylated alcohols, which has been accomplished by several methods,[1825] including treatment with SmI_2[1826] or Zn and Me_3SiCl,[1827] and by electrochemical[1828] and photochemical[1829] methods. Most of these methods have been used for intramolecular addition and most or all involve free radical intermediates. The Prins reaction of enol ethers led to tetrahydrofuran derivatives.[1830] Silyl enol ethers were used to prepare tetrahydropyran-4-one derivatives.[1831] A thia-Prins bicyclization was used to prepare dithia-bicycles.[1832] The reaction of allenylsilanes led to heterocyclic compounds.[1833]

There is an *aza-Prins reaction*, promoted by TiI_4 and I_2.[1834] Piperidine derivatives have been prepared via a supramolecular assembly-catalyzed bimolecular aza-Prins cyclization of formaldehyde with amines that have a distal alkene unit, and a transannular 1,5-hydride transfer as observed.[1835] Azabicycles have been prepared via cascade aza-Prins reactions.[1836]

OS **IV**, 786. See also, OS **VII**, 102.

16-54 The Benzoin Condensation

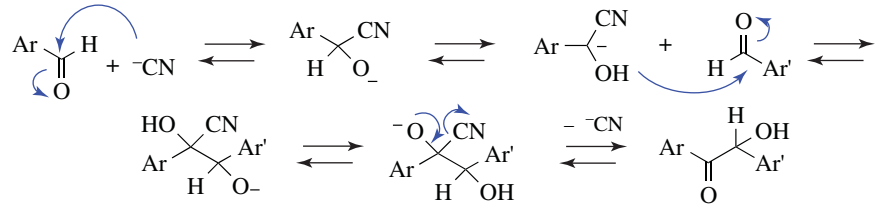


When certain aldehydes are treated with cyanide ion, *benzoins* (α-hydroxy-1,2-diarylethanone derivatives) are produced in a reaction called the *benzoin condensation*.

[1819] Papadopoulos, M.; Jenner, G. *Tetrahedron Lett.* ***1981***, *22*, 2773.
[1820] See Cartaya-Marin, C.P.; Jackson, A.C.; Snider, B.B. *J. Org. Chem.* ***1984***, *49*, 2443.
[1821] Jackson, A.C.; Goldman, B.E.; Snider, B.B. *J. Org. Chem.* ***1984***, *49*, 3988.
[1822] See Song, Z.; Beak, P. *J. Org. Chem.* ***1990***, *112*, 8126.
[1823] Benner, J.P.; Gill, G.B.; Parrott, S.J.; Wallace, B. *J. Chem. Soc., Perkin Trans. 1* ***1984***, 291, 315, 331. See Breugst, M.; Grée, R.; Houk, K.N. *J. Org. Chem.* ***2013***, *78*, 9892; Borker, P.; van der Weghe, P.; Reddy, B.V.S.; Yadav, J.S.; Grée, R. *Chem. Commun.* ***2012***, *48*, 9316.
[1824] Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* ***1990***, *112*, 3949.
[1825] See Ujikawa, O.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1989***, *30*, 2837; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1178–1179.
[1826] Ujikawa, O.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1989***, *30*, 2837.
[1827] Corey, E.J.; Pyne, S.G. *Tetrahedron Lett.* ***1983***, *24*, 2821.
[1828] See Shono, T.; Kashimura, S.; Mori, Y.; Hayashi, T.; Soejima, T.; Yamaguchi, Y. *J. Org. Chem.* ***1989***, *54*, 6001.
[1829] See Belotti, D.; Cossy, J.; Pete, J.P.; Portella, C. *J. Org. Chem.* ***1986***, *51*, 4196.
[1830] Gogoi, P.; Das, V.K.; Saikia, A.K. *J. Org. Chem.* ***2014***, *79*, 8592.
[1831] Tay, G.C.; Huang, C.Y.; Rychnovsky, S.D. *J. Org. Chem.* ***2014***, *79*, 8733.
[1832] Reddy, B.V.S.; Venkateswarlu, A.; Borkar, P.; Yadav, J.S.; Kanakaraju, M.; Kunwar, A.C.; Sridhar, B. *J. Org. Chem.* ***2013***, *78*, 6303.
[1833] Okada, T.; Shimoda, A.; Shinada, T.; Sakaguchi, K.; Ohfune, Y. *Org. Lett.* ***2012***, *14*, 6130.
[1834] Shimizu, M.; Baba, T.; Toudou, S.; Hachiya, I. *Chem. Lett.* ***2007***, *36*, 12.
[1835] Kaphan, D.M.; Toste, F.D.; Bergman, R.G.; Raymond, K.N. *J. Am. Chem. Soc.* ***2015***, *137*, 9202.
[1836] Chio, F.K.I.; Guesné, S.J.J.; Hassall, L.; McGuire, T.; Dobbs, A.P. *J. Org. Chem.* ***2015***, *80*, 9868.

The benzoin product results from self-condensation of the aryl aldehyde. The reaction only occurs with aromatic aldehydes, but not all of them,[1837] and for glyoxals RCOCHO. An aldehyde such as *p*-dimethylaminobenzaldehyde cannot condense with itself, but it can condense with benzaldehyde to give a benzoin. *N*-Alkyl-3-methylimidazolium salts catalyze the reaction,[1838] as does an imidazole-based solid-supported catalyst.[1839] The benzaldehyde lyase from *Pseudomonas fluorescens* has been reported to catalyze the stereoselective aliphatic aromatic cross benzoin reaction.[1840]

The accepted mechanism[1841] for this reversible reaction is shown, as originally proposed by Lapworth in 1903:[1842]



The key step, the loss of the aldehyde proton, can take place because the acidity of this C—H bond is increased by the electron-withdrawing power of the CN group. Thus, cyanide is a highly specific catalyst for this reaction, because, almost uniquely, it can perform three functions: (i) it acts as a nucleophile; (ii) its electron-withdrawing ability permits loss of the aldehyde proton; and (iii) having done this, it then acts as a leaving group.

Certain thiazolium salts can also catalyze the reaction.[1843] In this case, aliphatic aldehydes can also be used[1844] (the products are *acyloins*), and mixtures of aliphatic and aromatic aldehydes give mixed α-hydroxy ketones.[1845] The reaction has also been carried out without cyanide, by using the benzoylated cyanohydrin as one of the components in a phase-transfer catalyzed process. By this means, products can be obtained from aldehydes that normally fail to self-condense.[1846]

The condensation has also been done with excellent enantioselectivity.[1847] Enantiopure triazolium salts have been evaluated as catalysts in the enantioselective benzoin condensation.[1848] *N*-Heterocyclic carbene catalysts have been used for asymmetric

[1837] For a review, see Ide, W.S.; Buck, J.S. *Org. React.* ***1948***, *4*, 269.
[1838] Xu, L.-W.; Gao, Y.; Yin, J.-J.; Li, L.; Xia, C.-G. *Tetrahedron Lett.* ***2005***, *46*, 5317. See also, Iwamoto, K.; Kimura, H.; Oike, M.; Sato, M. *Org. Biomol. Chem.* ***2008***, *6*, 912.
[1839] Storey, J.M.D.; Williamson, C. *Tetrahedron Lett.* ***2005***, *46*, 7337.
[1840] Beigi, M.; Gauchenova, E.; Walter, L.; Waltzer, S.; Bonina, F.; Stillger, T.; Rother, D.; Pohl, M.; Müller, M. *Chem. Eur. J.* ***2016***, *22*, 13999.
[1841] See Kuebrich, J.P.; Schowen, R.L.; Wang, M.; Lupes, M.E. *J. Am. Chem. Soc.* ***1971***, *93*, 1214.
[1842] Lapworth, A. *J. Chem. Soc.* ***1903***, *83*, 995; ***1904***, *85*, 1206.
[1843] See Diederich, F.; Lutter, H. *J. Am. Chem. Soc.* ***1989***, *111*, 8438. Also see Lappert, M.F.; Maskell, R.K. *J. Chem. Soc., Chem. Commun.* ***1982***, 580.
[1844] Kuhlmann, H. *Org. Synth.* VII, 95; Matsumoto, T.; Ohishi, M.; Inoue, S. *J. Org. Chem.* ***1985***, *50*, 603.
[1845] Stetter, H.; Dämbkes, G. *Synthesis* ***1977***, 403.
[1846] Rozwadowska, M.D. *Tetrahedron* ***1985***, *41*, 3135.
[1847] Soeta, T.; Tabatake, Y.; Inomata, K.; Ukaji, Y. *Tetrahedron* ***2012***, *68*, 894; Rafiński, Z. *Tetrahedron* ***2016***, *72*, 1860.
[1848] See Baragwanath, L.; Rose, C.A.; Zeitler, K.; Connon, S.J. *J. Org. Chem.* ***2009***, *74*, 9214; Soeta, T.; Mizuno, S.; Hatanaka, Y.; Ukaji, Y. *Tetrahedron* ***2017***, *73*, 3430.

induction.[1849] Using aryl silyl ketones, $ArC(=O)SiMe_2Ph$ and aldehydes, with a La catalyst, a "mixed" benzoin condensation has been accomplished.[1850] The reaction of acylsilanes and aldehydes, catalyzed by metal cyanides, is known as the silyl-benzoin reaction.[1851] The aza-benzoin reaction has been reported.[1852]

OS **I**, 94; **VII**, 95.

16-55 Addition of Radicals to C=O, C=S, and C=N Compounds

Radical cyclization is not limited to reaction with a C=C unit (see **15-25** and **15-26**), and reactions with both C=N and C=O moieties are known. Reaction of $MeON{=}CH(CH_2)_3CHO$ with Bu_3SnH and AIBN, for example, led to *trans*-2-(methoxyamino)cyclopentanol in good yield.[1853] Conjugated ketones add to aldehydes via the β carbon under radical conditions (2 molar equivalents of Bu_3SnH and 0.1 equivalent of CuCl) to give a β-hydroxy ketone.[1854]

Radical addition to simple imines leads to aminocycloalkenes.[1855] Radicals also add to the carbonyl unit of phenylthio esters to give cyclic ketones.[1856] The reaction of α-bromo ketones with a Cu catalyst in the presence of an aryl hydroxylamine generated an α-keto radical that added to a nitrone, generated *in situ*, to give an α-amino ketone.[1857]

Secondary alkyl iodides add to *O*-alkyl oximes in the presence of BEt_3 and AIBN, and this methodology was used to convert $MeO_2C{-}CH{=}NOBn$ to $MeO_2C{-}CH(R)NOBn$.[1858] Benzylic halides add to imines under photochemical conditions and in the presence of 1-benzyl-1,4-dihydronicotinamide[1859] or with BEt_3 in aqueous methanol.[1860] *O*-Trityl oximes of 5- and 6-iodoaldehydes undergo radical cyclization to give oximes[1861] (also see **15-26**). Enantioselective radical addition reactions to *N*-benzoyl hydrazones used chiral ammonium salts.[1862] The Mn-mediated reaction of allyl iodides with chiral *N*-acyl hydrazones leads to chiral hydrazine derivatives.[1863] *N*,*N*-Dimethylaniline reacts with aldehydes under photochemical conditions to give acyl addition via the carbon atom of one

[1849] See Haghshenas, P.; Gravel, M. *Org. Lett.* ***2016***, *18*, 4518. See also, Haghshenas, P.; Quail, J.W.; Gravel, M. *J. Org. Chem.* ***2016***, *81*, 12075.
[1850] Bausch, C.C.; Johnson, J.S. *J. Org. Chem.* ***2004***, *69*, 4283.
[1851] Linghu, X.; Bausch, C.C.; Johnson, J.S. *J. Am. Chem. Soc.* ***2005***, *127*, 1833.
[1852] Wilde, M.M.D.; Gravel, M. *Org. Lett.* ***2014***, *16*, 5308; DiRocco, D.A.; Rovis, T. *Angew. Chem. Int. Ed.* ***2012***, *51*, 5904; Sun, L.-H.; Liang, Z.-Q.; Jia, W.-Q.; Ye, S. *Angew. Chem. Int. Ed.* ***2013***, *52*, 5803.
[1853] Tormo, J.; Hays, D.S.; Fu, G.C. *J. Org. Chem.* ***1998***, *63*, 201.
[1854] Ooi, T.; Doda, K.; Sakai, D.; Maruoka, K. *Tetrahedron Lett.* ***1999***, *40*, 2133.
[1855] Bowman, W.R.; Stephenson, P.T.; Terrett, N.K.; Young, A.R. *Tetrahedron Lett.* ***1994***, *35*, 6369.
[1856] Kim, S.; Jon, S.Y. *Chem. Commun.* ***1996***, 1335.
[1857] Fisher, D.J.; Burnett, G.L.; Velasco, R.; de Alaniz, J.R. *J. Am. Chem. Soc.* ***2015***, *137*, 11614.
[1858] Miyabe, H.; Ueda, M.; Yoshioka, N.; Yamakawa, K.; Naito, T. *Tetrahedron* ***2000***, *56*, 2413.
[1859] Jin, M.; Zhang, D.; Yang, L.; Liu, Y.; Liu, Z. *Tetrahedron Lett.* ***2000***, *41*, 7357.
[1860] McNabb, S.B.; Ueda, M.; Naito, T. *Org. Lett.* ***2004***, *6*, 1911.
[1861] Clive, D.L.J.; Pham, M.P.; Subedi, R. *J. Am. Chem. Soc.* ***2007***, *129*, 2713.
[1862] Jang, D.O.; Kim, S.Y. *J. Am. Chem. Soc.* ***2008***, *130*, 16152.
[1863] Friestad, G.K.; Marié, J.-C.; Suh, Y.S.; Qin, J. *J. Org. Chem.* ***2006***, *71*, 7016.

of the methyl groups.[1864] The reaction of $PhNMe_2$ and benzaldehyde, for example, gave $PhN(Me)CH_2CH(OH)Ph$ upon photolysis.

16.B.ii. Acyl Substitution Reactions

A. O, N, and S Nucleophiles

16-56 Hydrolysis of Acyl Halides

$$RCOCl + H_2O \longrightarrow RCOOH$$

Acyl halides are so reactive that hydrolysis is easily carried out.[1865] In fact, most simple acyl halides must be stored under anhydrous conditions or they may react with water in the air. Consequently, water is usually a strong enough nucleophile for the reaction, but in unreactive systems hydroxide ion may be required. The reactivity order is $F < Cl < Br < I$.[1866] If a carboxylic acid is used as the nucleophile, an exchange may take place (see **16-78**). The mechanis[1866] of hydrolysis can be either S_N1 or tetrahedral, the former occurring in highly polar solvents and in the absence of strong nucleophiles.[1867] There is also evidence for the S_N2 mechanism in some cases.[1868]

Hydrolysis of acyl halides is not usually catalyzed by acids, except for acyl fluorides, where hydrogen bonding can assist in the removal of a fluorine atom.[1869] There are several methods available for the hydrolysis of acyl fluorides.[1870]

OS **II**, 74.

16-57 Hydrolysis of Anhydrides

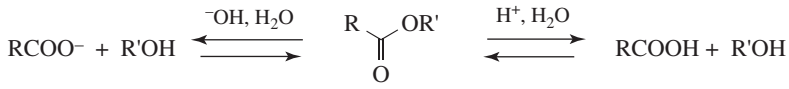
Anhydrides are somewhat more difficult to hydrolyze than acyl halides, but here too water is usually a strong enough nucleophile. The mechanism is usually tetrahedral.[1871] The S_N1 mechanism only occurs with acid catalysis and seldom even then.[1872] Anhydride hydrolysis can also be catalyzed by bases. Of course, hydroxide ion attacks more readily than water, but other bases can also catalyze the reaction. This phenomenon, called *nucleophilic catalysis* (Sec. 16.A.i, category 4), is actually the result of two successive tetrahedral mechanisms.

[1864] Kim, S.S.; Mah, Y.J.; Kim, A.R. *Tetrahedron Lett.* ***2001***, *42*, 8315.
[1865] See Bentley, T.W.; Shim, C.S. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 1659.
[1866] Talbot, R.J.E.in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 10, Elsevier, NY, ***1972***, pp. 226–257. See Kivinen, A. in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***, pp. 177–230.
[1867] Bender, M.L.; Chen, M.C. *J. Am. Chem. Soc.* ***1963***, *85*, 30. See also, Bentley, T.W.; Koo, I.S.; Norman, S.J. *J. Org. Chem.* ***1991***, *56*, 1604.
[1868] Guthrie, J.P.; Pike, D.C. *Can. J. Chem.* ***1987***, *65*, 1951. See also, Lee, I.; Sung, D.D.; Uhm, T.S.; Ryu, Z.H. *J. Chem. Soc., Perkin Trans. 2* ***1989***, 1697.
[1869] Bevan, C.W.L.; Hudson, R.F. J. *Chem. Soc.* ***1953***, 2187; Satchell, D.P.N. J. *Chem. Soc.* ***1963***, 555.
[1870] See Motie, R.E.; Satchell, D.P.N.; Wassef, W.N. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 1087.
[1871] See Wiseman, F.L. *J. Phys. Org. Chem.* ***2012***, *25*, 1105.
[1872] Satchell, D.P.N. *Q. Rev. Chem. Soc.* ***1963***, *17*, 160 (pp. 172–173). See Talbot, R.J.E. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 10, Elsevier, NY, ***1972***, pp. 280–287.

For example, pyridine catalyzes the hydrolysis of acetic anhydride in this manner.[1873] Many other nucleophiles similarly catalyze the reaction.

OS **I**, 408; **II**, 140, 368, 382; **IV**, 766; **V**, 8, 813.

16-58 Hydrolysis of Carboxylic Esters



Ester hydrolysis is usually catalyzed by acids or bases. Since OR is a much poorer leaving group than halide or OCOR, water alone does not hydrolyze most esters. When bases catalyze the reaction, the attacking species is the more powerful nucleophile $^-$OH and the product is the carboxylate anion, requiring treatment with aqueous acid to generate the carboxylic acid. This reaction is called *saponification* since treatment with base used to convert glyercols to the salts of long-chain fatty acids, which are soaps.[1874] Acids catalyze the reaction by making the carbonyl carbon more positive and therefore more susceptible to attack by the nucleophile. Both reactions are equilibrium reactions, so there must be a way to shift the equilibrium to the right for this to be useful. Since formation of the salt does just this, ester hydrolysis is almost always done for preparative purposes in basic solution, unless the compound is base sensitive.

Ester hydrolysis can also be catalyzed[1875] by metal ions, by cyclodextrins,[1876] by enzymes,[1877] and by nucleophiles.[1878] Other reagents used to cleave carboxylic esters include Dowex-50,[1879] Me_3SiI,[1880] and $InCl_3$ on moist silica gel using microwave irradiation.[1881] Cleavage of phenolic esters is usually faster than carboxylic esters derived from aliphatic acids. The Lewis acid-mediated selective mono-hydrolysis of geminal diesters has been reported.[1882] The reagent Sm/I_2 at -78 °C has been used,[1883] as have ammonium acetate in aqueous methanol,[1884] and Amberlyst 15 in methanol.[1885] Phenolic esters have been selectively hydrolyzed in the presence of alkyl esters on alumina with microwave

[1873] See Deady, L.W.; Finlayson, W.L. *Aust. J. Chem.* ***1983***, *36*, 1951.
[1874] Schumann, K.; Siekmann, K. "Soaps." *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, ***2000***; Beal, G.D. *Org. Synth.* ***1926***, *6*, 100.
[1875] For a list of catalysts and reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1959–1968.
[1876] See Bender, M.L.; Komiyama, M. *Cyclodextrin Chemistry*, Springer, NY, ***1978***, pp. 34–41. The mechanism is shown in Saenger, W. *Angew. Chem. Int. Ed.* ***1980***, *19*, 344.
[1877] For pig liver esterase hydrolysis of esters, see Zhu, L.; Tedford, M.C. *Tetrahedron* ***1990***, *46*, 6587; Ohno, M.; Otsuka, M. *Org. React.* ***1989***, *37*, 1. See Fotakopoulou, I.; Barbayianni, E.; Constantinou-Kokotou, V.; Bornscheuer, U.T.; Kokotos, G. *J. Org. Chem.* ***2007***, *72*, 782.
[1878] Wilk, B.K. *Synth. Commun.* ***1996***, *26*, 3859.
[1879] Basu, M.K.; Sarkar, D.C.; Ranu, B.C. *Synth. Commun.* ***1989***, *19*, 627.
[1880] See Olah, G.A.; Husain, A.; Singh, B.P.; Mehrotra, A.K. *J. Org. Chem.* ***1983***, *48*, 3667.
[1881] Ranu, B.C.; Dutta, P.; Sarkar, A. *Synth. Commun.* ***2000***, *30*, 4167.
[1882] Ilangovan, A.; Kumar, R.G.; Kaushik, M.P. *Synlett* ***2012***, *23*, 2093.
[1883] Yanada, R.; Negoro, N.; Bessho, K.; Yanada, K. *Synlett* ***1995***, 1261.
[1884] Ramesh, C.; Mahender, G.; Ravindranath, N.; Das, B. *Tetrahedron* ***2003***, *59*, 1049.
[1885] Das, B.; Banerjee, J.; Ramu, R.; Pal, R.; Ravindranath, N.; Ramesh, C. *Tetrahedron Lett.* ***2003***, *44*, 5465.

irradiation.[1886] Allylic esters were cleaved with DMSO/I_2.[1887] Allylic esters were also cleaved with 2% Me_3SiOTf in dichloromethane,[1888] with $CeCl_3 \bullet 7H_2O$/NaI,[1889] and with $NaHSO_4$•silica gel.[1890] Lactones also undergo the reaction[1891] (but if the lactone is five- or six-membered, the hydroxy acid often spontaneously reforms the lactone). Thiol esters (RCOSR′) give thiols R′SH using NaSMe in methanol,[1892] borohydride exchange resin and $Pd(OAc)_2$ was used for reductive cleavage of thiol esters to thiols,[1893] and $TiCl_4$/Zn was used for the conversion of phenyl thioacetates to thiophenols.[1894] Sterically hindered esters are hydrolyzed with difficulty (Sec. 10.G.i), but reaction of 2 equivalents of *t*-BuOK with 1 equivalent of water is effective.[1895] Hindered esters can also be cleaved by sequential treatment with zinc bromide and then water,[1896] with silica gel in refluxing toluene,[1897] and on alumina when irradiated with microwaves.[1898] For esters insoluble in water the rate of two-phase ester saponification can be greatly increased by the application of ultrasound,[1899] and phase-transfer techniques have been applied.[1900] Esters were converted to the carboxylic acid using a chloroaluminate ionic liquid as a catalyst and the medium.[1901] Sodium cyanide in HMPA selectively cleaves methyl esters in the presence of ethyl esters:[1902]

$$RCOOMe + CN^- \rightarrow MeCN + RCOO^-$$

Enzymatic hydrolysis of diesters with esterase has been shown to give the hydroxy ester,[1903] and selective hydrolysis of dimethyl succinate to monomethyl succinic acid was accomplished with aqueous NaOH in THF.[1904] Hydrolysis of vinyl esters leads to ketones, and the reaction of *C*-substituted vinyl acetates with an esterase derived from *Marchantia polymorpha* gave substituted ketones with high enantioselectivity.[1905] The chemoenzymatic hydrolysis of 2-monoacylglycerols has been reported.[1906] Enantiomerically enriched acetates were prepared using a lipase-catalyzed hydrolysis (*Candida antarctica* lipase B, CAL-B) in nonaqueous media using sodium.[1907] The "neutral hydrolysis of the neurotransmitter acetylcholine in water at 25 °C led to the extrapolated rate constant for the uncatalyzed (or neutral) hydrolysis of acetylcholine to be 3.9×10^{-7} s^{-1} at 25 °C

[1886] Varma, R.S.; Varma, M.; Chatterjee, A.K. *J. Chem. Soc., Perkin Trans. 1* ***1993***, 999.
[1887] Taksande, K.N.; Sakate, S.S.; Lokhande, P.D. *Tetrahedron Lett.* ***2006***, *47*, 643.
[1888] Nishizawa, M.; Yamamoto, H.; Seo, K.; Imagawa, H.; Sugihara, T. *Org. Lett.* ***2002***, *4*, 1947.
[1889] Yadav, J.S.; Reddy, B.V.S.; Rao, C.V.; Chand, P.K.; Prasad, A.R. *Synlett* ***2002***, 137.
[1890] Ramesh, C.; Mahender, G.; Ravindranath, N.; Das, B. *Tetrahedron Lett.* ***2003***, *44*, 1465.
[1891] See Gómez-Bombarelli, R.; Calle, E.; Casado, J. *J. Org. Chem.* ***2013***, *78*, 6868; 6880.
[1892] Wallace, O.B.; Springer, D.M. *Tetrahedron Lett.* ***1998***, *39*, 2693.
[1893] Choi, J.; Yoon, N.M. *Synth. Commun.* ***1995***, *25*, 2655.
[1894] Jin, C.K.; Jeong, H.J.; Kim, M.K.; Kim, J.Y.; Yoon, Y.-J.; Lee, S.-G. *Synlett* ***2001***, 1956,
[1895] Gassman, P.G.; Schenk, W.N. *J. Org. Chem.* ***1977***, *42*, 918.
[1896] Wu, Y.-g.; Limburg, D.C.; Wilkinson, D.E.; Vaal, M.J.; Hamilton, G.S. *Tetrahedron Lett.* ***2000***, *41*, 2847.
[1897] Jackson, R.W. *Tetrahedron Lett.* ***2001***, *42*, 5163.
[1898] Ley, S.V.; Mynett, D.M. *Synlett* ***1993***, 793.
[1899] Moon, S.; Duchin, L.; Cooney, J.V. *Tetrahedron Lett.* ***1979***, 3917.
[1900] Loupy, A.; Pedoussaut, M.; Sansoulet, J. *J. Org. Chem.* ***1986***, *51*, 740.
[1901] Wei, B.-M.; Zhang, Y.; Dai, Z.-Q.; Zhang, K.-C. *Monatsh. Chem.* ***2011***, *142*, 1029.
[1902] Müller, P.; Siegfried, B. *Helv. Chim. Acta* ***1974***, *57*, 987.
[1903] See Nair, R.V.; Shukla, M.R.; Patil, P.N.; Salunkhe, M.M. *Synth. Commun.* ***1999***, *29*, 1671.
[1904] Niwayama, S. *J. Org. Chem.* ***2000***, *65*, 5834.
[1905] Hirata, T.; Shimoda, K.; Kawano, T. *Tetrahedron: Asymmetry* ***2000***, *11*, 1063.
[1906] Whitten, K.M.; Makriyannis, A.; Vadivel, S.K. *Tetrahedron* ***2012***, *68*, 5422.
[1907] Merabet-Khelassi, M.; Houiene, Z.; Aribi-Zouioueche, L.; Riant, O. *Tetrahedron: Asymmetry* ***2012***, *23*, 828.

($\Delta H^{\ddagger} = 20.0$ kcal mol^{-1}; $T\Delta S^{\ddagger} = -6.1$ kcal mol^{-1}). These data showed that acetylcholine is more susceptible to neutral and base-catalyzed hydrolysis than ethyl acetate but less susceptible to acid-catalyzed hydrolysis."[1908]

Ingold[1909] has classified the acid- and base-catalyzed hydrolyses of esters (and the formation of esters, since these are reversible reactions and thus have the same mechanisms) into eight possible mechanisms,[1910] depending on the following criteria: (i) acid or base catalyzed, (ii) unimolecular or bimolecular, and (iii) acyl cleavage or alkyl cleavage.[1911] All eight of these are S_N1, S_N2, or tetrahedral mechanisms. The acid-catalyzed mechanisms are shown with reversible arrows. They are not only reversible, but also symmetrical; that is, the mechanisms for ester formation are exactly the same as for hydrolysis, except that H replaces R. Internal proton transfers may not actually be direct but may take place through the solvent. There is much physical evidence to show that esters are initially protonated on the carbonyl and not on the alkyl oxygen.[1912] Nevertheless the $A_{AC}1$ mechanism is shown as proceeding through the ether-protonated intermediate **A**, since it is difficult to envision OR′ as a leaving group here. It is of course possible for a reaction to proceed through an intermediate even if only a tiny concentration is present. The designations $A_{AC}1$, and so on, are those of Ingold. The $A_{AC}2$ and $A_{AC}1$ mechanisms are also called A2 and A1, respectively. Note that the $A_{AC}1$ mechanism is actually the same as the S_N1cA mechanism for this type of substrate and that $A_{AL}2$ is analogous to S_N2cA. Some authors use A1 and A2 to refer to all types of nucleophilic substitution in which the leaving group first acquires a proton. The base-catalyzed reactions are not shown with reversible arrows, since they are reversible only in theory and not in practice. Hydrolyses taking place under neutral conditions are classified as B mechanisms. Molecular dynamics has shown that "the rate of hydrolysis of methyl formate in pure water is consistent with mechanisms involving cooperative catalysis by autoionization-generated hydroxide and hydronium, a process known to have an activation free energy of 23.8 kcal mol^{-1} (99.6 kJ mol^{-1})."[1913]

Of the eight mechanisms, seven have actually been observed in the hydrolysis of carboxylic esters. The one that has not been observed is the $B_{AC}1$ mechanism.[1914] The most common mechanisms are the $B_{AC}2$ for basic catalysis and the $A_{AC}2$[1915] for acid catalysis, that is, the two tetrahedral mechanisms. Both involve acyl-oxygen cleavage. The evidence is: (i) hydrolysis with $H_2{}^{18}O$ results in the ^{18}O appearing in the acid and not in the alcohol;[1916] (ii) esters with chiral R′ groups give alcohols with *retention* of configuration;[1917] (iii) allylic R′ gives no allylic rearrangement;[1918] (iv) neopentyl R′ gives no

[1908] Wolfenden, R.; Yuan, Y. *J. Am. Chem. Soc.* ***2011***, *133*, 13821.
[1909] Ingold, C.K. *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1970***, pp. 1129–1131.
[1910] As given here, the IUPAC designations for $B_{AC}1$ and $B_{AL}1$ are the same, but Rule A.2 adds further symbols so that they can be distinguished: Su-AL for $B_{AL}1$ and Su-AC for $B_{AC}1$. See the IUPAC rules: Guthrie, R.D. *Pure Appl. Chem.* ***1989***, *61*, 23 (see p. 49).
[1911] Kirby, A.J. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 10, ***1972***, pp. 57–207; Euranto, E.K. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 505–588.
[1912] Cerfontain, H.; Koeberg-Telder, A.S.; Kruk, C. *Tetrahedron Lett.* ***1975***, 3639.
[1913] Gunaydin, H.; Houk, K.N. *J. Am. Chem. Soc.* ***2008***, *130*, 15232.
[1914] This is an S_N1 mechanism with OR' as leaving group, which does not happen.
[1915] See Zimmermann, H.; Rudolph, J. *Angew. Chem. Int. Ed.* ***1965***, *4*, 40.
[1916] See Polanyi, M.; Szabo, A.L. *Trans. Faraday Soc.* ***1934***, *30*, 508.
[1917] Holmberg, B. *Ber.* ***1912***, *45*, 2997.
[1918] Ingold, C.K.; Ingold, E.H. J. *Chem. Soc.* ***1932***, 758.

rearrangement.[1919] All these facts indicate that the O—R′ bond is not broken. It has been concluded that two molecules of water are required in the $A_{AC}2$ mechanism. This conclusion stems from a value of *w* (Sec. 8.C) of ~5, indicating that water acts as a proton donor here as well as a nucleophile.[1920] Termolecular processes are rare, but in this case the two water molecules are already connected by a hydrogen bond. (A similar mechanism, called $B_{AC}3$, also involving two molecules of water, has been found for esters that hydrolyze without a catalyst.[1921] Primarily, such esters are those containing halogen atoms in the R group.)

The other mechanism involving acyl cleavage is the $A_{AC}1$ mechanism, which is rare, being found only where R is very bulky, so that bimolecular attack is sterically hindered, and only in ionizing solvents. The mechanism has been demonstrated for esters of 2,4,6-trimethylbenzoic acid (mesitoic acid). This acid depresses the freezing point of sulfuric acid four times as much as would be predicted from its molecular weight, which is evidence for the equilibrium involving the acyliun ion. In a comparable solution of benzoic acid the freezing point is depressed only twice the predicted amount, indicating only a normal acid–base reaction. Further, a sulfuric acid solution of methyl mesitoate when poured into water gave mesitoic acid, while a similar solution of methyl benzoate similarly treated did not.[1922] The $A_{AC}1$ mechanism is also found when acetates of phenols or of primary alcohols are hydrolyzed in concentrated (>90%) H_2SO_4 (the mechanism under the more usual dilute acid conditions is the normal $A_{AC}2$).[1923]

The mechanisms involving alkyl-oxygen cleavage are ordinary S_N1 and S_N2 mechanisms in which OCOR (an acyloxy group) or its conjugate acid is the leaving group. Two of the three mechanisms, the $B_{AL}1$ and $A_{AL}1$ mechanisms, occur most readily when R′ comes off as a stable carbocation, that is, when R′ is tertiary alkyl, allylic, benzylic, and so on. For acid catalysis, most esters with this type of alkyl group (especially tertiary alkyl) cleave by this mechanism, but even for these substrates, the $B_{AL}1$ mechanism occurs only in neutral or weakly basic solution, where the rate of attack by hydroxide is so slowed that the normally slow (by comparison) unimolecular cleavage takes over. These two mechanisms have been established by kinetic studies, ^{18}O labeling, and isomerization of R′.[1924] Secondary and benzylic acetates hydrolyze by the $A_{AC}2$ mechanism in dilute H_2SO_4, but in concentrated acid the mechanism changes to $A_{AL}1$.[1665] Despite its designation, the $B_{AL}1$ mechanism is actually uncatalyzed (as is the unknown $B_{AC}1$ mechanism).

The two remaining mechanisms, $B_{AL}2$ and $A_{AL}2$, are very rare, the $B_{AL}2$ because it requires hydroxide ion to attack an alkyl carbon when an acyl carbon is also available,[1925] and the $A_{AL}2$ because it requires water to be a nucleophile in an S_N2 process. Both have been observed, however. The $B_{AL}2$ has been seen in (i) the hydrolysis of β-lactones under

[1919] Norton, H.M.; Quayle, O.R. *J. Am. Chem. Soc.* ***1940***, *62*, 1170.

[1920] Martin, R.B. *J. Am. Chem. Soc.* ***1962***, *84*, 4130. See also Yates, K. *Acc. Chem. Res.* ***1971***, *6*, 136; Huskey, W.P.; Warren, C.T.; Hogg, J.L. *J. Org. Chem.* ***1981***, *46*, 59.

[1921] See Euranto, E.K.; Kanerva, L.T. *Acta Chem. Scand. Ser. B* ***1988***, *42*, 717.

[1922] Treffers, H.P.; Hammett, L.P. *J. Am. Chem. Soc.* ***1937***, *59*, 1708. For other evidence for this mechanism, see Bender, M.L.; Chen, M.C. *J. Am. Chem. Soc.* ***1963***, *85*, 37.

[1923] Yates, K. *Acc. Chem. Res.* ***1971***, *6*, 136; Al-Shalchi, W.; Selwood, T.; Tillett J.G. *J. Chem. Res. (S)* ***1985***, 10.

[1924] For discussions, see Kirby, A.J. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 86–101; Ingold, C.K. *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Ithica, NY, ***1969***, pp. 1137–1142, 1157–1163.

[1925] Douglas, J.E.; Campbell, G.; Wigfield, D.C. *Can. J. Chem.* ***1993***, *71*, 1841.

neutral conditions[1926] (because cleavage of the C—O bond in the transition state opens the four-membered ring and relieves strain) and (ii) the alkaline hydrolysis of methyl 2,4,6-tri-*tert*-butyl benzoate.[1927] When it does occur, the $B_{AL}2$ mechanism is easy to detect, since it is the only one of the base-catalyzed mechanisms that requires inversion at R′. However, in the second example given, the mechanism is evident from the nature of the product, since the ether could have been formed in no other way. The $A_{AL}2$ mechanism has been reported in the acid cleavage of γ-lactones.[1928]

To sum up the acid-catalysis mechanisms:

- $A_{AC}2$ and $A_{AL}1$ are the common mechanisms, the latter for R′ that give stable carbocations, the former for practically all the rest.
- The $A_{AC}1$ mechanism is rare, being found mostly with strong acids and sterically hindered R.
- The $A_{AL}2$ mechanism is even rarer.
- For basic catalysis, $B_{AC}2$ is almost universal.
- $B_{AL}1$ occurs only with R′ that give stable carbocations and then only in weakly basic or neutral solutions.
- $B_{AL}2$ is very rare.
- $B_{AC}1$ has never been observed.

The above results pertain to reactions in solution. In the gas phase[1929] reactions can take a different course, as illustrated by the reaction of carboxylic esters with MeO^-, which in the gas phase was shown to take place only by the $B_{AL}2$ mechanism,[1930] even with aryl esters,[1931] where this means that an S_N2 mechanism takes place at an aryl substrate.

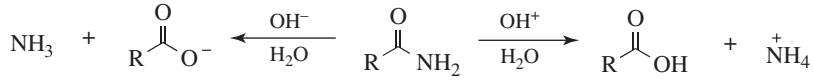
In the special case of alkaline hydrolysis of *N*-substituted aryl carbamates, there is another mechanism,[1932] involving elimination addition.[1933] This mechanism does not apply to unsubstituted or *N*,*N*-disubstituted aryl carbamates, which hydrolyze by the normal mechanisms. Carboxylic esters substituted in the α position by an electron-withdrawing group (e.g., CN or CO_2Et) can also hydrolyze by a similar mechanism involving a ketene intermediate.[1934] These elimination–addition mechanisms usually are referred to as E1cB mechanisms, because that is the name given to the elimination portion of the mechanism (Sec. 17.A.iii).

The acid-catalyzed hydrolysis of enol esters RCOOC(R′)═CR can take place either by the normal $A_{AC}2$ mechanism or by a mechanism involving initial protonation on the double-bond carbon, similar to the mechanism for the hydrolysis of enol ethers given in **10-6**,[1935] depending on reaction conditions.[1936] In either case, the products are the carboxylic acid RCO_2H and the aldehyde or ketone RCHCOR′.

[1926] Cowdrey, W.A.; Hughes, E.D.; Ingold, C.K.; Masterman, S.; Scott, A.D. J. *Chem. Soc.* ***1937***, 1264; Long, F.A.; Purchase, M. *J. Am. Chem. Soc.* ***1950***, *73*, 3267.
[1927] Barclay, L.R.C.; Hall, N.D.; Cooke, G.A. *Can. J. Chem.* ***1962***, *40*, 1981.
[1928] Moore, J.A.; Schwab, J.W. *Tetrahedron Lett.* ***1991***, *32*, 2331.
[1929] Takashima, K.; José, S.M.; do Amaral, A.T.; Riveros, J.M. *J. Chem. Soc., Chem. Commun.* ***1983***, 1255.
[1930] Comisarow, M. *Can. J. Chem.* ***1977***, *55*, 171.
[1931] Fukuda, E.K.; McIver Jr., R.T. *J. Am. Chem. Soc.* ***1979***, *101*, 2498.
[1932] See Williams, A.; Douglas, K.T. *Chem. Rev.* ***1975***, *75*, 627.
[1933] See Broxton, T.J.; Chung, R.P. *J. Org. Chem.* ***1986***, *51*, 3112.
[1934] See Isaacs, N.S.; Najem, T.S. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 557.
[1935] Allen, A.D.; Kitamura, T.; Roberts, K.A.; Stang, P.J.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1988***, *110*, 622.
[1936] See Euranto, E.K. *Pure Appl. Chem.* ***1977***, *49*, 1009.

OS **I**, 351, 360, 366, 379, 391, 418, 523; **II**, 1, 5, 53, 93, 194, 214, 258, 299, 416, 422, 474, 531, 549; **III**, 3, 33, 101, 209, 213, 234, 267, 272, 281, 300, 495, 510, 526, 531, 615, 637, 652, 705, 737, 774, 785, 809 (but see OS **V**, 1050), 833, 835; **IV**, 15, 55, 169, 317, 417, 444, 532, 549, 555, 582, 590, 608, 616, 628, 630, 633, 635, 804; **V**, 8, 445, 509, 687, 762, 887, 985, 1031; **VI**, 75, 121, 560, 690, 824, 913, 1024; **VII**, 4, 190, 210, 297, 319, 323, 356, 411; **VIII**, 43, 141, 219, 247, 258, 263, 298, 486, 516, 527.

16-59 Hydrolysis of Amides



Amides are quite useful in synthesis.[1937] Unsubstituted amides ($RCONH_2$) can be hydrolyzed with either acidic or basic catalysis, and the products are, respectively, the free acid and the ammonium ion or the salt of the acid and ammonia. *N*-Substituted ($RCONHR'$) and *N*,*N*-disubstituted ($RCONR_2'$) amides can be hydrolyzed analogously, and the product is the primary or secondary amine, respectively (or their salts), rather than ammonia. Twisting of the amide bond leads to an acceleration of water-promoted hydrolysis reactions.[1938] Lactams, imides, cyclic imides, hydrazides, and so on, also undergo the reaction.

Water alone is not sufficient to hydrolyze most amides[1939] since NH_2 is an even poorer leaving group than OR.[1940] Prolonged heating is often required, often with acidic or basic catalysts.[1941] Treatment of primary amides with phthalic anhydride at 250 °C and 4 atm gives the carboxylic acid and phthalimide.[1942] Hydrolysis of carbamates ($RNHCO_2R$) to the corresponding amine can be categorized in this section. Although the product is an amine and the carboxyl unit fragments, this reaction is simply a variation of amide hydrolysis. Strong acids, such as trifluoroacetic acid (in dichloromethane), are typically employed.[1943] Treatment of *N*-Boc derivatives ($RNHCO_2t$-Bu) with $AlCl_3$[1944] or with aqueous sodium *tert*-butoxide[1945] gave the amine. High temperature Boc deprotection has been reported using flow conditions (Sec. 7.D).[1946] The by-products of this reaction are typically carbon dioxide and isobutylene.

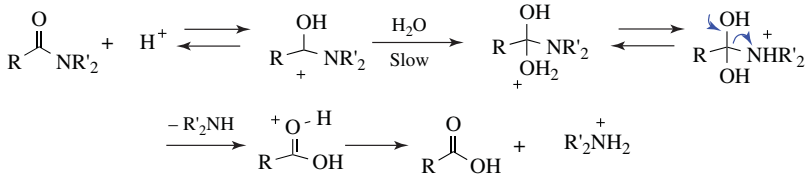
In difficult cases, nitrous acid, NOCl, N_2O_4,[1947] or a similar compound can be used (unsubstituted amides only) to give the carboxylic acid and nitrogen gas.[1948] These reactions involve a diazonium ion (see **13-19**) and are much faster than ordinary hydrolysis.

[1937] Ruider, S.A. Maulide, N. *Angew. Chem. Int. Ed.* ***2015***, *54*, 13856.
[1938] Mujika, J.I.; Mercero, J.M.; Lopez, X. *J. Am. Chem. Soc.* ***2005***, *127*, 4445. See Aubé, J. *Angew. Chem. Int. Ed.* ***2012***, *51*, 3063; Saeed, A.; Erben, M.F.; Bolte, M. *J. Org. Chem.* ***2012***, *77*, 4688.
[1939] See Zahn, D. *Eur. J. Org. Chem.* ***2004***, 4020.
[1940] See Kahne, D.; Still, W.C. *J. Am. Chem. Soc.* ***1988***, *110*, 7529.
[1941] For a list of catalysts, with references, see Larock, R.C. *Comprehensive Organic Transformatinos*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1976–1977. Also see, Bagno, A.; Lovato, G.; Scorrano, G. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 1091.
[1942] Chemat, F. *Tetrahedron Lett.* ***2000***, *41*, 3855.
[1943] Schwyzer, R.; Costopanagiotis, A.; Sieber, P. *Helv. Chim. Acta* ***1963***, *46*, 870.
[1944] Bose, D.S.; Lakshminarayana, V. *Synthesis* ***1999***, 66.
[1945] Tom, N.J.; Simon, W.M.; Frost, H.N.; Ewing, M. *Tetrahedron Lett.* ***2004***, *45*, 905.
[1946] Bogdan, A.R.; Charaschanya, M.; Dombrowski, A.W.; Wang, Y.; Djuric, S.W. *Org. Lett.* ***2016***, *18*, 1732.
[1947] Kim, Y.H.; Kim, K.; Park, Y.J. *Tetrahedron Lett.* ***1990***, *31*, 3893.
[1948] See Flynn, D.L.; Zelle, R.E.; Grieco, P.A. *J. Org. Chem.* ***1983***, *48*, 2424.

N-tert-Butylamides were converted to the corresponding carboxylic acids by simple nitrosation.[1949] The benzamide/nitrous acid reaction took place 2.5×10^7 times faster than ordinary hydrolysis, for example.[1950] In another method, the amide is treated with water and *t*-BuOK at room temperature.[1951] A kinetic study has been done on the alkaline hydrolyses of *N*-trifluoroacetyl aniline derivatives.[1952] Aromatic carboxamides reacted with 3 equivalents of amyl nitrite in acetic acid at 80 °C to give the corresponding aromatic carboxylic acid.[1953]

The same framework of eight possible mechanisms discussed for ester hydrolysis in **16-58** can also be applied to amide hydrolysis.[1954] Both the acid- and base-catalyzed hydrolyses are essentially irreversible, since alkoxide salts are formed in both cases as the tetrahedral intermediate. The mechanism is $B_{AC}2$ for basic catalysis.[1955] There is much evidence for this mechanism, similar to that discussed for ester hydrolysis. Molecular orbital studies on the mechanism of amide hydrolysis suggest a highly tetrahedral transition state.[1956] In certain cases, kinetic studies have shown that the reaction is second order in OH^-, indicating that the tetrahedral intermediate can lose a proton to give a dianion.[1957] Depending on the nature of R′, such a dianion can cleave directly to give the two negative ions or become *N*-protonated prior to or during the act of cleavage, in which case the products are obtained directly and a final proton transfer is not necessary.[1958] Studies of the effect on the rate of hydrolysis and on the ratio k_{-1}/k_2 of substituents on the aromatic rings in a series of amides $CH_3CONHAr$ led to the conclusion that path *a* is taken when Ar contains electron-withdrawing substituents and path *b* when electron-donating groups are present.[1959]

The presence of electron-withdrawing groups helps stabilize the negative charge on the nitrogen, so that $^-NR_2'$ can be a leaving group. Otherwise, the C—N bond does not cleave until the nitrogen is protonated (either prior to or in the act of cleavage), so that the leaving group, *even in the base-catalyzed reaction*, is not $^-NR_2'$ but the conjugate acid NHR_2'. It is known that formation of the tetrahedral intermediate is the rate-determining step in the $B_{AC}2$ mechanism, but only at high base concentrations. At lower concentrations of base, cleavage of the tetrahedral intermediate becomes rate determining.[1960]



[1949] Le, H.V.; Fan, L.; Ganem, B. *Tetrahedron Lett.* ***2011***, *52*, 2209.
[1950] Ladenheim, H.; Bender, M.L. *J. Am. Chem. Soc.* ***1960***, *82*, 1895.
[1951] Gassman, P.G.; Hodgson, P.K.G.; Balchunis, R.J. *J. Am. Chem. Soc.* ***1976***, *98*, 1275.
[1952] Hibbert, F.; Malana, M.A. *J. Chem. Soc., Perkin Trans. 2* ***1992***, 755.
[1953] Potter, G.T.; Jayson, G.C.; Miller, G.J.; Gardiner, J.M. *Tetrahedron Lett.* ***2015***, *56*, 5153.
[1954] O'Connor, C. *Q. Rev. Chem. Soc.* ***1970***, *24*, 553; Talbot, R.J.E. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 257–280; Challis, B.C.; Challis, J.C. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 731–857.
[1955] See DeWolfe, R.H.; Newcomb, R.C. *J. Org. Chem.* ***1971***, *36*, 3870.
[1956] Hori, K.; Kamimura, A.; Ando, K.; Mizumura, M.; Ihara, Y. *Tetrahedron* ***1997***, *53*, 4317. See Marlier, J.F.; Campbell, E.; Lai, C.; Weber, M.; Reinhardt, L.A.; Cleland, W.W. *J. Org. Chem.* ***2006***, *71*, 3829.
[1957] Khan, M.N.; Olagbemiro, T.O. *J. Org. Chem.* ***1982***, *47*, 3695.
[1958] Eriksson, S.O. *Acta Chem. Scand.* ***1968***, *22*, 892; *Acta Pharm. Suec.* ***1969***, *6*, 139.
[1959] See Kijima, A.; Sekiguchi, S. *J. Chem. Soc., Perkin Trans. 2* ***1987***, 1203.
[1960] Schowen, R.L.; Jayaraman, H.; Kershner, L. *J. Am. Chem. Soc.* ***1966***, *88*, 3373. See also, Bowden, K.; Bromley, K. *J. Chem. Soc., Perkin Trans. 2* ***1990***, 2103.

For acid catalysis, matters are less clear. The reaction is generally second order, and it is known that amides are primarily protonated on the oxygen. Because of these facts it has been generally agreed that most acid-catalyzed amide hydrolysis takes place by the $A_{AC}2$ mechanism. Further evidence for this mechanism is that a small but detectable amount of ^{18}O exchange (see Sec. 16.A.i, category 3) has been found in the acid-catalyzed hydrolysis of benzamide[1961] (^{18}O exchange has also been detected for the base-catalyzed process,[1962] in accord with the $B_{AC}2$ mechanism). Kinetic data have shown that three molecules of water are involved in the rate-determining step,[1963] suggesting that, as in the $A_{AL}2$ mechanism for ester hydrolysis (**16-58**), additional water molecules take part in a process.

The four mechanisms involving alkyl–N cleavage (the AL mechanisms) do not apply to this reaction. They are not possible for unsubstituted amides, since the only N—C bond is the acyl bond. They are possible for *N*-substituted and *N*,*N*-disubstituted amides, but in these cases they give entirely different products and are not amide hydrolyses at all.

Attack of hydroxide can rarely occur on an *N*-alkyl group to give the amide and an alcohol. While rare, it has been observed for various *N-tert*-butylamides in 98% sulfuric acid, where the mechanism was the $A_{AL}1$ mechanism,[1964] and for certain amides containing an azo group, where a $B_{AL}1$ mechanism was postulated.[1965] Of the two first-order acyl cleavage mechanisms, only the $A_{AC}1$ has been observed, in concentrated sulfuric acid solutions.[1966] Of course, the diazotization of unsubstituted amides might be expected to follow this mechanism, and there is evidence that this is true.[1950]

The hydrolysis of amides has been catalyzed by DNA.[1967]

OS **I**, 14, 111, 194, 201, 286; **II**, 19, 25, 28, 49, 76, 208, 330, 374, 384, 457, 462, 491, 503, 519, 612; **III**, 66, 88, 154, 256, 410, 456, 586, 591, 661, 735, 768, 813; **IV**, 39, 42, 55, 58, 420, 441, 496, 664; **V**, 27, 96, 341, 471, 612, 627; **VI**, 56, 252, 507, 951, 967; **VII**, 4, 287; **VIII**, 26, 204, 241, 339, 451.

B. Attack by OR at an Acyl Carbon

16-60 Alcoholysis of Acyl Halides

The reaction between acyl halides and alcohols or phenols is the best general method for the preparation of carboxylic esters. It is believed to proceed by a S_N2 mechanism.[1968] As with **16-56**, however, the mechanism can be S_N1 or tetrahedral.[1866] Lewis acids such as lithium perchlorate can be used.[1969] The reaction is of wide scope, and many functional groups do not interfere. A base is frequently added to combine with the HX formed. When aqueous

[1961] Bennet, A.J.; Slebocka-Tilk, H.; Brown, R.S.; Guthrie, J.P.; Jodhan, A. *J. Am. Chem. Soc.* ***1990***, *112*, 8497.
[1962] See Slebocka-Tilk, H.; Bennet, A.J.; Hogg, H.J.; Brown, R.S. *J. Am. Chem. Soc.* ***1991***, *113*, 1288.
[1963] See Yates, K.; Stevens, J.B. *Can. J. Chem.* ***1965***, *43*, 529; Yates, K.; Riordan, J.C. *Can. J. Chem.* ***1965***, *43*, 2328.
[1964] Lacey, R.N. J. *Chem. Soc.* ***1960***, 1633; Druet, L.M.; Yates, K. *Can. J. Chem.* ***1984***, *62*, 2401.
[1965] Stodola, F.H. *J. Org. Chem.* ***1972***, *37*, 178.
[1966] See Barnett, J.W.; O'Connor, C.J. *J. Chem. Soc., Perkin Trans. 2* ***1972***, 2378.
[1967] Zhou, C.; Avins, J.L.; Klauser, P.C.; Brandsen, B.M.; Lee, Y.; Silverman, S.K. *J. Am. Chem. Soc.* ***2016***, *138*, 2106.
[1968] Bentley, T.W.; Llewellyn, G.; McAlister, J.A. *J. Org. Chem.* ***1996***, *61*, 7927.
[1969] Bandgar, B.P.; Kamble, V.T.; Sadavarte, V.S.; Uppalla, L.S. *Synlett* ***2002***, 735.

alkali is used, this is called the *Schotten-Baumann procedure*, but pyridine is also frequently used. Indeed, pyridine catalyzes the reaction by the nucleophilic catalysis route (see **16-57**). Both R and R′ may be primary, secondary, or tertiary alkyl or aryl. Enol esters can also be prepared by this method, although *C*-acylation competes in these cases. In difficult cases, especially with hindered acids or tertiary R′, the alkoxide can be used instead of the alcohol.[1970]

Activated alumina has also been used as a catalyst, for tertiary R′.[1971] Thallium salts of phenols give very high yields of phenolic esters,[1972] and BiOCl is very effective for the preparation of phenolic acetates.[1973] Phase-transfer catalysis has been used for hindered phenols.[1974] Zinc has been used to couple alcohols and acyl chlorides,[1975] as have Zr compounds.[1976] Selective acylation is possible in some cases.[1977] The Cu-mediated trifluoromethylthiolation reaction of acid chlorides and (bpy)$CuSCF_3$ gave *S*-trifluoromethyl esters.[1978] Acid chlorides reacted with thiols in 1,1,1,3,3,3-hexafluoropropan-2-ol to give the thioester.[1979] The reaction of benzoyl chloride and a cyclic diol gave the monobenzoyl derivative in water using Me_2SnCl_2 as a catalyst.[1980] Diols were resolved using catalytic acetylization using a chiral confined imidodiphosphoric acid catalyst.[1981]

Acyl halides react with thiols, in the presence of zinc, to give the corresponding thioester.[1982] The reaction of acid chlorides or anhydrides (see **16-61**) with diphenyldiselenide, in the presence of $Sm/CoCl_2$[1983] or $Sm/CrCl_3$,[1984] gave the corresponding selenoester (PhSeCOMe). The reaction of acyl iodides and thiols gave the thioester.[1985]

OS **I**, 12; **III**, 142, 144, 167, 187, 623, 714; **IV**, 84, 263, 478, 479, 608, 616, 788; **V**, 1, 166, 168, 171; **VI**, 199, 259, 312, 824; **VII**, 190; **VIII**, 257, 516.

16-61 Alcoholysis of Anhydrides

The scope of this reaction is similar to that of **16-61**. Anhydrides are somewhat less reactive than acyl halides, but they are often used to prepare carboxylic esters. Acids,[1986] metal Lewis acids,[1987] and bases (such as pyridine) are often used as

[1970] See Kaiser, E.M.; Woodruff, R.A. *J. Org. Chem.* ***1970***, *35*, 1198.
[1971] Nagasawa, K.; Yoshitake, S.; Amiya, T.; Ito, K. *Synth. Commun.* ***1990***, *20*, 2033.
[1972] Taylor, E.C.; McLay, G.W.; McKillop, A. *J. Am. Chem. Soc.* ***1968***, *90*, 2422.
[1973] Ghosh, R.; Maiti, S.; Chakraborty, A. *Tetrahedron Lett.* ***2004***, *45*, 6775.
[1974] Illi, V.O. *Tetrahedron Lett.* ***1979***, 2431. For another method, see Nekhoroshev, M.V.; Ivakhnenko, E.P.; Okhlobystin, O.Yu. *J. Org. Chem.* USSR ***1977***, *13*, 608.
[1975] Yadav, J.S.; Reddy, G.S.; Svinivas, D.; Himabindu, K. *Synth. Commun.* ***1998***, *28*, 2337.
[1976] Ghosh, R.; Maiti, S.; Chakraborty, A. *Tetrahedron Lett.* ***2005***, *46*, 147.
[1977] Srivastava, V.; Tandon, A.; Ray, S. *Synth. Commun.* ***1992***, *22*, 2703.
[1978] Zhang, M.; Chen, J.; Chen, Z.; Weng, Z. *Tetrahedron* ***2016***, *72*, 3525.
[1979] Singh, P.; Peddinti, R.K. *Tetrahedron Lett.* ***2017***, *58*, 1875.
[1980] Muramatsu, W.; William, J.M.; Onomura, O. *J. Org. Chem.* ***2012***, *77*, 754.
[1981] Kim, J.H.; Čorić, I.; Palumbo, C.; List, B. *J. Am. Chem. Soc.* ***2015***, *137*, 1778.
[1982] Meshram, H.M.; Reddy, G.S.; Bindu, K.H.; Yadav, J.S. *Synlett* ***1998***, 877.
[1983] Chen, R.; Zhang, Y. *Synth. Commun.* ***2000***, *30*, 1331.
[1984] Liu, Y.; Zhang, Y. *Synth. Commun.* ***1999***, *29*, 4043.
[1985] Voronkov, M.G.; Grigor'eva, O.Yu.; Vlasova, N.N. *Russ. J. Org. Chem.* ***2011***, *47*, 1789.
[1986] Nafion-H has been used: Kumareswaran, R.; Pachamuthu, K.; Vankar, Y.D. *Synlett* ***2000***, 1652.
[1987] **Ce**: Dalpozzo, R.; DeNino, A.; Maiuolo, L.; Procopio, A.; Nardi, M.; Bartoli, G.; Romeo, R. *Tetrahedron Lett.* ***2003***, *44*, 5621. **Cu**: Saravanan, P.; Singh, V.K. *Tetrahedron Lett.* ***1999***, *40*, 2611. **In**: Chakraborti, A.K.;

catalysts.[1988] Acetic anhydride and $NiCl_2$ with microwave irradiation converts benzylic alcohols to the corresponding acetate.[1989] Pyridine is a nucleophilic type catalyst (see **16-57**), but 4-(*N*,*N*-dimethylamino)pyridine (DMAP) is superior and can be used in cases where pyridine fails.[1990] Nonaromatic amidine derivatives have been used to catalyze the reaction with acetic anhydride.[1991] Formic anhydride is not a stable compound but esters of formic acid can be prepared by treating alcohols[1992] or phenols[1993] with acetic-formic anhydride. The asymmetric alcoholysis of cyclic anhydrides has been reviewed.[1994] Cyclic anhydrides give monoesterified dicarboxylic acids.[1995] 1,2-Diols reacted with acetic anhydride and TBSOAc to give the monoacetylation product.[1996] Alcohols reacted with acetic anhydride and zinc catalyst to give the ester.[1997] The reaction of phenol derivatives and acetic anhydride gave the ester in the ionic liquid 1-butyl-3-methylimidazolium acetate.[1998] Secondary alcohols reacted with acetic anhydride mediated by a functionalized polystyrene to give the ester.[1999]

Alcohols or thiols reacted with acetic anhydride and AgOTf to give the ester or the thioester.[2000] Thioesters of the type ArS(C═O)Me have been prepared by simple reaction of thiols and anhydrides in the presence of potassium carbonate,[2001] and from diphenyl disulfide and PBu_3, followed by treatment with acetic anhydride.[2002]

OS **I**, 285, 418; **II**, 69, 124; **III**, 11, 127, 141, 169, 237, 281, 428, 432, 690, 833; **IV**, 15, 242, 304; **V**, 8, 459, 591, 887; **VI**, 121, 245, 560, 692; 486; **VIII**, 141, 258.

16-62 Esterification of Carboxylic Acids

$$\text{RCOOH} + \text{R'OH} \underset{}{\overset{\text{H}^+}{\rightleftharpoons}} \text{RCOOR'} + \text{H}_2\text{O}$$

The acid-catalyzed esterification of carboxylic acids with alcohols[2003] is the reverse of **16-59** and can be accomplished only if a means is available to drive the equilibrium to the

Gulhane, R. *Tetrahedron Lett.* ***2003***, *44*, 6749. **Li**: Nakae, Y.; Kusaki, I.; Sato, T. *Synlett* ***2001***, 1584. **Mg**: Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Sambri, L. *Eur. J. Org. Chem.* ***2003***, 4611. Ru: De, S.K. *Tetrahedron Lett.* ***2004***, *45*, 2919. **Ti**: Chandrasekhar, S.; Ramachandar, T.; Reddy, M.V.; Takhi, M. *J. Org. Chem.* ***2000***, *65*, 4729. **Yb**: Dumeunier, R.; Markó, I.E. *Tetrahedron Lett.* ***2004***, *45*, 825.

[1988] For a list of catalysts, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1955–1957.

[1989] Constantinou-Kokotou, V.; Peristeraki, A. *Synth. Commun.* ***2004***, *34*, 4227. Also see Bandgar, B.P.; Kasture, S.P.; Kamble, V.T. *Synth. Commun.* ***2001***, *31*, 2255.

[1990] Sakakura, A.; Kawajiri, K.; Ohkubo, T.; Kosugi, Y.; Ishihara, K. *J. Am. Chem. Soc.* ***2007***, *129*, 14775. See Scriven, E.F.V. *Chem. Soc. Rev.* ***1983***, *12*, 129.

[1991] Birman, V.B.; Li, X.; Han, Z. *Org. Lett.* ***2007***, *9*, 37.

[1992] See van Es, A.; Stevens, W. *Recl. Trav. Chim. Pays-Bas* ***1965***, *84*, 704.

[1993] See Sofuku, S.; Muramatsu, I.; Hagitani, A. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2942.

[1994] Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* ***2003***, *103*, 2965.

[1995] See Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* ***2000***, *122*, 9542.

[1996] Zhou, Y.; Rahm, M.; Wu, B.; Zhang, X.; Ren, B.; Dong, H. *J. Org. Chem.* ***2013***, *78*, 11618.

[1997] Kumar, N.U.; Reddy, B.S.; Reddy, V.P.; Bandichhor, R. *Tetrahedron Lett.* ***2014***, *55*, 910.

[1998] López, I.; Bravo, J.L.; Caraballo, M.; Barneto, J.L.; Silvero, G. *Tetrahedron Lett.* ***2011***, *52*, 3339.

[1999] Ma, S.; Toy, P.H. *Synlett* ***2016***, *27*, 1207.

[2000] Das, R.; Chakraborty, D. *Synthesis* ***2011***, *43*, 1621.

[2001] Temperini, A.; Annesi, D.; Testaferri, L.; Tiecco, M. *Tetrahedron Lett.* ***2010***, *51*, 5368.

[2002] Ayers, J.T.; Anderson, S.R. *Synth. Commun* ***1999***, *29*, 351. See Movassagh, B.; Lakouraj, M.M.; Fadaei, Z. *J. Chem. Res. (S)* ***2001***, 22.

[2003] For a review of some methods, see Haslam, E. *Tetrahedron* ***1980***, *36*, 2409.

right.[2004] There are many ways of doing this, among which are (i) addition of an excess of one of the reactants, usually the alcohol; (ii) removal of the ester or the water by distillation; (iii) removal of water by azeotropic distillation; and (iv) removal of water by use of a dehydrating agent, silica gel,[2005] or a molecular sieve.

When R′ is methyl, the most common way of driving the equilibrium is by adding excess MeOH; when R′ is ethyl or larger, it is preferable to remove water by azeotropic distillation.[2006]

The most common catalysts are H_2SO_4 and TsOH, but some reactive carboxylic acids (e.g., formic,[2007] trifluoroacetic[2008]) do not require a catalyst. Ammonium salts have been used to initiate esterification.[2009]

The R′ group may be primary or secondary alkyl groups other than methyl or ethyl, but tertiary alcohols usually give carbocations and elimination. Phenols can sometimes be used to prepare phenolic esters, but yields are generally very low. Selective esterification of an aliphatic carboxylic acid in the presence of an aromatic acid was accomplished with $NaHSO_4$•SiO_2 and methanol.[2010] Photoirradiation of carboxylic acid with CBr_4[2011] or CCl_4[2012] in methanol was shown to give the methyl ester, with high selectivity for nonconjugated acids in the case of CBr_4. Esterification has been accomplished in ionic liquids.[2013] A solid-state esterification was reported on P_2O_5/SiO_2.[2014] Vinyl acetate and iodine has been used for the acetylation of alcohols.[2015] The phase-transfer esterification of carboxylic acids has been reported using diethoxymethane as a solvent.[2016] Esters have been formed from carboxylic acids and alcohols in deep eutectic solvents.[2017] Graphene oxide was used as a catalyst for the reaction of carboxylic acids and alcohols to give esters.[2018] The Yamaguchi reagent (2,4,6-trichlorobenzoyl chloride) was used for the coupling of carboxylic acids and alcohols to give the ester.[2019] Methyl esters were formed from carboxylic acids via continuous flow (Sec. 7.D) diazotization of methylamine with 1,3-propanedinitrite in THF.[2020]

The Ir-catalyzed allylic esterification of carboxylates with allylic phosphates gave branched allylic esters.[2021] The *O*-alkylation of carboxylic acids with alkylboronic acids gave the ester using a Cu catalyst.[2022] The MnO_2 reaction of hydrazones of

[2004] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1932–1941.
[2005] Nascimento, M.de G.; Zanotto, S.P.; Scremin, M.; Rezende, M.C. *Synth. Commun.* ***1996***, *26*, 2715.
[2006] Newman, M.S. *An Advanced Organic Laboratory Course*, Macmillan, NY, ***1972***, pp. 8–10.
[2007] See Hill, D.R.; Hsiao, C.-N.; Kurukulasuriya, R.; Wittenberger, S.J. *Org. Lett.* ***2002***, *4*, 111.
[2008] Johnston, B.H.; Knipe, A.C.; Watts, W.E. *Tetrahedron Lett.* ***1979***, 4225.
[2009] See Ishihara, K.; Nakagawa, S.; Sakakura, A. *J. Am. Chem. Soc.* ***2005***, *127*, 4168.
[2010] Das, B.; Venkataiah, B.; Madhsudhan, P. *Synlett* ***2000***, 59.
[2011] Lee, A.S.-Y.; Yang, H.-C.; Su, F.-Y. *Tetrahedron Lett.* ***2001***, *42*, 301.
[2012] Hwu, J.R.; Hsu, C.-Y.; Jain, M.L. *Tetrahedron Lett.* ***2004***, *45*, 5151.
[2013] See Yoshino, T.; Imori, S.; Togo, H. *Tetrahedron* ***2006***, *62*, 1309.
[2014] Eshghi, H.; Rafei, M.; Karimi, M.H. *Synth. Commun.* ***2001***, *31*, 771.
[2015] Bosco, J.W.J.; Agrahari, A.; Saikia, A.K. *Tetrahedron Lett.* ***2006***, *47*, 4065.
[2016] Coleman, M.T. *Synth. Commun.* ***2012***, *42*, 1911.
[2017] De Santi, V.; Cardellini, F.; Brinchi, L.; Germani, R. *Tetrahedron Lett.* ***2012***, *53*, 5151.
[2018] Chen, Z.; Wen, Y.; Fu, Y.; Chen, H.; Ye, M.; Luo, G. *Synlett* ***2017***, *28*, 981.
[2019] Okuno, Y.; Isomura, S.; Nishibayashi, A.; Hosoi, A.; Fukuyama, K.; Ohba, M.; Takeda, K. *Synth. Commun.* ***2014***, *44*, 2854.
[2020] Audubert, C.; Lebel, H. *Org. Lett.* ***2017***, *19*, 4407.
[2021] Qu, J.; Roßberg, L.; Helmchen, G. *J. Am. Chem. Soc.* ***2014***, *136*, 1272.
[2022] Jacobson, C.E.; Martinez-Muñoz, N.; Gorin, D.J. *J. Org. Chem.* ***2015***, *80*, 7305.

benzaldehydes and aryl ketones gave the diazoalkane that reacted with carboxylic acids to form the ester.[2023] Carboxylic acids reacted with alcohols to give the ester using a macroporous polymeric acid catalyst.[2024] Carboxylic esters reacted with perfluorinated alcohols, mediated by XtalFluor-E [(diethylamino)difluorosulfonium tetrafluoroborate], to give the ester.[2025] Sulfonated polypyrene (S-PPR) was used as a catalyst for the reaction of carboxylic acids and alcohols to give the corresponding esters.[2026] Transition metal compounds of Ti,[2027] Fe,[2028] or Co[2029] catalyze esterification. Allylic sulfonium salts react with carboxylic acids to give allylic esters in the presence of CuBr.[2030] Triphenylphosphine dibromide is a useful esterification reagent.[2031] Phenols can be esterified using amide acetals.[2032] The reaction of a carboxylic acid with an alcohol, in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD), gives the corresponding ester. This reaction is known as the *Mitsunobu reaction* (see **10-17**). A variation of this esterification reaction used azopyridines to mediate formation of the ester.[2033]

Both γ- and δ-hydroxy acids are easily converted to a lactone by treatment with acids, or often simply on standing, but larger and smaller lactone rings cannot be made in this manner.[2034] Often the conversion of a group to a hydroxyl group gives the lactone directly when the hydroxy acid cyclizes too rapidly for isolation. Such groups include keto or halogen that are γ or δ to a carboxyl group. β-Substituted β-hydroxy acids can be converted to β-lactones by treatment with benzenesulfonyl chloride in pyridine at 0–5 °C.[2035] ε-Lactones (seven-membered rings) have been made by cyclization of ε-hydroxy acids at high dilution.[2036] Macrocyclic lactones[2037] can be prepared indirectly in very good yields by conversion of the hydroxy acids to 2-pyridinethiol esters and adding these to xylene at reflux.[2038]

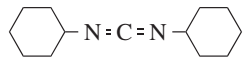
A closely related method, which often gives higher yields of a macrocyclic lactone, involves treatment of the hydroxy acids with 1-methyl- or 1-phenyl-2-halopyridinium salts, especially 1-methyl-2-chloropyridinium iodide (*Mukaiyama's reagent*).[2039] A macrocyclization technique has been developed based on formation of a mixed anhydride. The

[2023] Squitieri, R.A.; Shearn-Nance, G.P.; Hein, J.E.; Shaw, J.T. *J. Org. Chem.* ***2016***, *81*, 5278.
[2024] Minakawa, M.; Baek, H.; Yamada, Y.M.A.; Han, J.W.; Uozumi, Y. *Org. Lett.* ***2013***, *15*, 5798.
[2025] Vandamme, M.; Bouchard, L.; Gilbert, A.; Keita, M.; Paquin, J.-F. *Org. Lett.* ***2016***, *18*, 6468.
[2026] Tanemura, K.; Suzuki, T. *Tetrahedron Lett.* ***2013***, *54*, 1972.
[2027] Chen, C.-T.; Munot, Y.S. *J. Org. Chem.* ***2005***, *70*, 8625.
[2028] Weng, S.-S.; Chen, F.-K.; Ke, C.-S. *Synth. Commun.* ***2013***, *43*, 2615.
[2029] Velusamy, S.; Borpuzari, S.; Punniyamurthy, T. *Tetrahedron* ***2005***, *61*, 2011.
[2030] Sedighi, M.; Çalimsiz, S.; Lipton, M.A. *J. Org. Chem.* ***2006***, *71*, 9517.
[2031] Salomé, C.; Kohn, H. *Tetrahedron* ***2009***, *65*, 456.
[2032] Vorbrüggen, H. *Synlett* ***2008***, 1603.
[2033] Iranpoor, N.; Firouzabadi, H.; Khalili, D.; Motevalli, S. *J. Org. Chem.* ***2008***, *73*, 4882.
[2034] Wolfe, J.F.; Ogliaruso, M.A. in Patai, S. *The Chemistry of Acid Derivatives*, pt. 2, Wiley, NY, ***1979***, pp. 1062–1330. For a list of methods for converting hydroxy acids to lactones, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1989***, pp. 1861–1867.
[2035] Adam, W.; Baeza, J.; Liu, J. *J. Am. Chem. Soc.* ***1972***, *94*, 2000. Also see Merger, F. *Chem. Ber.* ***1968***, *101*, 2413; Blume, R.C. *Tetrahedron Lett.* ***1969***, 1047.
[2036] Lardelli, G.; Lamberti, V.; Weller, W.T.; de Jonge, A.P. *Recl. Trav. Chim. Pays-Bas* ***1967***, *86*, 481.
[2037] See Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* ***2006***, *106*, 911. See Bédard, A.-C.; Collins, S.K. *Chem. Eur. J.* ***2013***, *19*, 2108.
[2038] Thalmann, A.; Oertle, K.; Gerlach, H. *Org. Synth.* VII, 470. See also, Schmidt, U.; Heermann, D. *Angew. Chem. Int. Ed.* ***1979***, *18*, 308; Trost, B.M.; Chisholm, J.D. *Org. Lett.* ***2002***, *4*, 3743.
[2039] See Mukaiyama, T. *Angew. Chem. Int. Ed.* ***1979***, *18*, 707; Convers, E.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* ***2004***, *45*, 3401. For a microwave-assisted reaction, see Donati, D.; Morelli, C.; Taddei, M. *Tetrahedron Lett.* ***2005***, *46*, 2817.

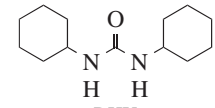
Yamaguchi protocol[2040] reacts a seco acid (the hydroxy acid precursor of a macrocyclic lactone) with 2,4,6-trichlorobenzoyl chloride, and the resulting mixed anhydride is heated with DMAP (4-*N*,*N*-dimethylaminopyridine) in toluene.

Esterification is catalyzed by acids (not bases), as discussed in **16-58**.[1911] The mechanisms are usually $A_{AC}2$, but $A_{AC}1$ and $A_{AL}1$ have also been observed.[2041] Certain acids, such as 2,6-di-ortho-substituted benzoic acids, cannot be esterified by the $A_{AC}2$ mechanism because of steric hindrance (Sec. 10.G.i, category 1). In such cases, esterification can be accomplished by dissolving the acid in 100% H_2SO_4 (forming the ion RCO^+) and pouring the solution into the alcohol ($A_{AC}1$ mechanism). The reluctance of hindered acids to undergo the normal $A_{AC}2$ mechanism can sometimes be put to advantage when, in a molecule containing two CO_2H groups, only the less hindered one is esterified. The $A_{AC}1$ pathway cannot be applied to unhindered carboxylic acids.

Another way to esterify a carboxylic acid is to treat it with an alcohol in the presence of a dehydrating agent.[2005] One such dehydrating agent is dicyclohexylcarbodiimide (DCC), which is converted in the process to dicyclohexylurea (DHU).



DCC



DHU

The mechanism[2042] has much in common with the nucleophilic catalysis mechanism; the acid is converted to a compound with a better leaving group, but the conversion is not by a tetrahedral mechanism (as it is in nucleophilic catalysis), since the C—O bond remains intact. The carboxylic acid adds to the electrophilic carbon of the diimide to give acyloxyurea. In effect, the H—CO—N unit (a putative urea) becomes a good leaving group, allowing reaction of the acyl group with the alcohol, and loss of dicyclohexylurea gives the ester. Evidence for this mechanism was the preparation of *O*-acylureas and the finding that when catalyzed by acids they react with alcohols to give esters.[2043] Hindered tertiary alcohols can be coupled via DCC to give the hindered ester.[2044]

There are limitations to the use of DCC for esterification. The yields are variable and *N*-acylureas are side products, which are sometimes very difficult to remove even by chromatography. Many other dehydrating agents[2045] have been used, including DCC and an aminopyridine,[2046] chlorosilanes,[2047] and *N*,*N*′-carbonyldiimidazole.[2048] In the latter case acyl imidazolides are intermediates that react with alcohols.

[2040] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* ***1979***, *52*, 1989; Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis*, 2nd ed., Wiley-Interscience, New Jersey, ***2005***, pp. 710–711. For a discussion of the mechanism, see Dhimitruka, I.; SantaLucia, Jr., J. *Org. Lett.* ***2006***, *8*, 47.

[2041] See Salomaa, P.; Kankaanperä, A.; Pihlaja, K. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 466–481.

[2042] Balcom, B.J.; Petersen, N.O. *J. Org. Chem.* ***1989***, *54*, 1922.

[2043] Doleschall, G.; Lempert, K. *Tetrahedron Lett.* ***1963***, 1195.

[2044] Shimizu, T.; Hiramoto, K.; Nakata, T. *Synthesis* ***2001***, 1027.

[2045] See Arrieta, A.; García, T.; Lago, J.M.; Palomo, C. *Synth. Commun.* ***1983***, *13*, 471.

[2046] Boden, E.P.; Keck, G.E. *J. Org. Chem.* ***1985***, *50*, 2394.

[2047] Brook, M.A.; Chan, T.H. *Synthesis* ***1983***, 201.

[2048] See Staab, H.A.; Rohr, W. *Newer Methods Prep. Org. Chem.* ***1968***, *5*, 61. See also, Morton, R.C.; Mangroo, D.; Gerber, G.E. *Can. J. Chem.* ***1988***, *66*, 1701.

Carboxylic acids were coupled with primary alcohols to give the esters using the water-soluble carbodiimide 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and (2,2-dimethyl-1,3-dioxolan-4-yl)methyl 2-cyano-2-(hydroxyimino)acetate.[2049] Methyl esters were formed by the reaction of carboxylic acids and methanol, catalyzed by polymer-supported triphenylphosphine/2,4,6-trichloro-1,3,5-triazine/Na_2CO_3.[2050]

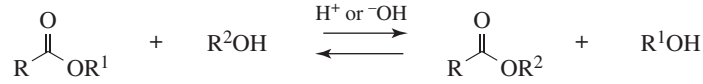
It is known that the Lewis acid BF_3 promotes esterification by converting an acid to an acylium ion so the reaction can proceed by an $A_{AC}1$ type of mechanism. The use of BF_3-etherate is simple and gives high yields.[2051] Other Lewis acids can be used.[2052]

Carboxylic esters can also be prepared by treating carboxylic acids with *tert*-butyl ethers and acid catalysts.[2053] Carboxylic esters can be formed from the carboxylate anion and a suitable alkylating agent (**10-26**). Aryl esters were formed by the reaction of carboxylic acids and diaryliodonium salts.[2054]

Thioesters of the type RSC(=S)R′ (a dithiocarboxylic ester) and RSC(C=O)R′ (a thiocarboxylic ester) can be generated by reaction of carboxylic acids with thiols. In one example, phosphorus pentasulfide was used in conjunction with a thiol to make dithiocarboxylic esters[2055] or thiocarboxylic esters.[2056] Thiocarboxylic esters were prepared from thiols and triflic acid.[2057]

OS **I**, 42, 138, 237, 241, 246, 254, 261, 451; **II**, 260, 264, 276, 292, 365, 414, 526; **III**, 46, 203, 237, 381, 413, 526, 531, 610; **IV**, 169, 178, 302, 329, 390, 398, 427, 506, 532, 635, 677; **V**, 80, 762, 946; **VI**, 471, 797; **VII**, 93, 99, 210, 319, 356, 386, 470; **VIII**, 141, 251, 597; **IX**, 24, 58; **75**, 116, 129. Also see, OS **III**, 536, 742.

16-63 Transesterification



Transesterification[2058] is catalyzed[2059] by acids[2060] or bases,[2061] or done under neutral conditions.[2062] It is an equilibrium reaction that must be shifted in the desired direction.[2063] In

[2049] Wang, Y.; Aleiwi, B.A.; Wang, Q.; Kurosu, M. *Org. Lett.* ***2012***, *14*, 4910.
[2050] Jaita, S.; Phakhodee, W.; Pattarawarapan, M. *Synlett* ***2015***, *26*, 2006.
[2051] See Kadaba, P.K. *Synth. Commun.* ***1974***, *4*, 167.
[2052] **Bi**: Carrigan, D.; Freiberg, D.A.; Smith, R.C.; Zerth, H.M.; Mohan, R.S. *Synthesis* ***2001***, 2091; Mohammadpoor-Baltork, I.; Khosropour, A.R.; Aliyan, H. *J. Chem. Res.* ***2001***, 280. **Ce**: Pan, W.-B.; Chang, F.-R.; Wei, L.-M.; Wu, M.J.; Wu, Y.-C. *Tetrahedron Lett.* ***2003***, *44*, 331. **Fe**: Sharma, G.V.M.; Mahalingam, A.K.; Nagarajan, M.; Ilangovan, P.; Radhakrishna, P. *Synlett* ***1999***, 1200; Zhang, G.-S. *Synth. Commun.* ***1999***, *29*, 607. **Hf**: Ishihara, K.; Nakayama, M.; Ohara, S.; Yamamoto, H. *Tetrahedron* ***2002***, *58*, 8179.
[2053] Derevitskaya, V.A.; Klimov, E.M.; Kochetkov, N.K. *Tetrahedron Lett.* ***1970***, 4269. See also, Mohacsi, E. *Synth. Commun.* ***1982***, *12*, 453.
[2054] Petersen, T.B.; Khanm R.; Olofsson, B. *Org. Lett.* ***2011***, *13*, 3462.
[2055] Sudalai, A.; Kanagasabapathy, S.; Benicewicz, B.C. *Org. Lett.* ***2000***, *2*, 3213.
[2056] Curphey, T.J. *Tetrahedron Lett.* ***2002***, *43*, 371.
[2057] Iimura, S.; Manabe, K.; Kobayashi, S. *Chem. Commun.* ***2002***, 94.
[2058] Otera, J. *Chem. Rev.* ***1993***, *93*, 1449.
[2059] For a list of catalysts, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1969–1973.
[2060] See Chavan, S.P.; Subbarao, Y.T.; Dantale, S.W.; Sivappa, R. *Synth. Commun.* ***2001***, *31*, 289.
[2061] See Mhasni, O.; Erray, I.; Rezgui, F. *Synth. Commun.* ***2014***, *44*, 3320.
[2062] See Imwinkelried, R.; Schiess, M.; Seebach, D. *Org. Synth.*, ***65***, 230; Bandgar, B.P.; Uppalla, L.S.; Sadavarte, V.S. *Synlett* ***2001***, 1715.
[2063] See Bose, D.S.; Satyender, A.; Rudra Das, A.P.; Mereyala, H.B. *Synthesis* ***2006***, 2392.

many cases low-boiling esters can be converted to higher-boiling ones by the distillation of the lower-boiling alcohol as fast as it is formed. Reagents used to catalyze[2064] transesterification include various Lewis acids.[2065] Transition metal catalysts have been used, including Fe,[2066] Zn,[2067] Pd,[2068] La,[2069] or Y compounds.[2070] Organocatalysts have also been used.[2071] Tetraethylammonium hydrogencarbonate has been used as a catalyst.[2072] Transesterification has been catalyzed by dilithium tetra-*tert*-butylzincate.[2073] A polymer-bound siloxane has been used to induce transesterification.[2074] A solvent-free transesterification has been reported using a ball-mill over an alumina surface.[2075] The high-pressure transesterification of sterically hindered esters has been reported.[2076] Enzymatic transesterification reactions are known.[2077]

Vinyl acetate has been used for transesterification, usually with a co-reagent or metal mediator,[2078] and is a method for the acylation of a primary OH in the presence of a secondary OH.[2079] Regioselectivity has also been accomplished by using enzymes (lipases) as catalysts.[2080] Lactones are easily opened by treatment with alcohols[2081] to give open-chain hydroxy esters. Transesterification has been carried out with phase-transfer catalysts, without an added solvent.[2082] Nonionic superbases (Sec. 8.A.i) of the type $P(RNCH_2CH_2)_3N$ catalyze the transesterification of carboxylic acid esters at 25 °C.[2083] Thioesters are converted to phenolic esters by treatment with triphosgene/pyridine and then phenol.[2084] The In/I_2 mediated conversion of dithioesters to esters has been reported.[2085]

Transesterification occurs by mechanisms[2086] that are identical with those of ester hydrolysis and transesterification reactions frequently fail when R′ is tertiary, since this

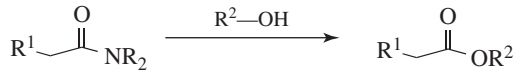
[2064] For a review, see Grasa, G.A.; Singh, R.; Nolan, S.P. *Synthesis* ***2004***, 971.
[2065] See Štefane, B.; Kočevar, M.; Polanc, S. *Synth. Commun.* ***2002***, *32*, 1703.
[2066] Weng, S.-S.; Ke, C.-S.; Chen, F.-K.; Lyu, Y.-F.; Lin, G.-Y. *Tetrahedron* ***2011***, *67*, 1640.
[2067] Maegawa, Y.; Agura, K.; Hayashi, Y.; Ohshima, T.; Mashima, K. *Synlett* ***2012***, *23*, 137.
[2068] See Xia, J.; Shao, A.; Tang, S.; Gao, X.; Gao, M.; Lei, A. *Org. Biomol. Chem.* ***2015***, *13*, 6154.
[2069] See Hatano, M.; Kamiya, S.; Moriyama, K.; Ishihara, K. *Org. Lett.* ***2011***, *13*, 430.
[2070] Dharma Rao, G.B.; Kaushik, M.P. *Tetrahedron Lett.* ***2011***, *52*, 5104.
[2071] Yang, Y.-C.; Leung, D.Y.C.; Toy, P.H. *Synlett* ***2013***, *24*, 1870; Chiarotto, I.; Feroci, M.; Sotgiu, G.; Inesi, A. *Eur. J. Org. Chem.* ***2013***, 326; Ishihara, K.; Niwa, M.; Kosugi, Y. *Org. Lett.* ***2008***, *10*, 2187.
[2072] Chiarotto, I. *Synth. Commun.* ***2016***, *46*, 1840.
[2073] Oshimura, M.; Oda, Y.; Kondoh, K.; Hirano, T.; Ute, K. *Tetrahedron Lett.* ***2016***, *57*, 2070.
[2074] Hagiwara, H.; Koseki, A.; Isobe, K.; Shimizu, K.-i.; Hoshi, T.; Suzuki, T. *Synlett* ***2004***, 2188.
[2075] Chatterjee, T.; Saha, D.; Ranu, B.C. *Tetrahedron Lett.* ***2012***, *53*, 4142.
[2076] Romanski, J.; Nowak, P.; Kosinski, K.; Jurczak, J. *Tetrahedron Lett.* ***2012***, *53*, 5287.
[2077] Hoang, H.N.; Matsuda, T. *Tetrahedron Lett.* ***2015***, *56*, 639; Kitayama, T.; Isomori, S.; Nakamura, K. *Tetrahedron: Asymmetry* ***2013***, *24*, 621. See Gładkowski, W.; Gliszczyńska, A.; Siepka, M.; Czarnecka, M.; Maciejewska, G. *Tetrahedron: Asymmetry* ***2015***, *26*, 702.
[2078] Shirae, Y.; Mino, T.; Hasegawa, T.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* ***2005***, *46*, 5877.
[2079] Yamada, S. *Tetrahedron Lett.* ***1992***, *33*, 2171. See also, Costa, A.; Riego, J.M. *Can. J. Chem.* ***1987***, *65*, 2327.
[2080] Wong, C.H.; Whitesides, G.M. in Baldwin, J.E. *Enzymes in Synthetic Organic Chemistry*, *Tetrahedron Organic Chemistry Series*, Vol. 12, Pergamon Press, NY, ***1994***; Faber, K. *Biotransformations in Organic Chemistry. A Textbook*, 2nd ed., Springer-Verlag, NY, ***1995***; Ciuffreda, P.; Casati, S.; Santaniello, E. *Tetrahedron Lett.* ***2003***, *44*, 3663.
[2081] Anand, R.C.; Sevlapalam, N. *Synth. Commun.* ***1994***, *24*, 2743.
[2082] Barry, J.; Bram, G.; Petit, A. *Tetrahedron Lett.* ***1988***, *29*, 4567. See also, Nishiguchi, T.; Taya, H. *J. Chem. Soc., Perkin Trans. 1* ***1990***, 172.
[2083] Ilankumaran, P.; Verkade, J.G. *J. Org. Chem.* ***1999***, *64*, 3086.
[2084] Joshi, U.M.; Patkar, L.N.; Rajappa, S. *Synth. Commun.* ***2004***, *34*, 33.
[2085] Chowdhury, S.; Koley, S.; Chanda, T.; Singh, M.S. *Tetrahedron Lett.* ***2015***, *56*, 5553.
[2086] See Koskikallio, E.A. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 103–136.

type of substrate most often reacts by alkyl-oxygen cleavage. In such cases, the reaction is of the Williamson type with OCOR as the leaving group (see **10-10**).

With enol esters, reaction with an alcohol gives an ester and the enol of a ketone, which readily tautomerizes to the ketone. Hence, enol esters are good acylating agents for alcohols.[2087] This transformation has been accomplished in ionic liquid media,[2088] and there is a $PdCl_2/CuCl_2$-mediated version.[2089] Isopropenyl acetate can also be used to convert other ketones to the corresponding enol acetates in an exchange reaction.[2090] Enol esters can also be prepared in the opposite type of exchange reaction, where a carboxylic acid reacts with an enol ester, catalyzed by mercuric acetate[2091] or Pd(II) chloride[2092] to give a new enol ester and another carboxylic acid.

OS **II**, 5, 122, 360; **III**, 123, 146, 165, 231, 281, 581, 605; **IV**, 10, 549, 630, 977; **V**, 155, 545, 863; **VI**, 278; **VII**, 4, 164, 411; **VIII**, 155, 201, 235, 263, 350, 444, 528. See also, OS **VII**, 87; **VIII**, 71.

16-64 Esters From Amides

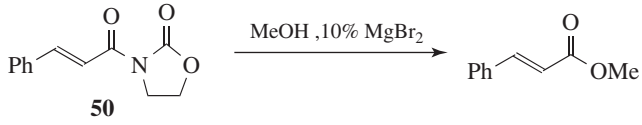


Alcoholysis of amides is possible,[2093] although it is usually difficult. It is most common with the imidazole type of amides, acylimidazoles. For other amides, an activating agent is usually necessary before the alcohol will replace the NR_2 unit. A scandium triflate $(ScOTf)_3$-catalyzed reaction of primary amides and esters gave the primary amide.[2094] The esterification of *N*-β-hydroxyethyl amides was catalyzed by manganese compounds.[2095]

Dimethylformamide reacted with primary alcohols in the presence of 2,4,6-trichloro-1,3,5-pyrazine (cyanuric acid) to give the corresponding formate ester.[2096] Treatment of an amide with triflic anhydride ($CF_3SO_2OSO_2CF_3$) in the presence of pyridine and then with an excess of alcohol leads to the ester,[2097] as does treatment with $Me_2NCH(OMe)_2$ followed by the alcohol.[2098] Trimethyloxonium tetrafluoroborate converted primary amides to methyl esters.[2099] Acyl hydrazides ($RCONHNH_2$) were converted to esters by reaction with alcohols and various reagents,[2100] and methoxyamides (RCONHOMe) were converted

[2087] Ilankumaran, P.; Verkade, J.G. *J. Org. Chem.* ***1999***, *64*, 9063.
[2088] Grasa, G.A.; Kissling, R.M.; Nolan, S.P. *Org. Lett.* ***2002***, *4*, 3583.
[2089] Bosco, J.W.J.; Saikia, A.K. *Chem. Commun.* ***2004***, 1116.
[2090] See House, H.O.; Trost, B.M. *J. Org. Chem.* ***1965***, *30*, 2502.
[2091] See Mondal, M.A.S.; van der Meer, R.; German, A.L.; Heikens, D. *Tetrahedron* ***1974***, *30*, 4205.
[2092] Henry, P.M. *J. Am. Chem. Soc.* ***1971***, *93*, 3853; *Acc. Chem. Res.* ***1973***, *6*, 16.
[2093] For example, see Czarnik, A.W. *Tetrahedron Lett.* ***1984***, *25*, 4875. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 197–198.
[2094] Atkinson, B.N.; Williams, J.M.J. *Tetrahedron Lett.* ***2014***, *55*, 6935.
[2095] Nishii, Y.; Akiyama, S.; Kita, Y.; Mashima, K. *Synlett* ***2015***, *26*, 1831.
[2096] DeLuca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* ***2002***, *67*, 5152.
[2097] Charette, A.B.; Chua, P. *Synlett* ***1998***, 163.
[2098] Anelli, P.L.; Brocchetta, M.; Palano, D.; Visigalli, M. *Tetrahedron Lett.* ***1997***, *38*, 2367.
[2099] Kiessling, A.J.; McClure, C.K. *Synth. Commun.* ***1997***, *27*, 923.
[2100] See Yamaguchi, J.-i.; Aoyagi, T.; Fujikura, R.; Suyama, T. *Chem. Lett.* ***2001***, 466.

to esters with $TiCl_4$/ROH.[2101] The reaction of an oxazolidinone amide **50** with methanol and 10% $MgBr_2$ gave the corresponding methyl ester.[2102]



50

Thioesters were prepared via the solvent-free reaction of thioamide derivatives with alkyl halides, with DABCO and with small quantities of water.[2103] *N*-Alkoxy amides were converted to esters using an electrochemical method using *n*-Bu_4NI as the redox catalyst as well as the supporting electrolyte.[2104]

C. Attack by OCOR at an Acyl Carbon

16-65 Acylation of Carboxylic Acids With Acyl Halides

$$RCOCl + R'COO^- \longrightarrow RCOOCOR'$$

Unsymmetrical, as well as symmetrical, anhydrides are often prepared by the treatment of an acyl halide with a carboxylic acid salt. If a metallic salt is used, Na^+, K^+, or Ag^+ are the most common cations, but more often pyridine or another tertiary amine is added to the free acid and the resulting salt is subsequently treated with the acyl halide. Zinc/DMF has been used to mediate the synthesis of symmetrical anhydrides from acid chlorides.[2105] Cobalt(II) chloride ($CoCl_2$) has been used as a catalyst.[2106] Mixed formic anhydrides are prepared from sodium formate and an aryl halide, by use of a solid-phase copolymer of pyridine-1-oxide.[2107] Symmetrical anhydrides can be prepared by reaction of the acyl halide with aqueous NaOH or $NaHCO_3$ under phase-transfer conditions,[2108] or with sodium bicarbonate with ultrasound.[2109] Using a Sc catalyst, anhydrides were formed from twisted amides.[2110]

OS **III**, 28, 422, 488; **IV**, 285; **VI**, 8, 910; **VIII**, 132. See also, OS **VI**, 418.

16-66 Acylation of Carboxylic Acids With Carboxylic Acids

$$2\ RCOOH \underset{}{\overset{P_2O_5}{\rightleftharpoons}} (RCO)_2O + H_2O$$

Anhydrides can be formed from two molecules of an ordinary carboxylic acid only if a dehydrating agent is present so that the equilibrium can be driven to the right.

[2101] Fisher, L.E.; Caroon, J.M.; Stabler, S.R.; Lundberg, S.; Zaidi, S.; Sorensen, C.M.; Sparacino, M.L.; Muchowski, J.M. *Can. J. Chem.* ***1994***, *72*, 142.
[2102] Orita, A.; Nagano, Y.; Hirano, J.; Otera, J. *Synlett* ***2001***, 637.
[2103] Boeini, H.Z.; Zali, A. *Synth. Commun.* ***2010–2011***, *41*, 2421.
[2104] Subramanian, K.; Yedage, S.L.; Bhanage, B.M. *J. Org. Chem.* ***2017***, *82*, 10025.
[2105] Serieys, A.; Botuha, C.; Chemla, F.; Ferreira, F.; Pérez-Luna, A. *Tetrahedron Lett.* ***2008***, *49*, 5322.
[2106] Srivastava, R.R.; Kabalka, G.W. *Tetrahedron Lett.* ***1992***, *33*, 593.
[2107] Fife, W.K.; Zhang, Z. *J. Org. Chem.* ***1986***, *51*, 3744. For a review of acetic formic anhydride, see Strazzolini, P.; Giumanini, A.G.; Cauci, S. *Tetrahedron* ***1990***, *46* 1081.
[2108] Plusquellec, D.; Roulleau, F.; Lefeuvre, M.; Brown, E. *Tetrahedron* ***1988***, *44*, 2471; Wang, J.; Hu, Y.; Cui, W. *J. Chem. Res. (S)* ***1990***, 84.
[2109] Hu, Y.; Wang, J.-X.; Li, S. *Synth. Commun.* ***1997***, *27*, 243.
[2110] Liu, Y.; Liu, R.; Szostak, M. *Org. Biomol. Chem.* ***2017***, *15*, 1780.

Common dehydrating agents[2111] are acetic anhydride, trifluoroacetic anhydride, dicyclohexylcarbodiimide,[2112] and P_2O_5. Triphenylphosphine/CCl_3CN with triethylamine has also been used with benzoic acid derivatives.[2113] The method is very poor for the formation of mixed anhydrides, which in any case generally undergo disproportionation to the two simple anhydrides when they are heated. However, simple heating of dicarboxylic acids does give cyclic anhydrides, provided that the ring formed contains five, six, or seven members. Malonic acid and its derivatives, which would give four-membered cyclic anhydrides, do not give this reaction when heated, but undergo decarboxylation (**12-39**) instead.

Carboxylic acids exchange with amides and esters; these methods are sometimes used to prepare anhydrides if the equilibrium can be shifted. Enolic esters are especially good for this purpose, because the equilibrium is shifted by formation of the ketone. The combination of KF with 2-acetoxypropene under microwave conditions was effective.[2114] Carboxylic acids also exchange with anhydrides; indeed, this is how acetic anhydride acts as a dehydrating agent in this reaction.

Anhydrides can be formed from certain carboxylic acid salts, as exemplified by the treatment of trimethylammonium carboxylates with phosgene[2115] or of thallium(I) carboxylates with thionyl chloride,[1973] or of sodium carboxylates with CCl_4 and a catalyst such as CuCl or $FeCl_2$.[2116]

OS **I**, 91, 410; **II**, 194, 368, 560; **III**, 164, 449; **IV**, 242, 630, 790; **V**, 8, 822; **IX**, 151. Also see, OS **VI**, 757; **VII**, 506.

16-67 Preparation of Mixed Organic-Inorganic Anhydrides

$$(RCO)_2O + HONO_2 \longrightarrow RCOONO_2$$

Mixed organic-inorganic anhydrides are seldom isolated, although they are often intermediates when acylation is carried out with acid derivatives catalyzed by inorganic acids. Sulfuric, perchloric, phosphoric, and other acids form similar anhydrides, most of which are unstable or not easily obtained because the equilibrium lies in the wrong direction. These intermediates are formed from amides, carboxylic acids, and esters, as well as anhydrides. Organic anhydrides of phosphoric acid are more stable than most others; for example, $RCOOPO(OH)_2$ can be prepared in the form of its salts.[2117] Mixed anhydrides of carboxylic and sulfonic acids ($RCOOSO_2R'$) are obtained in high yields by treatment of sulfonic acids with acyl halides or (less preferred) with anhydrides.[2118]

OS **I**, 495; **VI**, 207; **VII**, 81.

[2111] For lists of other dehydrating agents with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1930–1932; Ogliaruso, M.A.; Wolfe, J.F. in Patai, S. *The Chemistry of Acid Derivatives*, pt.1, Wiley, NY, ***1979***, pp. 437–438.

[2112] See Rammler, D.H.; Khorana, H.G. *J. Am. Chem. Soc.* ***1963***, *85*, 1997. See also, Hata, T.; Tajima, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***1968***, *41*, 2746.

[2113] Kim, J.; Jang, D.O. *Synth. Commun.* ***2001***, *31*, 395.

[2114] Villemin, D.; Labiad, B.; Loupy, A. *Synth. Commun.* ***1993***, *23*, 419.

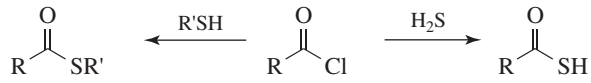
[2115] Rinderknecht, H.; Ma, V. *Helv. Chim. Acta* ***1964***, *47*, 152. See also, Nangia, A.; Chandrasekaran, S. *J. Chem. Res. (S)* ***1984***, 100.

[2116] Weiss, J.; Havelka, F.; Nefedov, B.K. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1978***, *27*, 193.

[2117] Avison, A.W.D. J. *Chem. Soc.* ***1955***, 732.

[2118] Karger, M.H.; Mazur, Y. *J. Org. Chem.* ***1971***, *36*, 528.

16-68 Attack by SH or SR at an Acyl Carbon[2119]



Thiol acids and thiol esters[2120] can be prepared from acid chlorides, which is analogous to **16-56** and **16-63**. Anhydrides[2121] and aryl esters (RCOOAr)[2122] are also used as substrates, but the reagents in these cases are usually HS^- and RS^-. Thiol esters can also be prepared by treatment of carboxylic acids with P_4S_{10}/Ph_3SbO,[2123] or with a thiol (RSH) and either polyphosphate ester or phenyl dichlorophosphate ($PhOPOCl_2$).[2124] Carboxylic acids are converted to thioacids with *Lawesson's reagent* (structure **13** in **16-10**).[2125] Esters (RCOOR′) can be converted to thiol esters ($RCOSR^2$) by treatment with trimethylsilyl sulfides (Me_3SiSR^2) and $AlCl_3$.[2126]

OS **III**, 116, 599; **IV**, 924, 928; **VII**, 81; **VIII**, 71.

16-69 Transamidation

It is sometimes necessary to replace one amide group with another, particularly when the group attached to nitrogen functions as a protecting group.[2127] Transamidation has been catalyzed by transition metals, as in the reaction of carboxamides with a Sb[2128] or Zr[2129] catalyst, with an Fe catalyst and water,[2130] or under solvent-free conditions.[2131] Boric acid,[2132] L-proline,[2133] and hydroxylamine hydrochloride[2134] have been used as catalysts. *N*-Benzyl amides can be converted to the corresponding *N*-allyl amide with allylamine and Ti catalysts.[2135] Reaction of *N*-Boc 2-phenylethylamine with $Ti(O\textit{i}\text{-}Pr)_4$ and benzyl alcohol,

[2119] See Satchell, D.P.N. *Q. Rev. Chem. Soc.* ***1963***, *17*, 160 (pp. 182–184).
[2120] See Scheithauer, S.; Mayer, R. *Top. Sulfur Chem.* ***1979***, *4*, 1.
[2121] Ahmad, S.; Iqbal, J. *Tetrahedron Lett.* ***1986***, *27*, 3791.
[2122] Hirabayashi, Y.; Mizuta, M.; Mazume, T. *Bull. Chem. Soc. Jpn.* ***1965***, *38*, 320.
[2123] Nomura, R.; Miyazaki, S.; Nakano, T.; Matsuda, H. *Chem. Ber.* ***1990***, *123*, 2081.
[2124] Imamoto, T.; Kodera, M.; Yokoyama, M. *Synthesis* ***1982***, 134. See also, Dellaria Jr., F.F.; Nordeen, C.; Swett, L.R. *Synth. Commun.* ***1986***, *16*, 1043.
[2125] Rao, Y.; Li, X.; Nagorny, P.; Hayashida, J.; Danishefsky, S.J. *Tetrahedron Lett.* ***2009***, *50*, 6684.
[2126] Mukaiyama, T.; Takeda, T.; Atsumi, K. *Chem. Lett.* ***1974***, 187. See also, Cohen, T.; Gapinski, R.E. *Tetrahedron Lett.* ***1978***, 4319.
[2127] See Knipe, A.C. *J. Chem. Soc., Perkin Trans. 2* ***1973***, 589. For a review of nonclassical amide-forming reactions, see de Figueiredo, R.M.; Suppo, J.-S.; Campagne, J.-M. *Chem. Rev.* ***2016***, *116*, 12029.
[2128] Ojeda-Porras, A.; Gamba-Sánchez, D. *Tetrahedron Lett.* ***2015***, *56*, 4308.
[2129] Atkinson, B.N.; Chhatwal, A.R.; Lomax, H.V.; Walton, J.W.; Williams, J.M.J. *Chem. Commun.* ***2012***, *48*, 11626.
[2130] Becerra-Figueroa, L.; Ojeda-Porras, A.; Gamba-Sánchez, D. *J. Org. Chem.* ***2014***, *79*, 4544.
[2131] Ali, Md.A.; Siddiki, S.M.A.H.; Kon, K.; Shimizu, K.-i. *Tetrahedron Lett.* ***2014***, *55*, 1316.
[2132] Nguyen, T.B.; Sorres, J.; Tran, M.Q.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* ***2012***, *14*, 3202.
[2133] Rao, S.N.; Mohan, D.C.; Adimurthy, S. *Org. Lett.* ***2013***, *15*, 1496.
[2134] Allen, C.L.; Atkinson, B.N.; Williams, J.M.J. *Angew. Chem. Int. Ed.* ***2012***, *51*, 1383.
[2135] Eldred, S.E.; Stone, D.A.; Gellman, S.H.; Stahl, S.S. *J. Am. Chem. Soc.* ***2003***, *125*, 3422.

for example, gives the *N*-Cbz derivative (Cbz = carbobenzoxycarbonyl).[2136] *N*-Carbamoyl amines were converted to *N*-acetyl amines with acetic anhydride, Bu_3SnH, and a Pd catalyst.[2137]

Aryl amides with a N(Ph)Boc unit reacted with secondary amines and triethylamine to give the transamidation product, $ArCONR_2$.[2138] Microwave irradiation of primary amides with primary amines in 1,4-dioxane gave the secondary amide.[2139] Microwave irradiation of nonactivated carboxamides with amines in an ionic liquid led to transamidation.[2140] The reaction of amines with formamide and NaOMe gave the new formamide.[2141] A related process reacts acetamide with amines and aluminum chloride to give the *N*-acetyl amine.[2142]

Thioamides can be prepared from amides by reaction with an appropriate sulfur reagent. Lawesson's reagent has been used to convert amides to thioamides.[2143] The reaction of *N*,*N*-dimethylacetamide, under microwave irradiation, with a polymer-bound reagent gave a thioamide.[2144] Ammonium phosphorodithioate has been used to convert amides to thioamides.[2145] Thioamides were converted to the amide with visible light-mediated, eosin Y-catalyzed aerobic desulfurization.[2146] Reaction of the thioamide with $Bi(NO_3)_3 \cdot 5H_2O$ regenerates the amide.[2147] Other methods are known to convert a thioamide to an amide.[2148] Selenoamides ($RC(=Se)NR'_2$ have also been prepared from amides.[2149]

D. Attack by Halogen

16-70 The Conversion of Carboxylic Acids to Alkyl Halides

$$RCOOH \longrightarrow R{-}X$$

In certain cases, carboxyl groups can be replaced by halides. Acrylic acid derivatives ArCH=CHCOOH, for example, react with 3 molar equivalents of Oxone in the presence of NaBr to give a vinyl bromide ArCH=CHBr.[2150] Diphosphorus tetraiodide/tetraethylammonium bromide (TEAB) readily converts conjugated acids to vinyl bromides.[2151] In other cases, conjugated acids have been converted to the vinyl bromide by reaction with *N*-bromosuccinimide (NBS, reaction **14-3**) and LiOAc.[2152]

[2136] Shapiro, G.; Marzi, M. *J. Org. Chem.* ***1997***, *62*, 7096.
[2137] Roos, E.C.; Bernabé, P.; Hiemstra, H.; Speckamp, W.N.; Kaptein, B.; Boesten, W.H.J. *J. Org. Chem.* ***1995***, *60*, 1733.
[2138] Liu, Y.; Shi, S.; Achtenhagen, M.; Liu, R.; Szostak, M. *Org. Lett.* ***2017***, *19*, 1614.
[2139] Vanjari, R.; Allam, B.K.; Singh, K.N. *Tetrahedron Lett.* ***2013***, *54*, 2553.
[2140] Fu, R.; Yang, Y.; Chen, Z.; Lai, W.; Ma, Y.; Wang, Q.; Yuan, R. *Tetrahedron* ***2014***, *70*, 9492.
[2141] Joseph, S.; Das, P.; Srivastava, B.; Nizar, H.; Prasad, M. *Tetrahedron Lett.* ***2013***, *54*, 929.
[2142] Bon, E.; Bigg, D.C.H.; Bertrand, G. *J. Org. Chem.* ***1994***, *59*, 4035.
[2143] Kayukova, L.A.; Praliyev, K.D.; Gut'yar, V.G.; Baitursynova, G.P. *Russ. J. Org. Chem.* ***2015***, *51*, 148.
[2144] Ley, S.V.; Leach, A.G.; Storer, R.I. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 358.
[2145] Kaboudin, B.; Malekzadeh, L. *Synlett* ***2011***, *22*, 2807.
[2146] Yadav, A.K.; Srivastava, V.P.; Yadav, L.D.S. *New J. Chem.* ***2013***, 4119.
[2147] Mohammadpoor-Baltork, I.; Khodaei, M.M.; Nikoofar, K. *Tetrahedron Lett.* ***2003***, *44*, 591.
[2148] Inamoto, K.; Shiraishi, M.; Hiroya, K.; Doi, T. *Synthesis* ***2010***, 3087.
[2149] Saravanan, V.; Mukherjee, C.; Das, S.; Chandrasekaran, S. *Tetrahedron Lett.* ***2004***, *45*, 681.
[2150] You, H.-W.; Lee, K.-J. *Synlett* ***2001***, 105.
[2151] Telvekar, V.N.; Chettiar, S.N. *Tetrahedron Lett.* ***2007***, *48*, 4529.
[2152] Cho, C.-G.; Park, J.-S.; Jung, I.-H.; Lee, H. *Tetrahedron Lett.* ***2001***, *42*, 1065.

Alkyl chlorides were prepared from carboxylic acids by treatment with $CuCl_2$ with a $GaCl_3$ catalyst and a hydrosiloxane.[2153] The Ir-catalyzed conversion of carboxylic acids to alkyl bromides was reported.[2154]

E. Attack by Nitrogen at an Acyl Carbon[2155]

16-71 Acylation of Amines by Acyl Halides

$$RCOX + NH_3 \longrightarrow RCONH_2 + HX$$

The treatment of acyl halides with ammonia or amines is a very general reaction for the preparation of amides.[2156] The reaction is exothermic and must be carefully controlled, usually by cooling or dilution. Ammonia gives unsubstituted amides, primary amines give *N*-substituted amides,[2157] and secondary amines give *N*,*N*-disubstituted amides. Arylamines can be similarly acylated. Hydroxamic acids have been prepared by this route.[2158] In some cases, aqueous alkali is added to combine with the liberated HCl. This is called the *Schotten-Baumann procedure*, as in **16-60**. Activated Zn can be used to increase the rate of amide formation when hindered amines and/or acid chlorides are used.[2159] A solvent-free reaction was reported using DABCO and methanol.[2160] Metal-mediated reactions using In,[2161] Sm,[2162] or a BiOCl-mediated reaction[2163] have been reported. Formic acid and iodine react with amines to give the formamide.[2164] The Ag-catalyzed reaction of amines and acyl chlorides gave the amide.[2165]

Hydrazine and hydroxylamine also react with acyl halides to give, respectively, hydrazides ($RCONHNH_2$)[2166] and hydroxamic acids (RCONHOH).[2167] When phosgene is the acyl halide, both aliphatic and aromatic primary amines give chloroformamides (ClCONHR) that lose HCl to give isocyanates (RNCO).[2168] This is one of the most common methods for the preparation of isocyanates.[2169] Similar treatment with thiophosgene[2170]

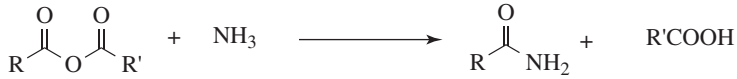
[2153] Sakai, N.; Nakajima, T.; Yoneda, S.; Konakahara, T.; Ogiwara, Y. *J. Org. Chem.* ***2014***, *79*, 10619.
[2154] Moriya, T.; Yoneda, S.; Kawana, K.; Ikeda, R.; Konakahara, T.; Sakai, N. *Org. Lett.* ***2012***, *14*, 4842.
[2155] See Challis, M.S.; Butler, A.R. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 279–290.
[2156] See Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 73–185; Jedrzejczak, M.; Motie, R.E.; Satchell, D.P.N. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 599.
[2157] See Bhattacharyya, S.; Gooding, O.W.; Labadie, J. *Tetrahedron Lett.* ***2003***, *44*, 6099.
[2158] Reddy, A.S.; Kumar, M.S.; Reddy, G.R. *Tetrahedron Lett.* ***2000***, *41*, 6285.
[2159] Meshram, H.M.; Reddy, G.S.; Reddy, M.M.; Yadav, J.S. *Tetrahedron Lett.* ***1998***, *39*, 4103.
[2160] Hajipour, A.R.; Mazloumi, Gh. *Synth. Commun.* ***2002***, *32*, 23.
[2161] Cho, D.H.; Jang, D.O. *Tetrahedron Lett.* ***2004***, *45*, 2285.
[2162] Shi, F.; Li, J.; Li, C.; Jia, X. *Tetrahedron Lett.* ***2010***, *51*, 6049.
[2163] Ghosh, R.; Maiti, S.; Chakraborty, A. *Tetrahedron Lett.* ***2004***, *45*, 6775.
[2164] Kim, J.-G.; Jang, D.O. *Synlett* ***2010***, 2093. For other formylation reactions, see Brahmachari, G.; Laskar, S. *Tetrahedron Lett.* ***2010***, *51*, 2319; Rahman, M.; Kundu, D.; Hajra, A.; Majee, A. *Tetrahedron Lett.* ***2010***, *51*, 2896.
[2165] Leggio, A.; Belsito, E.L.; Di Gioia, M.L.; Leotta, V.; Romio, E.; Siciliano, C.; Liguori, A. *Tetrahedron Lett.* ***2015***, *56*, 199.
[2166] Paulsen, H.; Stoye, D. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 515–600.
[2167] For an improved method, see Ando, W.; Tsumaki, H. *Synth. Commun.* ***1983***, *13*, 1053.
[2168] Richter, R.; Ulrich, H. pp. 619–818, and Drobnica, L.; Kristián, P.; Augustín, J. pp. 1003–1221, in Patai, S. *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 2, Wiley, NY, ***1977***.
[2169] See Ozaki, S. *Chem. Rev.* ***1972***, *72*, 457 (see pp. 457–460). For a review of the industrial preparation of isocyanates by this reaction, see Twitchett, H.J. *Chem. Soc. Rev.* ***1974***, *3*, 209.
[2170] For a review of thiophosgene, see Sharma, S. *Sulfur Rep.* ***1986***, *5*, 1.

gives isothiocyanates. A safer substitute for phosgene in this reaction is trichloromethyl chloroformate (CCl_3OCOCl).[2171] When chloroformates (ROCOCl) are treated with primary amines, carbamates (ROCONHR′) are obtained.[2172] An example of this reaction is the use of benzyl chloroformate to protect the amino group of amino acids and peptides.

The $PhCH_2OCO$ group is the carbobenzoxy group,[2173] and is often abbreviated Cbz or Z, but it is really a benzyl carbamate when the Cbz group is attached to nitrogen. Another important group similarly used is Boc, which is a *tert*-butyl carbamate when the Boc group is attached to nitrogen. In this case, the chloride ($Me_3COCOCl$) is unstable, so the anhydride, $(Me_3COCO)_2O$ is used instead, in an example of **16-72**. Amino groups in general are often protected by conversion to amides.[2174] The reactions proceed by the tetrahedral mechanism.[2175] Weinreb amides were prepared by the reaction of carboxylic acids and MeNHOMe in the presence of PCl_3.[2176]

OS **I**, 99, 165; **II**, 76, 208, 278, 328, 453; **III**, 167, 375, 415, 488, 490, 613; **IV**, 339, 411, 521, 620, 780; **V**, 201, 336; **VI**, 382, 715; **VII**, 56, 287, 307; **VIII**, 16, 339; **IX**, 559; **81**, 254. See also, OS **VII**, 302.

16-72 Acylation of Amines by Anhydrides



This reaction, similar in scope and mechanism[2177] to **16-71**, can be carried out with ammonia or primary or secondary amines.[2178] Note that there is a report where a tertiary amine (an *N*-alkylpyrrolidine) reacted with acetic anhydride at 120 °C, in the presence of a BF_3•etherate catalyst, to give *N*-acetylpyrrolidine (an acylative dealkylation).[2179] Amino acids can be *N*-acylated using acetic anhydride and ultrasound.[2180] However, ammonia and primary amines can also give imides, in which two acyl groups are attached to the nitrogen. The conversion of cyclic anhydrides to cyclic imides is generally facile,[2181] although elevated temperatures are occasionally required to generate the imide.[2182] Microwave

[2171] Kurita, K.; Iwakura, Y. *Org. Synth.* VI, 715.
[2172] See Shrikhande, J.J.; Gawande, M.B.; Jayaram, R.V. *Tetrahedron Lett.* ***2008***, *49*, 4799.
[2173] See Yasuhara, T.; Nagaoka, Y.; Tomioka, K. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2233.
[2174] Greene, T.W. *Protective Groups in Organic Synthesis*, Wiley, NY, ***1980***, pp. 222–248, 324–326; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis*, 2nd ed., Wiley, NY, ***1991***, pp. 327–330; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, NY, ***1999***, pp. 518–525, 737–739; Wuts, P.G.M. *Greene's Protective Groups in Organic Synthesis*, 5th ed., Wiley, New Jersey, ***2014***, pp. 812–827, 990–1024.
[2175] Kivinen, A. in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***; Bender, M.L.; Jones, J.M. *J. Org. Chem.* ***1962***, *27*, 3771. See also, Song, B.D.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 8479.
[2176] Niu, T.; Wang, K.-H.; Huang, D.; Xu, C.; Su, Y.; Hu, Y.; Fu, Y. *Synthesis* ***2014***, *46*, 320.
[2177] For a discussion of the mechanism, see Kluger, R.; Hunt, J.C. *J. Am. Chem. Soc.* ***1989***, *111*, 3325.
[2178] See Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 86–96. See also, Naik, S.; Bhattacharjya, G.; Talukdar, B.; Patel, B.K. *Eur. J. Org. Chem.* ***2004***, 1254.
[2179] Dave, P.R.; Kumar, K.A.; Duddu, R.; Axenrod, T.; Dai, R.; Das, K.K.; Guan, X.-P.; Sun, J.; Trivedi, N.J.; Gilardi, R.D. *J. Org. Chem.* ***2000***, *65*, 1207.
[2180] Anuradha, M.V.; Ravindranath, B. *Tetrahedron* ***1997***, *53*, 1123.
[2181] See Wheeler, O.H.; Rosado, O. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 335–381; Hargreaves, M.K.; Pritchard, J.G.; Dave, H.R. *Chem. Rev.* ***1970***, *70*, 439 (cyclic imides).
[2182] Tsubouchi, H.; Tsuji, K.; Ishikawa, H. *Synlett* ***1994***, 63.

irradiation of formamide and a cyclic anhydride generates the cyclic imide.[2183] Cyclic imides have been formed in ionic liquids.[2184] Cyclic imides were also formed by microwave irradiation of a polymer-bound phthalate after initial reaction with an amine.[2185] The second step for imide formation, which is much slower than the first, is the attack of the amide nitrogen on the carboxylic carbon. Unsubstituted and *N*-substituted amides have been used instead of ammonia. Since the other product of this reaction is RCOOH, this is a way of "hydrolyzing" such amides in the absence of water.[2186] The reaction of *meso*-diamines with benzoic anhydride in the presence of 4-(dimethylamino)pyridine, and a chiral amide–thiourea co-catalyst gave desymmetrization and formation of the monobenzamide.[2187] The Fe-catalyzed amide-forming reaction is known.[2188]

Even though formic anhydride is not a stable compound (see **11-17**), amines can be formylated with the mixed anhydride of acetic and formic acids HCOOCOMe[2189] or with a mixture of formic acid and acetic anhydride. Acetamides are not formed with these reagents. Secondary amines can be acylated in the presence of a primary amine by conversion to their salts and addition of 18-crown-6.[2190] The crown ether complexes the primary ammonium salt, preventing its acylation, while the secondary ammonium salts, which do not fit easily into the cavity, are free to be acylated. Dimethyl carbonate can be used to prepare methyl carbamates in a related procedure.[2191] *N*-Acetylsulfonamides were prepared from acetic anhydride and a primary sulfonamide, catalyzed by Montmorillonite K10/FeO[2192] or sulfuric acid.[2193]

OS **I**, 457; **II**, 11; **III**, 151, 456, 661, 813; **IV**, 5, 42, 106, 657; **V**, 27, 373, 650, 944, 973; **VI**, 1; **VII**, 4, 70; **VIII**, 132; **76**, 123.

16-73 Acylation of Amines by Carboxylic Acids

$$RCOOH + NH_3 \longrightarrow RCOO^-NH_4^+ \xrightarrow{\text{Pyrolysis}} RCONH_2$$

When carboxylic acids are treated with ammonia or amines, salts are obtained.[2194] The salts of ammonia or primary or secondary amines can be pyrolyzed to give amides,[2195] but the method is less convenient than **16-71**, **16-72**, and **16-74** and is of less preparative value.[2196] Heating in the presence of a base such as hexamethyldisilazide makes the amide-forming process more efficient.[2197] Boronic acids catalyze the direct conversion

[2183] Kacprzak, K. *Synth. Commun.* ***2003***, *33*, 1499.
[2184] Le, Z.-G.; Chen, Z.-C.; Hu, Y.; Zheng, Q.-G. *Synthesis* ***2004***, 995.
[2185] Martin, B.; Sekljic, H.; Chassaing, C. *Org. Lett.* ***2003***, *5*, 1851.
[2186] Eaton, J.T.; Rounds, W.D.; Urbanowicz, J.H.; Gribble, G.W. *Tetrahedron Lett.* ***1988***, *29*, 6553.
[2187] De, C.K.; Seidel, D. *J. Am. Chem. Soc.* ***2011***, *133*, 14538.
[2188] Li, Y.; Ma, L.; Jia, F.; Li, Z. *J. Org. Chem.* ***2013***, *78*, 5638.
[2189] Vlietstra, E.J.; Zwikker, J.W.; Nolte, R.J.M.; Drenth, W. *Recl. Trav. Chim. Pays-Bas* ***1982***, *101*, 460.
[2190] Barrett, A.G.M.; Lana, J.C.A. *J. Chem. Soc., Chem. Commun.* ***1978***, 471.
[2191] Vauthey, I.; Valot, F.; Gozzi, C.; Fache, F.; Lemaire, M. *Tetrahedron Lett.* ***2000***, *41*, 6347.
[2192] Singh, D.U.; Singh, P.R.; Samant, S.D. *Tetrahedron Lett.* ***2004***, *45*, 4805.
[2193] Martin, M.T.; Roschangar, F.; Eaddy, J.F. *Tetrahedron Lett.* ***2003***, *44*, 5461.
[2194] See Charville, H.; Jackson, D.A.; Hodges, G.; Whiting, A.; Wilson, M.R. *Eur. J. Org. Chem.* ***2011***, 5981. For a review, see Lanigan, R.M.; Sheppard, T.D. *Eur. J. Org. Chem.* ***2013***, 7453.
[2195] See Gooßen, L.J.; Ohlmann, D.M.; Lange, P.P. *Synthesis* ***2009***, 160.
[2196] See Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 105–109.
[2197] Chou, W.-C.; Chou, M.-C.; Lu, Y.-Y.; Chen, S.-F. *Tetrahedron Lett.* ***1999***, *40*, 3419. Also see White, J.M.; Tunoori, A.R.; Turunen, B.J.; Georg, G.I. *J. Org. Chem.* ***2004***, *69*, 2573.

of carboxylic acids and amines to amides.[2198] Polymer-bound reagents have also been used.[2199] Triphenylphosphine/trichloroisocyanuric acid converts acids and amides to the amide.[2200] The *Burgess reagent* ($Et_3N^+ \ ^-SO_2NCO_2Me$; see **17-27**) activates carboxylic acids for amide formation.[2201] The reaction of a carboxylic acid and imidazole under microwave irradiation gives the amide.[2202] Microwave irradiation of a secondary amine, formic acid, 2-chloro-4,6-dimethoxy[1,3,5]triazine, and a catalytic amount of DMAP (4-dimethylaminopyridine) leads to the formamide.[2203] Ammonium bicarbonate and formamide converts acids to amides with microwave irradiation.[2204] The coupling reaction of lithium, sodium, or potassium carboxylates with amines in the presence of *i*-Pr_2NEt and lithium 5-bromo-1*H*-pyrrole-2-carboxylate gave the amide.[2205] The PPh_3-catalyzed reaction of carboxylic acids and amines gave the amide.[2206] The activation of carboxylic acids, catalyzed by polymer-bound PPh_3, with 2,4,6-trichloro-1,3,5-triazine was followed by reaction with an amine to give the amide.[2207] Similarly, ion-supported PPh_3 has been used to prepare amides.[2208] Metal catalysts such as Zr,[2209] W,[2210] Ti,[2211] Cu,[2212] Au,[2213] or Al[2214] have been used for the coupling of carboxylic acids and amines.

Although treatment of carboxylic acids with amines does not directly give amides, the reaction can be made to proceed in good yield at room temperature or slightly above by the use of coupling agents,[2215] the most important of which is dicyclohexylcarbodiimide (DCC, see **16-62**). This reagent is very convenient and is used[2216] a great deal in peptide synthesis.[2217] A polymer-supported carbodiimide has been used.[2218] An anhydride

[2198] Ishihara, K.; Kondo, S.; Yamamoto, H. *Synlett* ***2001***, 1371.
[2199] See Crosignani, S.; Gonzalez, J.; Swinnen, D. *Org. Lett.* ***2004***, *6*, 4579.
[2200] Rodrigues, R.da C.; Barros, I.M.A.; Lima, E.L.S. *Tetrahedron Lett.* ***2005***, *46*, 5945.
[2201] Wodka, D.; Robbins, M.; Lan, P.; Martinez, R.L.; Athanasopoulos, J.; Makara, G.M. *Tetrahedron Lett.* ***2006***, *47*, 1825.
[2202] See Khalafi-Nezhad, A.; Mokhtari, B.; Rad, M.N.S. *Tetrahedron Lett.* ***2003***, *44*, 7325. See also, Bose, A.K.; Ganguly, S.N.; Manhas, M.S.; Guha, A.; Pombo-Villars, E. *Tetrahedron Lett.* ***2006***, *47*, 4605.
[2203] De Luca, L.; Giacomelli, G.; Porcheddu, A.; Salaris, M. *Synlett* ***2004***, 2570.
[2204] Peng, Y.; Song, G. *Org. Prep. Proceed. Int.* ***2002***, *34*, 95.
[2205] Goodreid, J.D.; Duspara, P.A.; Bosch, C.; Batey, R.A. *J. Org. Chem.* ***2014***, *79*, 943.
[2206] Lenstra, D.C.; Rutjes, F.P.J.T.; Mecinović, J. *Chem. Commun.* ***2014***, *50*, 5763.
[2207] Duangkamol, C.; Jaita, S.; Wangngae, S.; Phakhodee, W.; Pattarawarapan, M. *Tetrahedron Lett.* ***2015***, *56*, 4997.
[2208] Kawagoe, Y.; Moriyama, K.; Togo, H. *Tetrahedron* ***2013***, *69*, 3971.
[2209] Lundberg, H.; Tinnis, F.; Zhang, J.; Algarra, A.G.; Himo, F.; Adolfsson, H. *J. Am. Chem. Soc.* ***2017***, *139*, 2286; Lenstra, D.C.; Nguyen, D.T.; Mecinović, J. *Tetrahedron* ***2015***, *71*, 5547; Allen, C.L.; Chhatwal, A.R.; Williams, J.M.J. *Chem. Commun.* ***2012***, *48*, 666l.
[2210] Pathare, S.P.; Sawant, R.V.; Akamanchi, K.G. *Tetrahedron Lett.* ***2012***, *53*, 3259.
[2211] Lundberg, H.; Tinnis, F.; Adolfsson, H. *Synlett* ***2012***, *23*, 2201.
[2212] Xiong, B.; Zhu, L.; Feng, X.; Lei, J.; Chen, T.; Zhou, Y.; Han, L.-B.; Au, C.-T.; Yin, S.-F. *Eur. J. Org. Chem.* ***2014***, 4244.
[2213] Wang, Y.; Tang, D.Z.L.; Wang, S.; Wang, Z. *Angew. Chem. Int. Ed.* ***2011***, *50*, 8917.
[2214] Li, J.; Subramaniam, K.; Smith, D.; Qiao, J.X.; Li, J.J.; Qian-Cutrone, J.; Kadow, J.F.; Vite, G.D.; Chen, B.-C. *Org. Lett.* ***2012***, *14*, 214; Chung, S.W.; Uccello, D.P.; Choi, H.; Montgomery, J.I.; Chen, J. *Synlett* ***2011***, *22*, 2072.
[2215] See Klausner, Y.S.; Bodansky, M. *Synthesis* ***1972***, 453.
[2216] It was first used this way by Sheehan, J.C.; Hess, G.P. *J. Am. Chem. Soc.* ***1955***, *77*, 1067.
[2217] See Gross, E.; Meienhofer, J. *The Peptides*, 3 Vols., Academic Press, NY, ***1979–1981***. See Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*, Springer, NY, ***1984***.
[2218] Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* ***2001***, *42*, 6667.

intermediate has been isolated from a DCC reaction mixture and then used to acylate an amine.[2219]

The synthetically important *Weinreb amides* [RCON(Me)OMe, see **16-29**] can be prepared from the carboxylic acid and MeO(Me)NH•HCl in the presence of tributylphosphine and 2-pyridine-*N*-oxide disulfide.[2220] Di(2-pyridyl)carbonate has been used in a related reaction that generates amides directly.[2221] Other promoting agents[2222] are $ArB(OH)_2$ reagents,[2223] *N*,*N*′-carbonyldiimidazole,[2224] $POCl_3$,[2225] $TiCl_4$,[2226] molecular sieves,[2227] *Lawesson's reagent* (**16-10**),[2228] and $(MeO)_2POCl$.[2229] Certain dicarboxylic acids form amides simply on treatment with primary aromatic amines. In these cases, the cyclic anhydride is an intermediate and is the species actually attacked by the amine.[2230] Carboxylic acids can also be converted to amides with sulfonic acids, or phosphoric acids,[2231] or by treatment with trisalkylaminoboranes [$B(NHR')_3$].

Lactams are readily produced from γ- or δ-amino acids.[2232] This lactonization process can be promoted by enzymes, such as pancreatic porcine lipase.[2233] Reduction of ω-azide carboxylic acids leads to macrocyclic lactams.[2234]

Many other methods have been developed. The activation of carboxylic acids by the reagent combination of trimethyl phosphite and iodine allowed the reaction with aromatic amines to give the amide.[2235] The coupling of carboxylic acids and amines, catalyzed by *ortho*-iodophenylboronic acids with molecular sieve 4 Å gave the corresponding amide.[2236] Amides have been prepared using $B(OCH_2CF_3)_3$[2237] or (2-(thiophen-2-ylmethyl)phenyl)boronic acid[2238] as the catalyst. Primary alkylboronic acids have been used to couple α-hydroxycarboxylic acids and amines.[2239] A solid-supported

[2219] See Rebek, J.; Feitler, D. *J. Am. Chem. Soc.* ***1974***, *96*, 1606. Also see Rebek, J.; Feitler, D. *J. Am. Chem. Soc.* ***1973***, *95*, 4052.

[2220] Banwell, M.; Smith, J. *Synth. Commun.* ***2001***, *31*, 2011. For another procedure, see Kim, M.; Lee, H.; Han, K.-J.; Kay, K.-Y. *Synth. Commun.* ***2003***, *33*, 4013.

[2221] Shiina, I.; Suenaga, Y.; Nakano, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 2811.

[2222] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1941–1949.

[2223] Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* ***1996***, *61*, 4196.

[2224] See Vaidyanathan, R.; Kalthod, V.G.; Ngo, D.; Manley, J.M.; Lapekas, S.P. *J. Org. Chem.* ***2004***, *69*, 2565. Also see Grzyb, J.A.; Batey, R.A. *Tetrahedron Lett.* ***2003***, *44*, 7485.

[2225] Klosa, J. *J. Prakt. Chem.* ***1963***, *[4] 19*, 45.

[2226] Wilson, J.D.; Weingarten, H. *Can. J. Chem.* ***1970***, *48*, 983.

[2227] Cossy, J.; Pale-Grosdemange, C. *Tetrahedron Lett.* ***1989***, *30*, 2771.

[2228] Thorsen, M.; Andersen, T.P.; Pedersen, U.; Yde, B.; Lawesson, S. *Tetrahedron* ***1985***, *41*, 5633.

[2229] Jászay, Z.M.; Petneházy, I.; Töke, L. *Synth. Commun.* ***1998***, *28*, 2761.

[2230] Higuchi, T.; Miki, T.; Shah, A.C.; Herd, A.K. *J. Am. Chem. Soc.* ***1963***, *85*, 3655.

[2231] Zhmurova, I.N.; Voitsekhovskaya, I.Yu.; Kirsanov, A.V. *J. Gen. Chem. USSR* ***1959***, *29*, 2052. See also, Liu, H.; Chan, W.H.; Lee, S.P. *Synth. Commun.* ***1979***, *9*, 31.

[2232] See Bladé-Font, A. *Tetrahedron Lett.* ***1980***, *21*, 2443. Also see Wei, Z.-Y.; Knaus, E.E. *Tetrahedron Lett.* ***1993***, *34*, 4439 for a variation of this reaction.

[2233] Gutman, A.L.; Meyer, E.; Yue, X.; Abell, C. *Tetrahedron Lett.* ***1992***, *33*, 3943.

[2234] Bosch, I.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* ***1993***, *34*, 4671. See Bai, D.; Shi, Y. *Tetrahedron Lett.* ***1992***, *33*, 943 for the preparation of lactam units in para-cyclophanes.

[2235] Luo, Q.-L.; Lv, L.; Li, Y.; Tan, J.-P.; Nan, W.; Hui, Q. *Eur. J. Org. Chem.* ***2011***, 6916.

[2236] Gernigon, N.; Al-Zoubi, R.M.; Hall, D.G. *J. Org. Chem.* ***2012***, *77*, 8386.

[2237] See Lanigan, R.; Karaluka, V.; Sabatini, M.T.; Starkov, P.; Badland, M.; Boulton, L.; Sheppard, T.D. *Chem. Commun.* ***2016***, *52*, 8846.

[2238] El Dine, T.M.; Erb, W.; Berhault, Y.; Rouden, J.; Blanchet, J. *J. Org. Chem.* ***2015***, *80*, 4532.

[2239] Yamashita, R.; Sakakura, A.; Ishihara, K. *Org. Lett.* ***2013***, *15*, 3654.

ortho-iodoarylboronic acid has been used to catalyze the reaction.[2240] 2-Furanylboronic acid was used as a catalyst.[2241] Mesoporous silica SBA-15 has been used as a catalyst.[2242]

Mechanosynthesis has been used with the carbonylimidazole approach under solvent-free conditions.[2243] The fluorine-containing catalyst XtalFluor-E has been used to couple carboxylic acids and amines.[2244] The reaction of amines with prop-2-ene-1-sulfinyl chloride gave the sulfinylamide that reacted with carboxylic acids to give the amide.[2245] Carboxylic acids reacted with imidazole under solvent-free conditions to form the carbonylimidazole, which reacted with secondary amines to give the amide.[2246] Amines and carboxylic acids were coupled using the uronium salt (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylaminomorpholinocarbenium hexafluorophosphate) as a coupling reagent, with 2,6-lutidine, and TPGS-750-M [DL-α-tocopherol methoxypolyethylene glycol succinate solution] to give the amide.[2247] The Pd-catalyzed coupling of organoboronic acids and amines gave tertiary amides in the presence of CO and O_2.[2248] The photogeneration of Vilsmeier-Haack reagents (**12-16**) from DMF and CBr_4 mediated the coupling of carboxylic acids and amines to give the amide.[2249]

The reaction of thiocarboxylic acids and azides, in the presence of triphenylphosphine, gives the corresponding amide.[2250] Heating secondary amines and carboxylic acids with sulfur gave the thioamide.[2251]

Before leaving this section, it is important to mention the peptide synthesis protocol discovered by R.B. Merrifield[2252] and used for the synthesis of many peptides.[2253] This methodology is called *solid-phase synthesis* or *polymer-supported synthesis*.[2254] The reactions used are the same as in ordinary synthesis, but one of the reactants is anchored onto a solid polymer. For example, if it is desired to couple two amino acids (to form a dipeptide), the polymer selected might be polystyrene with CH_2Cl side chains. One of the amino

[2240] Gernigon, N.; Zheng, H.; Hall, D.G. *Tetrahedron Lett.* ***2013***, *54*, 4475.
[2241] Tam, E.K.W.; Rita; Liu, L.Y.; Chen, A. *Eur. J. Org. Chem.* ***2015***, 1100.
[2242] Tamura, M.; Murase, D.; Komura, K. *Synthesis* ***2015***, *47*, 769.
[2243] Métro, T.-X.; Bonnamour, J.; Reidon, T.; Sarpoulet, J.; Martinez, J.; Lamaty, F. *Chem. Commun.* ***2012***, *48*, 11781; Štrukil, V.; Bartolec, B.; Portada, T.; Đilović, I.; Halasz, I.; Margetić, D. *Chem. Commun.* ***2012***, *48*, 12100.
[2244] Orliac, A.; Pardo, D.G.; Bombrun, A.; Cossy, J. *Org. Lett.* ***2013***, *15*, 902.
[2245] Bai, J.; Zambroń, B.K.; Vogel, P. *Org. Lett.* ***2014***, *16*, 604.
[2246] Verma, S.K.; Ghorpade, R.; Pratap, A.; Kaushik, M.P. *Tetrahedron Lett.* ***2012***, *53*, 2373.
[2247] Gabriel, C.M.; Keener, M.; Gallou, F; Lipshutz, B.H. *Org. Lett.* ***2015***, *17*, 3968.
[2248] Ren, L.; Li, X.; Jiao, N. *Org. Lett.* ***2016***, *18*, 5852.
[2249] McCallum, T.; Barriault, L. *J. Org. Chem.* ***2015***, *80*, 2874.
[2250] Park, S.-D.; Oh, J.-H.; Lim, D. *Tetrahedron Lett.* ***2002***, *43*, 6309.
[2251] Guntreddi, T.; Vanjari, R.; Singh, K.N. *Org. Lett.* ***2014***, *16*, 3624.
[2252] Merrifield, R.B. *J. Am. Chem. Soc.* ***1963***, *85*, 2149.
[2253] Birr, C. *Aspects of the Merrifield Peptide Synthesis*, Springer, NY, ***1978***. For reviews, see Bayer, E. *Angew. Chem. Int. Ed.* ***1991***, *30*, 113; Kaiser, E.T. *Acc. Chem. Res.* ***1989***, *22*, 47; Andreev, S.M.; Samoilova, N.A.; Davidovich, Yu.A.; Rogozhin, S.V. *Russ. Chem. Rev.* ***1987***, *56*, 366; in Gross, E.; Meienhofer, J. *The Peptides*, Vol. 2, Academic Press, NY, ***1980***, see the articles by Barany, G.; Merrifield, R.B. pp. 1–184 and Fridkin, M. pp. 333–363; see Erickson, B.W.; Merrifield, R.B. in Neurath, H.; Hill, R.L.; Boeder, C.-L. *The Proteins*, 3rd ed., Vol. 2, Academic Press, NY, ***1976***, pp. 255–527. For R.B. Merrifield's Nobel Prize lecture, see Merrifield, R.B. *Angew. Chem. Int. Ed.* ***1985***, *24*, 799.
[2254] Laszlo, P. *Preparative Organic Chemistry Using Supported Reagents*, Academic Press, NY, ***1987***; Mathur, N.K.; Narang, C.K.; Williams, R.E. *Polymers as Aids in Organic Chemistry*, Academic Press, NY ***1980***; Hodge, P.; Sherrington, D.C. *Polymer-Supported Reactions in Organic Synthesis*, Wiley, NY, ***1980***. For reviews, see Pillai, V.N.R.; Mutter, M. *Top. Curr. Chem.* ***1982***, *106*, 119; Akelah, A.; Sherrington, D.C. *Chem. Rev.* ***1981***, *81*, 557; Crowley, J.I.; Rapoport, H. *Acc. Chem. Res.* ***1976***, *9*, 135; Patchornik, A.; Kraus, M.A. *Pure Appl. Chem.* ***1975***, *43*, 503.

acids, protected by a Boc,[2255] would then be coupled to the side chains. It is not necessary that all the side chains be converted, but a random selection will be. The Boc group is then removed by hydrolysis with trifluoroacetic acid in CH_2Cl_2 and the second amino acid is coupled to the first, using DCC or some other coupling agent. The second Boc group is removed, resulting in a dipeptide that is still anchored to the polymer. If this dipeptide is the desired product, it can be cleaved from the polymer by various methods,[2256] one of which is treatment with HF. If a longer peptide is wanted, additional amino acids can be added by repeating the requisite steps.

The basic advantage of the polymer-support techniques is that the polymer (including all chains attached to it) is easily separated from all other reagents, because it is insoluble in the solvents used. Excess reagents, other reaction products (e.g., dicyclohexylurea), side products, and the solvents themselves are quickly washed away. Purification of the polymeric species is rapid and complete. The process can even be automated,[2257] and commercial automated peptide synthesizers are now available.[2258]

Although the solid-phase technique was first developed for the synthesis of peptide chains and has seen considerable use for this purpose, it has also been used to synthesize chains of polysaccharides and polynucleotides; in the latter case, solid-phase synthesis has almost completely replaced synthesis in solution.[2259] The technique has been applied less often to reactions in which only two molecules are brought together (nonrepetitive syntheses), but many examples have been reported.[2260] Combinatorial chemistry in some ways can be viewed as an extension of the Merrifield synthesis, particularly when applied to peptide synthesis, and continues as an important part of modern organic chemistry.[2261]

OS **I**, 3, 82, 111, 172, 327; **II**, 65, 562; **III**, 95, 328, 475, 590, 646, 656, 768; **IV**, 6, 62, 513; **V**, 670, 1070; **VIII**, 241; **81**, 262. Also see, OS **III**, 360; **VI**, 263; **VIII**, 68.

16-74 Acylation of Amines by Carboxylic Esters

$$RCOOR' + NH_3 \longrightarrow RCONH_2 + R'OH$$

The conversion of carboxylic esters to amides is a useful reaction; unsubstituted, *N*-substituted, and *N*,*N*-disubstituted amides can be prepared this way from the appropriate

[2255] See Jaratjaroonphong, J.; Tuengpanya, S.; Ruengsangtongkul, S. *J. Org. Chem.* ***2015***, *80*, 559.

[2256] See Whitney, D.B.; Tam, J.P.; Merrifield, R.B. *Tetrahedron* ***1984***, *40*, 4237.

[2257] Merrifield, R.B.; Stewart, J.M.; Jernberg, N. *Anal. Chem.* ***1966***, *38*, 1905.

[2258] See Pedersen, S.L.; Jensen, K.J. *Methods Mol. Biol.* ***2013***, *1047*, 215; Stephenson, K.A.; Zubieta, J.; Banerjee, S.R.; Levadala, M.K.; Taggart, L.; Ryan, L.; McFarlane, N.; Boreham, D.R.; Maresca, K.P.; Babich, J.W.; Valliant, J.F. *Bioconjugate Chem.* ***2004***, *15*, 128; Gausepohl, H.; Boulin, C.; Kraft, M.; Frank, R.W. *Peptide Res.* ***1992***, *5*, 315.

[2259] See Seeberger, P.J. *Acc. Chem. Res.* ***2015***, *48*, 1450; Hahm, H.S.; Hurevich, M.; Seeberger, P.H. *Nature Comm.* ***2016***, *7*, 12482 | DOI: 10.1038/ncomms12482; Bannwarth, W. *Chimia* ***1987***, *41*, 302.

[2260] Fréchet, J.M.J. *Tetrahedron* ***1981***, *37*, 663; Fréchet, J.M.J. in Hodge, P.; Sherrington, D.C. *Polymer-Supported Reactions in Organic Synthesis*, Wiley, NY, ***1980***, pp. 293–342, Leznoff, C.C. *Acc. Chem. Res.* ***1978***, *11*, 327; *Chem. Soc. Rev.* ***1974***, *3*, 64.

[2261] De Lue, N. *Chemical Innovation* ***2001***, *31*, 33; Liu, R.; Li, X.; Lam, K.S. *Curr. Opinion Chem. Biol.* ***2017***, *38*, 117; Czarnik, A.W.; DeWitt, S.H. *A Practical Guide to Combinatorial Chemistry*, American Chemical Society, Washington, DC, ***1997***; Chaiken, I.N.; Janda, K.D. *Molecular Diversity and Combinatorial Chemistry: Libraries and Drug Discovery*, American Chemical Society, Washington, DC, ***1996***; Balkenhol, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed.* ***1996***, *35*, 2289; Thompson, L.A.; Ellman, J.A. *Chem. Rev.* ***1996***, *96*, 555; Crowley, J.I.; Rapoport, H. *Acc. Chem. Res.* ***1976***, *9*, 135; Leznoff, C.C. *Acc. Chem. Res.* ***1978***, *11*, 327.

amine[2262] or ammonia.[2263] Both R and R′ can be alkyl or aryl, but *an especially good leaving group is p-nitrophenyl*. Ethyl trifluoroacetate was found to react selectively with primary amines to form the corresponding trifluoroacetyl amide.[2264] Many simple esters (R = Me, Et, etc.) are not very reactive, and strongly basic catalysis has been used in such cases,[2265] but catalysis by cyanide ion[2266] and acceleration by high pressure[2267] have been reported. Methyl esters[2268] and ethyl esters[2269] have been converted to the corresponding amide under microwave irradiation. The metal-catalyzed reaction of esters and amines gave the amide, using Mg,[2270] In,[2271] Ru,[2272] Au,[2273] Al,[2274] Sm,[2275] La,[2276] Zr,[2277] or Ta[2278] catalysts. Lithium amides have been used to convert esters to amides as well.[2279] β-Keto esters undergo the reaction especially easily.[2280] Aniline was treated with *n*-butyllithium to form the lithium amide, which reacted with an ester to give the amide.[2281] An enzyme-mediated amidation is known using amino cyclase I.[2282] The reaction of dimethyl carbonate and an amine is an effective way to prepare methyl carbamates.[2283] Amides have been prepared from nonnucleophilic amines using flow conditions (Sec. 7.D).[2284] Acetic acid has been used as a catalyst.[2285] The biocatalytic *N*-formylation of amines used ethyl formate as the formylating reagent.[2286]

Amines reacted with the solid-phase reagents macroporous polystyrene-bound 1-hydroxybenzotriazole (P-HOBt) and silica-bound 1-hydroxybenzotriazole (Si-HOBt) to prepare small combinatorial libraries of acetamides and benzamides.[2287] The solvent-free

[2262] Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 96–105. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1973–1976. See Ojeda-Porras, A.; Gamba-Sánchez, D. *J. Org. Chem.* ***2016***, *81*, 11548.

[2263] See Mizuhara, T.; Hioki, K.; Yamada, M.; Sasaki, H.; Morisaki, D.; Kunishima, M. *Chem. Lett.* ***2008***, *37*, 1190. Magnesium nitride is a useful source of ammonia in this reaction. See Veitch, G.E.; Bridgwood, K.L.; Ley, S.V. *Org. Lett.* ***2008***, *10*, 3623.

[2264] Xu, D.; Prasad, K.; Repič, O.; Blacklock, T.J. *Tetrahedron Lett.* ***1995***, *36*, 7357.

[2265] Matsumoto, K.; Hashimoto, S.; Uchida, T.; Okamoto, T.; Otani, S. *Chem. Ber.* ***1989***, *122*, 1357.

[2266] Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.* ***1987***, *52*, 2033.

[2267] Matsumoto, K.; Hashimoto, S.; Uchida, T.; Okamoto, T.; Otani, S. *Chem. Ber.* ***1989***, *122*, 1357.

[2268] Varma, R.S.; Naicker, K.P. *Tetrahedron Lett.* ***1999***, *40*, 6177.

[2269] Zradni, F.-Z.; Hamelin, J.; Derdour, A. *Synth. Commun.* ***2002***, *32*, 3525.

[2270] Guo, Z.; Dowdy, E.D.; Li, W.-S.; Polniaszek, R.; Delaney, E. *Tetrahedron Lett.* ***2001***, *42*, 1843.

[2271] Ranu, B.C.; Dutta, P. *Synth. Commun.* ***2003***, *33*, 297.

[2272] Gnanaprakasam, B.; Milstein, D. *J. Am. Chem. Soc.* ***2011***, *133*, 1682.

[2273] Bao, Y.-S.; Baiyin, M.; Agula, B.; Jia, M.; Zhaorigetu, B. *J. Org. Chem.* ***2014***, *79*, 6715.

[2274] Desrat, S.; Ducousso, A.; Gapil, S.; Remeur, C.; Roussi, F. *Synlett* ***2015***, *26*, 385.

[2275] Campbell, J.B.; Sparks, R.B.; Dedinas, R.F. *Synlett* ***2011***, *22*, 357.

[2276] Morimoto, H.; Fujiwara, R.; Shimizu, Y.; Morisaki, K.; Ohshima, T. *Org. Lett.* ***2014***, *16*, 2018.

[2277] Homerin, G.; Baudelet, D.; Dufrénoy, P.; Rigo, B.; Lipka, E.; Dezitter, X.; Furman, C.; Millet, R.; Ghinet, A. *Tetrahedron Lett.* ***2016***, *57*, 1165.

[2278] Tsuji, H.; Yamamoto, H. *J. Am. Chem. Soc.* ***2016***, *138*, 14218.

[2279] Wang, J.; Rosingana, M.; Discordia, R.P.; Soundararajan, N.; Polniaszek, R. *Synlett* ***2001***, 1485.

[2280] Labelle, M.; Gravel, D. *J. Chem. Soc., Chem. Commun.* ***1985***, 105.

[2281] Ooi, T.; Tayama, E.; Yamada, M.; Maruoka, K. *Synlett.* ***1999***, 729.

[2282] Youshko, M.I.; van Rantwijk, F.; Sheldon, R.A. *Tetrahedron: Asymmetry* ***2001***, *12*, 3267.

[2283] Distaso, M.; Quaranta, E. *Tetrahedron* ***2004***, *60*, 1531.

[2284] Vrijdag, J.L.; Delgado, F.; Alonso, N.; De Borggraeve, W.M.; Pérez-Macias, N.; Alcázar, J. *Chem. Commun.* ***2014***, *50*, 15094.

[2285] Sharley, D.D.S.; Williams, J.M.J. *Chem. Commun.* ***2017***, *53*, 2020.

[2286] Patre, R.E.; Mal, S.; Nilkanth, P.R.; Ghorai, S.K.; Deshpande, S.H.; El Qacemi, M.; Smejkal, T.; Pal, S.; Manjunath, B. *Chem. Commun.* ***2017***, *53*, 2382.

[2287] Vokkaliga, S.; Jeong, J.; LaCourse, W.R.; Kalivretenos, A. *Tetrahedron Lett.* ***2011***, *52*, 2722.

formylation of amines in protic ionic liquids has been reported.[2288] The solvent-free amidation of esters used ammonium nitrate as a catalyst.[2289]

Lactones give lactams when treated with ammonia or primary amines.[2290] Lactams are also produced from γ- and δ-amino esters in an internal example of this reaction. Lactonization has been accomplished in ionic liquids.[2291]

The mechanism of the acylation of amines with carboxylic esters has been extensively studied.[2292] The mechanistic details of the amidation of esters mediated by sodium formate has been studied.[2293] In its broad outlines, the mechanism appears to be essentially $B_{AC}2$.[2294] Under the normal basic conditions, the reaction is general base catalyzed,[2295] indicating that a proton is being transferred in the rate-determining step and that two molecules of amine are involved.[2296] Alternatively, another base, such as H_2O or ^-OH, can substitute for the second molecule of amine. With some substrates and under some conditions, especially at low pH, the breakdown of the tetrahedral intermediate can become rate determining.[2297] The reaction also takes place under acidic conditions and is general acid catalyzed, so that reaction of the tetrahedral intermediate is rate determining.[2298] The reagent used to protonate the alkoxide moiety of the tetrahedral intermediate may be $R^2NH_3^+$ or another acid. Even under basic conditions, a proton donor may be necessary to assist leaving-group removal. Evidence for this is that the rate is lower with $^-NR_2$ in liquid ammonia than with NHR_2 in water, apparently owing to the lack of acids to protonate the leaving oxygen.[2299]

In the special case of β-lactones, where small-angle strain is an important factor, alkyl-oxygen cleavage is observed ($B_{AL}2$ mechanism, as in the similar case of hydrolysis of β-lactones, **16-58**), and the product is not an amide but a β-amino acid (β-alanine). A similar result has been found for certain sterically hindered esters.[2300] This reaction is similar to **10-30**, with OCOR as the leaving group. Other lactones have been opened to ω-hydroxy amides with Dibal:$BnNH_2$.[2301]

As in **16-71**, hydrazides and hydroxamic acids can be prepared from carboxylic esters, with hydrazine and hydroxylamine,[2302] respectively. Both hydrazine and hydroxylamine

[2288] Majumdar, S.; De, J.; Hossain, J.; Basak, A. *Tetrahedron Lett.* ***2013***, *54*, 262. Also see Fu, R.; Yang, Y.; Ma, Y.; Yang, F.; Li, J.; Chai, W.; Wang, Q.; Yuan, R. *Tetrahedron Lett.* ***2015***, *56*, 4527.

[2289] Ramesh, P.; Fadnavis, N.W. *Chem. Lett.* ***2015***, *44*, 138.

[2290] Kim, K.; Hong, S.H. *J. Org. Chem.* ***2015***, *80*, 4152.

[2291] Orrling, K.M.; Wu, X.; Russo, F.; Larhed, M. *J. Org. Chem.* ***2008***, *73*, 8627.

[2292] Satchell, D.P.N.; Satchell, R.S. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 410–431; Ilieva, S.; Galabov, B.; Musaev, D.G.; Morokuma, K.; Schaefer III, H.F. *J. Org. Chem.* ***2003***, *68*, 1496.

[2293] Ramirez, A.; Mudryk, B.; Rossano, L.; Tummala, S. *J. Org. Chem.* ***2012***, *77*, 775.

[2294] Bruice, T.C.; Donzel, A.; Huffman, R.W.; Butler, A.R. *J. Am. Chem. Soc.* ***1967***, *89*, 2106.

[2295] Bunnett, J.F.; Davis, G.T. *J. Am. Chem. Soc.* ***1960***, *82*, 665, Jencks, W.P.; Carriuolo, J. *J. Am. Chem. Soc.* ***1960***, *82*, 675; Bruice, T.C.; Mayahi, M.F. *J. Am. Chem. Soc.* ***1960***, *82*, 3067.

[2296] See Felton, S.M.; Bruice, T.C. *J. Am. Chem. Soc.* ***1969***, *91*, 6721; Nagy, O.B.; Reuliaux,V.; Bertrand, N.; van der Mensbrugghe, A.; Leseul, J.; Nagy, J.B. *Bull. Soc. Chim. Belg.* ***1985***, *94*, 1055.

[2297] Gresser, M.J.; Jencks, W.P. *J. Am. Chem. Soc.* ***1977***, *99*, 6963, 6970. See also, Um, I.-H.; Lee, J.-Y.; Lee, H.W.; Nagano, Y.; Fujio, M.; Tsuno, Y. *J. Org. Chem.* ***2005***, *70*, 4980.

[2298] Blackburn, G.M.; Jencks, W.P. *J. Am. Chem. Soc.* ***1968***, *90*, 2638.

[2299] Bunnett, J.F.; Davis, G.T. *J. Am. Chem. Soc.* ***1960***, *82*, 665.

[2300] Zaugg, H.E.; Helgren, P.F.; Schaefer, A.D. *J. Org. Chem.* ***1963***, *28*, 2617. See also, Harada, R.; Kinoshita, Y. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2706.

[2301] Huang, P.-Q.; Zheng, X.; Deng, X.-M. *Tetrahedron Lett.* ***2001***, *42*, 9039. See also, Taylor, S.K.; Ide, N.D.; Silver, M.E.; Stephan, M. *Synth. Commun.* ***2001***, *31*, 2391.

[2302] Ho, C.Y.; Strobel, E.; Ralbovsky, J.; Galemmo, Jr., R.A. *J. Org. Chem.* ***2005***, *70*, 4873.

react more rapidly than ammonia or primary amines (the alpha effect, Sec. 10.G.ii). Isopropenyl formate is a useful compound for the formylation of primary and secondary amines.[2303]

A computational study of the aminolysis of thiolactones has been reported.[2304]

OS **I**, 153, 179; **II**, 67, 85; **III**, 10, 96, 108, 404, 440, 516, 536, 751, 765; **IV**, 80, 357, 441, 486, 532, 566, 819; **V**, 168, 301, 645; **VI**, 203, 492, 620, 936; **VII**, 4, 30, 41, 411; **VIII**, 26, 204, 528. Also see, OS **I**, 5; **V**, 582; **VII**, 75.

16-75 Acylation of Amines by Amides

$$RCONH_2 + R'\overset{+}{N}H_3 \longrightarrow RCONHR' + NH_4{}^+$$

This is an exchange reaction and is usually carried out with the salt of the amine.[2305] The leaving group is usually NH_2 rather than NHR or NR_2 and primary amines (in the form of their salts) are the most common reagents. Boron trifluoride can be added to complex with the leaving ammonia. Neutral amines also react in some cases to give the new amide.[2306] The reaction is catalyzed by Al(III).[2307] The reaction is often used to convert urea to substituted ureas:[2308]

$$NH_2CONH_2 + RNH_3{}^+ \rightarrow NH_2CONHR + NH_4{}^+$$

N-Alkyl substituted amides (alkyl = R) are converted to *N*-substituted amides (alkyl = R′) by treatment with N_2O_4 to give an *N*-nitroso compound, followed by treatment of this with a primary amine $R'NH_2$.[2309] Lactams can be converted to ring-expanded lactams if a side chain containing an amino group is present on the nitrogen. A strong base is used to convert the NH_2 to NH^-, which then acts as a nucleophile, expanding the ring by means of a transamidation.[2310] The discoverers call it the *Zip reaction*.[2311] Lactams can be opened to ω-amino amides by reaction with amines at 10 kbar.[2312] An *N*-aryl group of a urea can be converted to a *N*,*N*-dialkyl group by heating the urea with the amine in an autoclave.[2313]

OS **I**, 302 (but see **V**, 589), 450, 453; **II**, 461; **III**, 151, 404; **IV**, 52, 361. See also, OS **VIII**, 573.

[2303] van Melick, J.E.W.; Wolters, E.T.M. *Synth. Commun.* ***1972***, *2*, 83.
[2304] Desmet, G.B.; D'hooge, D.R.; Sabbe, M.K.; Marin, G.B.; Du Prez, F.E.; Espeel, P.; Reyniers, M.-F. *J. Org. Chem.* ***2015***, *80*, 8520.
[2305] For a list of procedures, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1978–1982.
[2306] Murakami, Y.; Kondo, K.; Miki, K.; Akiyama, Y.; Watanabe, T.; Yokoyama, Y. *Tetrahedron Lett.* ***1997***, *38*, 3751.
[2307] Hoerter, J.M.; Otte, K.M.; Gellman, S.H.; Stahl, S.S. *J. Am. Chem. Soc.* ***2006***, *128*, 5177.
[2308] See Chimishkyan, A.L.; Snagovskii, Yu.S.; Gulyaev, N.D.; Leonova, T.V.; Kusakin, M.S. *J. Org. Chem.* USSR ***1985***, *21*, 1955.
[2309] Garcia, J.; Vilarrasa, J. *Tetrahedron Lett.* ***1982***, *23*, 1127.
[2310] Askitoglu, E.; Guggisberg, A.; Hesse, M. *Helv. Chim. Acta* ***1985***, *68*, 750 and references cited therein. For a carbon analog, see Süsse, M.; Hájicek, J.; Hesse, M. *Helv. Chim. Acta* ***1985***, *68*, 1986.
[2311] See Stach, H.; Hesse, M. *Tetrahedron* ***1988***, *44*, 1573.
[2312] Kotsuki, H.; Iwasaki, M.; Nishizawa, H. *Tetrahedron Lett.* ***1992***, *33*, 4945.
[2313] Yang, Y.; Lu, S. *Org. Prep. Proceed. Int.* ***1999***, *31*, 559.

16-76 Acylation of Amides by Miscellaneous Methods

$$RCOX + H_2NCOR' \longrightarrow RCONHCOR'$$

Many acid derivatives, including amides, thiol acids RCOSH, thiol esters RCOSR,[2314] acyloxyboranes $RCOB(OR')_2$,[2315] α-keto nitriles, acyl azides, and nonenolizable ketones (see the *Haller-Bauer reaction*, **12-33**) can be converted to imide derivatives. *N*-Acylsulfonamides react with primary amines to form the amide (AcNHR).[2316] Carbonylation reactions can be used to prepare amides and related compounds. The reaction of a primary amine and an alkyl halide with CO_2, in the presence of Cs_2CO_3/Bu_4NI, gave the corresponding carbamate.[2317]

OS **III**, 394; **IV**, 6, 569; **V**, 160, 166; **VI**, 1004.

Imides can be prepared by the attack of amides or their salts on acyl halides, anhydrides, and carboxylic acids or esters.[2318] A good synthetic method for the preparation of acyclic imides is the reaction between an amide and an anhydride at 100 °C, catalyzed by H_2SO_4.[2319] When acyl chlorides are treated with amides in a 2:1 molar ratio at low temperatures in the presence of pyridine, the products are *N*,*N*-diacylamides, $(RCO)_3N$.[2320] This reaction is often used to prepare urea derivatives, an important example being the preparation of barbituric acid, **51**.[2321]

51

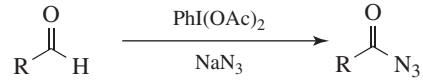
Heating hydroxylamines with $PSCl_3/H_2O/NEt_3$ gave the thioamide.[2322] The acylation of amines or amides with potassium acyltrifloroborates has been reported.[2323] Tertiary amines reacted with arylketenes to form zwitterions, which undergo amine-catalyzed dealkylation to form *N*,*N*-disubstituted amides.[2324] Isocyanates reacted with trimethyl ketene imines gave the amide.[2325] The ruthenium/*N*-heterocyclic carbene-catalyzed dehydrogenation of methanol allowed reaction with primary or secondary amines to give formamides.[2326] Isonitriles have been important precursors to complex amides.[2327] The boric

[2314] See Douglas, K.T. *Acc. Chem. Res.* ***1986***, *19*, 186.
[2315] See Collum, D.B.; Chen, S.; Ganem, B. *J. Org. Chem.* ***1978***, *43*, 4393.
[2316] Coniglio, S.; Aramini, A.; Cesta, M.C.; Colagioia, S.; Curti, R.; D'Alessandro, F.; D'anniballe, G.; D'Elia, V.; Nano, G.; Orlando, V.; Allegretti, M. *Tetrahedron Lett.* ***2004***, *45*, 5375.
[2317] Salvatore, R.N.; Shin, S.I.; Nagle, A.S.; Jung, K.W. *J. Org. Chem.* ***2001***, *66*, 1035.
[2318] For a review, see Challis, B.C.; Challis, J.A. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 759–773.
[2319] See Baburao, K.; Costello, A.M.; Petterson, R.C.; Sander, G.E. J. *Chem. Soc*. C ***1968***, 2779.
[2320] See LaLonde, R.T.; Davis, C.B. *J. Org. Chem.* ***1970***, *35*, 771.
[2321] See Bojarski, J.T.; Mokrosz, J.L.; Barton, H.J.; Paluchowska, M.H. *Adv. Heterocycl. Chem.* ***1985***, *38*, 229.
[2322] Pandey, L.K.; Pathak, U.; Mathur, S.; Suryanarayana, M.V.S. *Synthesis* ***2012***, *44*, 377.
[2323] Gálvez, A.O.; Schaack, C.P.; Noda, H.; Bode, J.W. *J. Am. Chem. Soc.* ***2017***, *139*, 1826.
[2324] Allen, A.D.; Andraos, J.; Tidwell, T.T.; Vukovic, S. *J. Org. Chem.* ***2014***, *79*, 679.
[2325] Qin, W.; Long, S.; Panunzio, M.; Bongini, A. *Synthesis* ***2012***, *44*, 3191.
[2326] Ortega, N.; Richter, C.; Glorius, F. *Org. Lett.* ***2013***, *15*, 1776.
[2327] For a review, see Wilson, R.M.; Stockdill, J.L.; Wu, X.; Li, X.; Vadola, P.A.; Park, P.K.; Wang, P.; Danishefsky, S.J. *Angew. Chem. Int. Ed.* ***2012***, *51*, 2834.

acid-catalyzed amidation of 8-methoxy-8-oxooctanoic acid with pyridin-3-amine, using *N*,*N*,*N*′,*N*′-tetramethylpropane-1,3-diamine as an additive, gave the amide.[2328] The Cu-catalyzed reaction of *N*-hydroxysuccinimide with aldehydes, followed by reaction with an amide, gave the amide.[2329] The *N*-acylation of lactams, oxazolidinones, and imidazolidinones by reaction with aldehydes was mediated by *Shvo's catalyst*, an organoruthenium compound.[2330] A Ru catalyst was used for the *N*-formylation of lactams by reaction with paraformaldehyde.[2331]

OS **II**, 60, 79, 422; **III**, 763; **IV**, 245, 247, 496, 566, 638, 662, 744; **V**, 204, 944.

16-77 Acylation of Azides



The reaction of an aldehyde with sodium azide and $Et_4{}^+ {}^-I(OAc)_2$ or polymer-bound $PhI(OAc)_2$ leads to an acyl azide.[2332] Acyl azides are also prepared directly from aldehydes using *tert*-butyl hypochlorite.[2333] Acyl azides were prepared by the reaction of carboxylic acids with sodium azide using trichloroisocyanuric acid/triphenylphosphine.[2334]

F. Attack by Halogen at an Acyl Carbon

16-78 Formation of Acyl Halides from Carboxylic Acids

$$\text{RCOOH} + \text{Halogenating agent} \longrightarrow \text{RCOX}$$

$$\text{Halogenating agent} = SOCl_2,\ SOBr_2,\ PCl_3,\ POCl_3,\ PBr_3, \text{ and so on}$$

The inorganic acid halides that convert alcohols to alkyl halides (**10-47**) for the most part also convert carboxylic acids to acyl halides.[2335] The reaction is the best and the most common method for the preparation of acyl chlorides. Bromides and iodides[2336] are also made in this manner, but much less often. Thionyl chloride[2337] is a good reagent, since the by-products are gases and the acyl halide is easily isolated, but PX_3 and PX_5 (X = Cl or Br) are also commonly used.[2338] Acyl bromides can be prepared with BBr_3 on alumina[2339] or with ethyl tribromoacetate/PPh_3.[2340]

[2328] Yun, F.; Cheng, C.; Zhang, J.; Li, J.; Liu, X.; Xie, R.; Tang, P.; Yuan, Q. *Synthesis* ***2017***, *49*, 1583.
[2329] Pilo, M.; Porcheddu, A.; De Luca, L. *Org. Biomol. Chem.* ***2013***, *11*, 8241.
[2330] Zhang, J.; Hong, S.H. *Org. Lett.* ***2012***, *14*, 4646.
[2331] Lee, H.; Kang, B.; Lee, S.-I.; Hong, S.H. *Synlett* ***2015***, *26*, 1077.
[2332] Marinescu, L.G.; Pedersen, C.M.; Bols, M. *Tetrahedron* ***2005***, *61*, 123. See Hünig, S.; Schaller, R. *Angew. Chem. Int. Ed.* ***1982***, *21*, 36.
[2333] Arote, N.D.; Akamanchi, K.G. *Tetrahedron Lett.* ***2007***, *48*, 5661.
[2334] Akhlaghinia, B.; Rouhi-Saadabad, H. *Can. J. Chem.* ***2013***, *91*, 181.
[2335] See Ansell, M.F. in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***, pp. 35–68.
[2336] See Keinan, E.; Sahai, M. *J. Org. Chem.* ***1990***, *55*, 3922.
[2337] See Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 321–357. See Mohanazadeh, F.; Momeni, A.R. *Org. Prep. Proceed. Int.* ***1996***, *28*, 492.
[2338] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1929–1930.
[2339] Bains, S.; Green, J.; Tan, L.C.; Pagni, R.M.; Kabalka, G.W. *Tetrahedron Lett.* ***1992***, *33*, 7475.
[2340] Kang, D.H.; Joo, T.Y.; Lee, E.H.; Chaysripongkul, S.; Chavasiri, W.; Jang, D.O. *Tetrahedron Lett.* ***2006***, *47*, 5693.

Hydrogen halides do not give the reaction. A particularly mild procedure, similar to one mentioned in **10-47**, involves reaction of the acid with Ph_3P in CCl_4, whereupon acyl chlorides are produced without obtaining any acidic compounds as by-products.[2341] The reaction of aryl iodides with CO and a chloride ion source, with a Pd catalyst, gave the acid chloride.[2342] *tert*-Butyl esters reacted with thionyl chloride and water to give the corresponding acid chloride.[2343]

Oxalyl chloride and oxalyl bromide are mild and often superior reagents, since the oxalic acid by-product decomposes to CO and CO_2, and the equilibrium is thus driven to the side of the other acyl halide.[2344] These reagents are commonly the reagent of choice, particularly when sensitive functionality is present elsewhere in the molecule.

Acyl halides are also used as reagents in an exchange reaction, which probably involves an anhydride intermediate. This is an equilibrium reaction that must be driven to the desired side. When halide exchange is done, it is always acyl bromides and iodides that are made from chlorides, since chlorides are by far the most readily available.[2345]

OS **I**, 12, 147, 394; **II**, 74, 156, 169, 569; **III**, 169, 490, 547, 555, 613, 623, 712, 714; **IV**, 34, 88, 154, 263, 339, 348, 554, 608, 616, 620, 715, 739, 900; **V**, 171, 258, 887; **VI**, 95, 190, 549, 715; **VII**, 467; **VIII**, 441, 486, 498.

$$(RCO)_2O + HF \longrightarrow RCOF$$
$$RCOCl + HF \longrightarrow RCOF$$

These reactions are most important for the preparation of acyl fluorides.[2346] Acyl fluorides can be prepared by treatment of carboxylic acids with cyanuric fluoride.[2347] *C*,*N*-Chelated di-*n*-butyltin(IV) fluoride has been used to prepared acyl fluorides.[2348] Acid salts are also sometimes used as substrates. Acyl chlorides and anhydrides can be converted to acyl fluorides by treatment with polyhydrogen fluoride/pyridine solution[2349] or with liquid HF at −10 °C.[2350] Formyl fluoride, which is a stable compound, was prepared by the latter procedure from the mixed anhydride of formic and acetic acids.[2351] Acyl fluorides can also be obtained by reaction of acyl chlorides with KF in acetic acid[2352] or with diethylaminosulfur trifluoride (DAST).[2353]

OS **II**, 528; **III**, 422; **V**, 66, 1103; **IX**, 13. See also, OS **IV**, 307.

[2341] Lee, J.B. *J. Am. Chem. Soc.* ***1966***, *88*, 3440. See Venkataraman, K.; Wagle, D.R. *Tetrahedron Lett.* ***1979***, 3037; Devos, A.; Remion, J.; Frisque-Hesbain, A.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* ***1979***, 1180.

[2342] Quesnel, J.S.; Arndtsen, B.A. *J. Am. Chem. Soc.* ***2013***, *135*, 16841.

[2343] Greenberg, J.A.; Sammakia, T. *J. Org. Chem.* ***2017***, *82*, 3245.

[2344] Adams, R.; Ulich, L.H. *J. Am. Chem. Soc.* ***1920***, *42*, 599; Wood, T.R.; Jackson, F.L.; Baldwin, A.R.; Longenecker, H.E. *J. Am. Chem. Soc.* ***1944***, *66*, 287; Zhang, A.; Nie, J. *J. Agric. Food Chem.* ***2005***, *53*, 2451.

[2345] See Schmidt, A.H.; Russ, M.; Grosse, D. *Synthesis* ***1981***, 216; Hoffmann, H.M.R.; Haase, K. *Synthesis* ***1981***, 715.

[2346] For lists of reagents converting acid derivatives to acyl halides, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1950–1951, 1955, 1968.

[2347] Olah, G.A.; Nojima, M.; Kerekes, I. *Synthesis* ***1973***, 487. For other methods of preparing acyl fluorides, see Mukaiyama, T.; Tanaka, T. *Chem. Lett.* ***1976***, 303; Ishikawa, N.; Sasaki, S. *Chem. Lett.* ***1976***, 1407.

[2348] Švec, P.; Eisner, A.; Kolářová, L.; Weidlich, T.; Pejchal, V.; Růžička, A. *Tetrahedron Lett.* ***2008***, *49*, 6320.

[2349] Olah, G.A.; Welch, J.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979***, *44*, 3872. See also, Yin, J.; Zarkowsky, D.S.; Thomas, D.W.; Zhao, M.W.; Huffman, M.A. *Org. Lett.* ***2004***, *6*, 1465.

[2350] Olah, G.A.; Kuhn, S.J. *J. Org. Chem.* ***1961***, *26*, 237.

[2351] Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* ***1960***, *82*, 2380.

[2352] Emsley, J.; Gold, V.; Hibbert, F.; Szeto, W.T.A. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 923.

[2353] Markovski, L.N.; Pashinnik, V.E. *Synthesis* ***1975***, 801.

G. Attack by Carbon at an Acyl Carbon[2354]

16-79 The Coupling of Acyl Halides

$$2\,RCOCl \xrightarrow{\text{Pyrophoric Pb}} RCOCOR$$

Acyl halides can be coupled with pyrophoric lead to give symmetrical α-diketones in a *Wurtz-type reaction*.[2355] The reaction has been performed with R = Me and Ph. Samarium iodide[2356] gives the same reaction. The photochemical coupling of acyl iodides gives α-diketones.[2357] Benzoyl chloride was coupled to give benzil by subjecting it to ultrasound in the presence of Li wire:[2358]

$$2PhCOCl + Li \rightarrow PhCOCOPh$$

Unsymmetrical α-diketones RCOCOR′ have been prepared by treatment of an acyl halide (RCOCl) with an acyltin reagent ($R'COSnBu_3$), with a Pd complex catalyst.[2359]

16-80 Acylation at a Carbon Bearing an Active Hydrogen

This reaction is similar to **10-67**, but there are fewer examples.[2360] Either Z or Z′ may be any of the electron-withdrawing groups listed in **10-67** (such as CO_2R, COR, CN, etc.).[2361] Anhydrides react similarly but are used less often. The product actually contains three Z groups, since RCO is also a Z group. One or two of these can be cleaved (**12-39**, **12-42**). In this way a compound ZCH_2Z' can be converted to ZCH_2Z^2 or an acyl halide (RCOCl) can be converted to a methyl ketone ($RCOCH_3$). *O*-Acylation is sometimes a side reaction.[2362] When thallium(I) salts of ZCH_2Z' are used, it is possible to achieve regioselective acylation at either the C or the O position. For example, treatment of the thallium(I) salt of $MeCOCH_2COMe$ with acetyl chloride at −78 °C gave >90% *O*-acylation, while acetyl

[2354] House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 691–694, 734–765.
[2355] Mészáros, L. *Tetrahedron Lett.* ***1967***, 4951.
[2356] Souppe, J.; Namy, J.; Kagan, H.B. *Tetrahedron Lett.* ***1984***, *25*, 2869. See also, Collin, J.; Namy, J.; Dallemer, F.; Kagan, H.B. *J. Org. Chem.* ***1991***, *56*, 3118.
[2357] Voronkov, M.G.; Belousova, L.I.; Vlasov, A.V.; Vlasova, N.N. *Russ. J. Org. Chem.* ***2008***, *44*, 929.
[2358] Han, B.H.; Boudjouk, P. *Tetrahedron Lett.* ***1981***, *22*, 2757.
[2359] Verlhac, J.; Chanson, E.; Jousseaume, B.; Quintard, J. *Tetrahedron Lett.* ***1985***, *26*, 6075. For another procedure, see Olah, G.A.; Wu, A. *J. Org. Chem.* ***1991***, *56*, 902.
[2360] For examples of reactions in this section, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1484–1485, 1522–1527.
[2361] For an improved procedure, see Rathke, M.W.; Cowan, P.J. *J. Org. Chem.* ***1985***, *50*, 2622.
[2362] When phase-transfer catalysts are used, *O*-acylation becomes the main reaction: Jones, R.A.; Nokkeo, S.; Singh, S. *Synth. Commun.* ***1977***, *7*, 195.

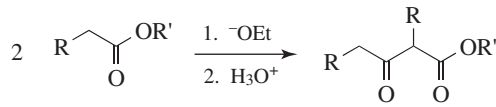
fluoride at room temperature gave >95% *C*-acylation.[2363] The use of an alkyl chloroformate gives triesters.[2364]

The application of this reaction to simple ketones[2365] (in parallel with **10-68**) requires a strong base, such as $NaNH_2$ or Ph_3CNa, and is often complicated by *O*-acylation, which in many cases becomes the principal pathway because acylation at the oxygen is usually much faster. It is possible to increase the proportion of *C*-acylated product by employing an excess (2–3 molar equivalents) of enolate anion (and adding the substrate to this, rather than vice versa), by the use of a relatively nonpolar solvent and a metal ion (e.g., Mg^{2+}) which is tightly associated with the enolate oxygen atom, by the use of an acyl halide rather than an anhydride,[2366] and by working at low temperatures.[2367] Simple ketones can also be acylated by treatment of their silyl enol ethers with an acyl chloride in the presence of $ZnCl_2$ or $SbCl_3$.[2368] Ketones can be acylated by anhydrides to give β-diketones, with BF_3 as catalyst.[2369] Simple esters RCH_2CO_2Et can be acylated at the α carbon (at −78 °C) if a strong base such as lithium *N*-isopropylcyclohexylamide is used to remove the proton.[2370]

Silyl enol esters react with acetic anhydride, in the presence of a chiral Fe complex, to give a chiral β-keto ester.[2371]

OS **II**, 266, 268, 594, 596; **III**, 16, 390, 637; **IV**, 285, 415, 708; **V**, 384, 937; **VI**, 245; **VII**, 213, 359; **VIII**, 71, 326, 467. See also, OS **VI**, 620.

16-81 Acylation of Carboxylic Esters by Carboxylic Esters: The *Claisen* and *Dieckmann Condensations*



When carboxylic esters containing an α hydrogen are treated with a strong base, such as sodium ethoxide, a condensation occurs to give a β-keto ester via an ester enolate anion.[2372] This reaction is called the *Claisen condensation*. When it is carried out with a mixture of two different esters, each of which possesses an α hydrogen (this reaction is called a *mixed Claisen* or a *crossed Claisen condensation*), a mixture of all four products is generally obtained and the reaction is seldom useful synthetically.[2373] However, if only one of the esters has an α hydrogen, the mixed reaction is frequently satisfactory. Among esters lacking α hydrogen atoms (hence acting as the substrate ester) that are commonly used in this way are esters of aromatic acids, ethyl carbonate, and ethyl oxalate. When the ester

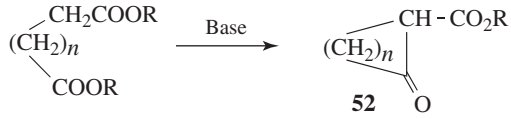
[2363] Taylor, E.C.; Hawks III, G.H.; McKillop, A. *J. Am. Chem. Soc.* ***1968***, *90*, 2421.
[2364] See Skarzewski, J. *Tetrahedron* ***1989***, *45*, 4593.
[2365] Hegedus, L.S.; Williams, R.E.; McGuire, M.A.; Hayashi, T. *J. Am. Chem. Soc.* ***1980***, *102*, 4973.
[2366] See House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 762–765; House, H.O.; Auerbach, R.A.; Gall, M.; Peet, N.P. *J. Org. Chem.* ***1973***, *38*, 514.
[2367] Seebach, D.; Weller, T.; Protschuk, G.; Beck, A.K.; Hoekstra, M.S. *Helv. Chim. Acta* ***1981***, *64*, 716.
[2368] Tirpak, R.E.; Rathke, M.W. *J. Org. Chem.* ***1982***, *47*, 5099.
[2369] See Hauser, C.R.; Swamer, F.W.; Adams, J.T. *Org. React.* ***1954***, *8*, 59 (pp. 98–106).
[2370] See Hayden, W.; Pucher, R.; Griengl, H. *Monatsh. Chem.* ***1987***, *118*, 415.
[2371] Mermerian, A.H.; Fu, G.C. *J. Am. Chem. Soc.* ***2005***, *127*, 5604.
[2372] See Rablen, P.R.; Bentrup, K.L.H. *J. Am. Chem. Soc.* ***2003***, *125*, 2142.
[2373] See Tanabe, Y. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 1917.

enolate reacts with ethyl carbonate, the product is a malonic ester, and reaction with ethyl formate introduces a formyl group. Claisen condensation of phenyl esters with $ZrCl_4$ and diisopropylethylamine (*Hünigs base*) gave the corresponding keto ester.[2374] Titanium compounds catalyze a crossed-Claisen condensation.[2375] Boron(III) compounds also catalyzed ester condensation reactions.[2376]

As with ketone enolate anions (see **16-34**), the use of amide bases under kinetic control conditions (strong base with a weak conjugate acid, aprotic solvents, low temperatures), allows a mixed Claisen condensation to proceed. Self-condensation of the lithium enolate with the parent ester remains a problem even when LDA is used as a base,[2377] but self-condensation is minimized with LICA.[2378] Note that solvent-free Claisen condensation reactions have been reported.[2379] The In-catalyzed reaction of carboxylic acids and ketene silyl acetals in the presence of $(MeO)_3SiH$ gave the β-keto ester product.[2380] Acetate derivatives reacted with formate esters in the presence of $TiCl_4/NEt_3$ to give (*E*)-β-alkoxy- and (*E*)-β-aryloxyacrylate products.[2381] A phosphorus Claisen condensation is known.[2382]

Retro-Claisen reactions have been reported.[2383]

When the two ester groups are involved in an intramolecular condensation, the product is a cyclic β-keto ester (**52**) and the reaction is called the *Dieckmann condensation*:[2384]



52

The Dieckmann condensation is most successful for the formation of five-, six-, and seven-membered rings, and yields for rings of 9–12 members are very low or nonexistent. Reactions that form large rings are generally assisted by high dilution. A solvent-free Dieckmann condensation has been reported on solid potassium *tert*-butoxide.[2385] Dieckmann condensation of unsymmetrical substrates can be made regioselective by the use of solid-phase supports.[2386] The Dieckmann condensation has also been done using $TiCl_3/NBu_3$ with a TMSOTf catalyst.[2387] A Dieckmann-like condensation was reported where an α,ω-dicarboxylic acid was heated to 450 °C on graphite, with microwave irradiation, to give

[2374] Tanabe, Y.; Hamasaki, R.; Funakoshi, S. *Chem. Commun.* ***2001***, 1674.
[2375] Misaki, T.; Nagase, R.; Matsumoto, K.; Tanabe, Y. *J. Am. Chem. Soc.* ***2005***, *127*, 2854.
[2376] Maki, T.; Ishihara, K.; Yamamoto, H. *Tetrahedron* ***2007***, *63*, 8645.
[2377] Sullivan, D.F.; Woodbury, R.P.; Rathke, M.W. *J. Org. Chem.* ***1977***, *42*, 2038.
[2378] Rathke, M.W.; Lindert, A. *J. Am. Chem. Soc.* ***1971***, *93*, 2318.
[2379] Yoshizawa, K.; Toyota, S.; Toda, F. *Tetrahedron Lett.* ***2001***, *42*, 7983.
[2380] Nishimoto, Y.; Okita, A.; Yasuda, M.; Baba, A. *Angew. Chem. Int. Ed.* ***2011***, *50*, 8623.
[2381] Álvarez-Calero, J.M.; Jorge, Z.D.; Massanet, G.M. *Org. Lett.* ***2016***, *18*, 6344.
[2382] Gavara, L.; Gelat, F.; Montchamp, J.L. *Tetrahedron Lett.* ***2013***, *54*, 817.
[2383] Maji, T.; Ramakumar, K.; Tunge, J.A. *Chem. Commun.* ***2014***, *50*, 13045; Kawata, A.; Takata, K.; Kuninobu, Y.; Takai, K. *Angew. Chem. Int. Ed.* ***2007***, *46*, 7793. See Zhu, Y.; Zhang, L.; Luo, S. *J. Am. Chem. Soc.* ***2016***, *138*, 3978.
[2384] See Schaefer, J.P.; Bloomfield, J.J. *Org. React.* ***1967***, *15*, 1.
[2385] Toda, F.; Suzuki, T.; Higa, S. *J. Chem. Soc., Perkin Trans. 1* ***1998***, 3521.
[2386] Crowley, J.I.; Rapoport, H. *J. Org. Chem.* ***1980***, *45*, 3215. For another method, see Yamada, Y.; Ishii, T.; Kimura, M.; Hosaka, K. *Tetrahedron Lett.* ***1981***, *22*, 1353.
[2387] Yoshida, Y.; Hayashi, R.; Sumihara, H.; Tanabe, Y. *Tetrahedron Lett.* ***1997***, *38*, 8727.

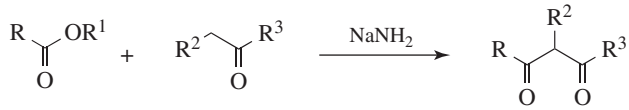
the cyclic ketone.[2388] Piperazine-2,5-diones were prepared by a Dieckmann cyclization route.[2389]

The mechanism of the Claisen and Dieckmann reactions is the ordinary *tetrahedral mechanism*,[2390] with one molecule of ester being converted to an enolate anion by the base and the other serving as the substrate. This reaction illustrates the fact that carboxylic esters react via acyl substitution whereas aldehydes and ketones react via acyl addition.

Ordinary esters react quite well, that is, two Z groups are not needed. A lower degree of acidity (pK_a about 24–25 for an ester versus pK_a 19–20 for a ketone; Sec. 8.A.i) is sufficient that deprotonation occurs upon treatment with strong base. The initial acid–base deprotonation is an equilibrium but sufficient enolate anion is present to attack the ester substrate. The use of a stronger base, such as $NaNH_2$, NaH, or KH,[2391] often increases the yield.

OS **I**, 235; **II**, 116, 194, 272, 288; **III**, 231, 300, 379, 510; **IV**, 141; **V**, 288, 687, 989; **VIII**, 112.

16-82 Acylation of Ketones and Nitriles by Carboxylic Esters



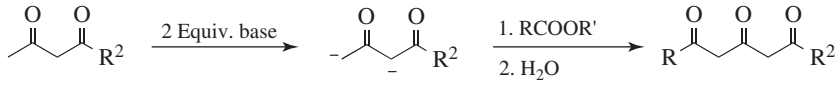
Carboxylic esters can be treated with ketones to give β-diketones. The reaction is so similar to the Claisen condensation that it is sometimes also called the *Claisen reaction*, but this usage may be confusing. A strong base, such as sodium amide or sodium hydride, is required. Yields can be increased by the catalytic addition of crown ethers.[2392] Esters of formic acid (R = H) give β-keto aldehydes and ethyl carbonate gives β-keto esters. β-Keto esters can also be obtained by treating the lithium enolates of ketones with methyl cyanoformate MeOCOCN[2393] (in this case CN is the leaving group) and by treating ketones with KH and diethyl dicarbonate, $(EtOCO)_2O$.[2394] This reaction has been used to effect cyclization, especially to prepare five- and six-membered rings. Nitriles are frequently used instead of ketones, the products being β-keto nitriles.

Other nucleophilic carbon reagents, such as acetylide ions and ions derived from α-methylpyridines, can be used. A particularly useful nucleophile is the methylsulfinyl carbanion $CH_3SOCH_2^-$ (the conjugate base of DMSO),[2395] since the β-keto sulfoxide produced can easily be reduced to a methyl ketone (see **10-67**). The methylsulfonyl carbanion $CH_2SO_2CH_2^-$ (the conjugate base of dimethyl sulfone) behaves similarly,[2396] and the product can be similarly reduced. Certain carboxylic esters, acyl halides, and DMF will acylate

[2388] Marquié, J.; Laporterie, A.; Dubac, J.; Roques, N. *Synlett* ***2001***, 493.
[2389] Aboussafy, C.L.; Clive, D.L.J. *J. Org. Chem.* ***2012***, *77*, 5125.
[2390] An SET mechanism may be involved: Ashby, E.C.; Park, W. *Tetrahedron Lett.* ***1983***, 1667. See Nishimura, T.; Sunagawa, M.; Okajima, T.; Fukazawa, Y. *Tetrahedron Lett.* ***1997***, *38*, 7063.
[2391] Brown, C.A. *Synthesis* ***1975***, 326.
[2392] Popik, V.V.; Nikolaev, V.A. *J. Org. Chem.* USSR ***1989***, *25*, 1636.
[2393] Mander, L.N.; Sethi, P. *Tetrahedron Lett.* ***1983***, *24*, 5425.
[2394] Hellou, J.; Kingston, J.F.; Fallis, A.G. *Synthesis* ***1984***, 1014.
[2395] See Durst, T. *Adv. Org. Chem.* ***1969***, *6*, 285 (pp. 296–301).
[2396] Schank, K.; Hasenfratz, H.; Weber, A. *Chem. Ber.* ***1973***, *106*, 1107, House, H.O.; Larson, J.K. *J. Org. Chem.* ***1968***, *33*, 61.

1,3-dithianes[2397] (see **10-71**) to give, after oxidative hydrolysis with NBS or NCS, α-keto aldehydes or α-diketones.[2398]

As in **10-67**, a ketone is deprotonated at the most acidic proton first and the second most acidic position after that if 2 equivalents of base are used, to give dianion **53**. Thus, β-diketones have been converted to 1,3,5-triketones.[2399] Side reactions are condensation of the ketone with itself (**16-34**), of the ester with itself, and of the ketone with the ester but with the ester supplying the α position (**16-36**). The mechanism is the same as in **16-81**.[2400] These ions can also be acylated on treatment with a carboxylic ester[2401] to give salts of β-keto acids.

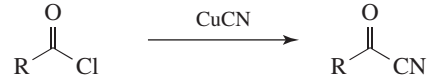


53

As seen previously (**10-70**), dianions of carboxylic acids can be alkylated in the α position. The carboxylic acid can be of the form RCH_2CO_2H or RR^2CHCO_2H. If the ester is ethyl formate, an α-formyl carboxylate salt ($R' = H$) is formed, which on acidification spontaneously decarboxylates into an aldehyde.[2402] This method accomplishes the conversion $RCH_2CO_2H \rightarrow RCH_2CHO$, and is an alternative to the reduction methods discussed in **19-43**. When the carboxylic acid is of the form RR^2CHCO_2H, better yields are obtained by acylating with acyl halides rather than esters.[2403]

OS **I**, 238; **II**, 126, 200, 287, 487, 531; **III**, 17, 251, 291, 387, 829; **IV**, 174, 210, 461, 536; **V**, 187, 198, 439, 567, 718, 747; **VI**, 774; **VII**, 351.

16-83 Preparation of Acyl Cyanides



Acyl cyanides[2404] can be prepared by treatment of acyl halides with copper cyanide. The mechanism could be free radical or nucleophilic substitution. The reaction has also been accomplished with thallium(I) cyanide,[2405] with Me_3SiCN and an $SnCl_4$ catalyst,[2406] and with Bu_3SnCN,[2407] but these reagents are successful only when R = aryl or tertiary alkyl.

[2397] Corey, E.J.; Seebach, D. *J. Org. Chem.* ***1975***, *40*, 231.
[2398] See Corey, E.J.; Erickson, B.W. *J. Org. Chem.* ***1971***, *36*, 3553.
[2399] Miles, M.L.; Harris, T.M.; Hauser, C.R. *J. Org. Chem.* ***1965***, *30*, 1007.
[2400] Hill, D.G.; Burkus, T.; Hauser, C.R. *J. Am. Chem. Soc.* ***1959***, *81*, 602.
[2401] Kuo, Y.; Yahner, J.A.; Ainsworth, C. *J. Am. Chem. Soc.* ***1971***, *93*, 6321; Angelo, B. *C.R. Seances Acad. Sci. Ser. C* ***1973***, *276*, 293.
[2402] Koch, G.K.; Kop, J.M.M. *Tetrahedron Lett.* ***1974***, 603.
[2403] Krapcho, A.P.; Kashdan, D.S.; Jahngen Jr., E.G.E.; Lovey, A.J. *J. Org. Chem.* ***1977***, *42*, 1189; Lion, C.; Dubois, J.E. *J. Chem. Res. (S)* ***1980***, 44.
[2404] See Hünig, S.; Schaller, R. *Angew. Chem. Int. Ed.* ***1982***, *21*, 36.
[2405] Taylor, E.C.; Andrade, J.G.; John, K.C.; McKillop, A. *J. Org. Chem.* ***1978***, *43*, 2280.
[2406] Olah, G.A.; Arvanaghi, M.; Prakash, G.K.S. *Synthesis* ***1983***, 636.
[2407] Tanaka, M. *Tetrahedron Lett.* ***1980***, *21*, 2959. See also, Tanaka, M.; Koyanagi, M. *Synthesis* ***1981***, 973.

KCN has also been used, along with ultrasound,[2408] as has NaCN with phase-transfer catalysts.[2409]

OS **III**, 119.

16-84 Ketones via Decarboxylation of Carboxylic Acids[2410]

$$2\,\mathrm{RCOOH} \xrightarrow[\mathrm{ThO_2}]{400\text{–}500\ ^\circ\mathrm{C}} \mathrm{RCOR} + \mathrm{CO_2}$$

Carboxylic acids can be converted to symmetrical ketones by pyrolysis in the presence of thorium oxide. In a mixed reaction, formic acid and another acid were heated over thorium oxide and gave aldehydes. Mixed alkyl aryl ketones have been prepared by heating mixtures of ferrous salts.[2411] When the R group is large, the methyl ester rather than the acid can be decarbmethoxylated over thorium oxide to give the symmetrical ketone.

The reaction has been performed on dicarboxylic acids, whereupon cyclic ketones are obtained. This process, called *Ruzicka cyclization*, is good for the preparation of rings of six and seven members and, with lower yields, of C_8–C_{10} to C_{30} cyclic ketones.[2412]

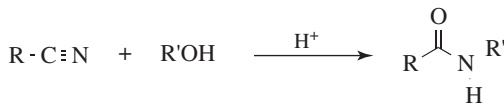
Not much work has been done on the mechanism of this reaction. However, a free-radical mechanism has been suggested on the basis of a thorough study of all the side products.[2413]

OS **I**, 192; **II**, 389; **IV**, 854; **V**, 589. Also see, OS **IV**, 55, 560.

16.B.iii. Reactions in Which Carbon Adds to the Heteroatom

A. Oxygen Adding to the Carbon

16-85 The Ritter Reaction



Alcohols can be added to nitriles in an entirely different manner from that seen in reaction **16-8**. In this reaction, the alcohol is converted by a strong acid to an oxonium ion, which loses water to give a carbocation, which is attacked by the nucleophilic nitrogen atom to give **54**. Subsequent addition of water to the electrophilic carbon atom leads to the enol form of the amide, which tautomerizes (Sec. 2.N.i) to the *N*-alkyl amide.

[2408] Ando, T.; Kawate, T.; Yamawaki, J.; Hanafusa, T. *Synthesis* ***1983***, 637.

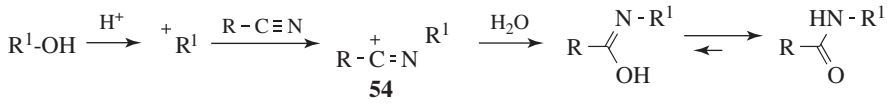
[2409] Koenig, K.E.; Weber, W.P. *Tetrahedron Lett.* ***1974***, 2275. See also, Sukata, K. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 1085.

[2410] See Kwart, H.; King, K. in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 362–370.

[2411] Granito, C.; Schultz, H.P. *J. Org. Chem.* ***1963***, *28*, 879.

[2412] See Ruzicka, L.; Stoll, M.; Schinz, H. *Helv. Chim. Acta* ***1926***, *9*, 249; ***1928***, *11*, 1174; Ruzicka, L.; Brugger, W.; Seidel, C.F.; Schinz, H. *Helv. Chim. Acta* ***1928***, *11*, 496.

[2413] Hites, R.A.; Biemann, K. *J. Am. Chem. Soc.* ***1972***, *94*, 5772. See also, Bouchoule, C.; Blanchard, M.; Thomassin, R. *Bull. Soc. Chim. Fr.* ***1973***, 1773.



54

Only alcohols that give rise to fairly stable carbocations react (secondary, tertiary, benzylic, etc.); nonbenzylic primary alcohols do not give the reaction. The carbocation need not be generated from an alcohol but may come from protonation of an alkene or from other sources. In any case, the reaction is called the *Ritter reaction*.[2414] Lewis acids, such as $Mg(HSO_4)_2$, have been used to promote the reaction.[2415] Highly sterically hindered nitriles have been converted to *N*-methyl amides by heating with methanol and sulfuric acid.[2416] HCN also gives the reaction, the product being a formamide. Trimethylsilyl cyanide has also been used.[2417]

Since the amides (especially the formamides) are easily cleaved to amines under hydrolysis conditions, the Ritter reaction provides a method for achieving the conversions R′OH → R′NH_2 (see **10-31**) and alkene → R′NH_2 (see **15-8**) in those cases where R′ can form a relatively stable carbocation. The reaction is especially useful for the preparation of tertiary alkyl amines because there are few alternate ways of preparing these compounds. The reaction can be extended to primary alcohols by treatment with triflic anhydride[2418] or Ph_2CCl^+ $SbCl_6^-$ or a similar salt[2419] in the presence of the nitrile. A mixture of P_2O_5 and silica gel has been used to mediate the Ritter reaction.[2420] There is a Nafion-catalyzed, microwave-assisted variation,[2421] as well as Fe-catalyzed[2422] and iodine-catalyzed[2423] reactions. Organocatalysts have been used.[2424] Amides have been prepared by the Ritter reaction in ionic liquids.[2425]

In a related reaction, cyclic alkanes reacted with a Cu catalyst, $Zn(OTf)_2$, and F-TEDA-PF_6 [1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate), a greener Selectfluor reagent] to give the *N*-alkylacetamide.[2426]

Alkenes of the form RCH═CHR′ and RR′C═CH_2 add to nitriles in the presence of mercuric nitrate to give, after treatment with $NaBH_4$, the same amides that would be obtained

[2414] Ritter, J.J.; Minieri, P.P. *J. Am. Chem. Soc.* ***1948***, *70*, 4045. See Krimen, L.I.; Cota, D.J. *Org. React.* ***1969***, *17*, 213; Tongco, E.C.; Prakash, G.K.S.; Olah, G.A. *Synlett* ***1997***, 1193.

[2415] Salehi, P.; Khodaei, M.M.; Zolfigol, M.A.; Keyvan, A. *Synth. Commun.* ***2001***, *31*, 1947.

[2416] Lebedev, M.Y.; Erman, M.B. *Tetrahedron Lett.* ***2002***, *43*, 1397.

[2417] Chen, H.G.; Goel, O.P.; Kesten, S.; Knobelsdorf, J. *Tetrahedron Lett.* ***1996***, *37*, 8129.

[2418] Martinez, A.G.; Alvarez, R.M.; Vilar, E.T.; Fraile, A.G.; Hanack, M.; Subramanian, L.R. *Tetrahedron Lett.* ***1989***, *30*, 581.

[2419] Barton, D.H.R.; Magnus, P.D.; Garbarino, J.A.; Young, R.N. *J. Chem. Soc., Perkin Trans. 1* ***1974***, 2101. See also, Top, S.; Jaouen, G. *J. Org. Chem.* ***1981***, *46*, 78.

[2420] Tamaddon, F.; Khoobi, M.; Keshavarz, E. *Tetrahedron Lett.* ***2007***, *48*, 3643.

[2421] Polshettiwar, V.; Varma, R.S. *Tetrahedron Lett.* ***2008***, *49*, 2661.

[2422] See Jefferies, L.R.; Cook, S.P. *Tetrahedron* ***2014***, *70*, 4204; Basavaprabhu, H.; Sureshbabu, V.V. *Org. Biomol. Chem.* ***2012***, *10*, 2528.

[2423] Theerthagiri, P.; Lalitha, A.; Arunachalam, P.N. *Tetrahedron Lett.* ***2010***, *51*, 2813. See Kiyokawa, K.; Takemoto, K.; Minakata, S. *Chem. Commun.* ***2016***, *52*, 13082.

[2424] Khaksar, S.; Fattahi, E.; Fattahi, E. *Tetrahedron Lett.* ***2011***, *52*, 5943.

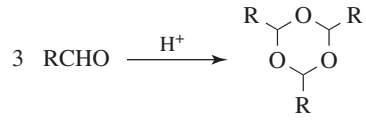
[2425] Kalkhambkar, R.G.; Waters, S.N.; Laali, K.K. *Tetrahedron Lett.* ***2011***, *52*, 867. See Khodaei, M.M.; Nazari, E. *Tetrahedron Lett.* ***2012***, *53*, 2881.

[2426] Michaudel, Q.; Thevenet, D.; Baran, P.S. *J. Am. Chem. Soc.* ***2012***, *134*, 2547.

by the Ritter reaction.[2427] This method has the advantage of avoiding strong acids. The Ritter reaction can be applied to cyanamides RNHCN to give ureas RNHCONHR′.[2428]

OS **V**, 73, 471.

16-86 The Addition of Aldehydes to Aldehydes

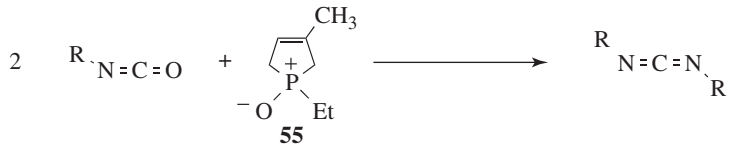


When catalyzed by acids, low molecular weight aldehydes add to each other to give cyclic acetals, the most common product being the trimer.[2429] The cyclic trimer of formaldehyde is called *trioxane*,[2430] and that of acetaldehyde is known as *paraldehyde*. Under certain conditions, it is possible to get tetramers[2431] or dimers. Aldehydes can also polymerize to linear polymers, but a small amount of water is required to form hemiacetal groups at the ends of the chains. The linear polymer formed from formaldehyde is called *paraformaldehyde*. Since trimers and polymers of aldehydes are acetals, they are stable to bases but can be hydrolyzed by acids. Because formaldehyde and acetaldehyde have low boiling points, it is often convenient to use them in the form of their trimers or polymers.

Unsymmetrical alkenes were formed by the reductive coupling of two different aldehydes by reaction of the first aldehyde with a phosphanyl phosphonate to give a phosphaalkene intermediate which, upon activation by hydroxide, reacts with the second aldehyde to give an unsymmetrical (*E*)-alkene.[2432]

B. Nitrogen Adding to the Carbon

16-87 The Addition of Isocyanates to Isocyanates (Formation of Carbodiimides)

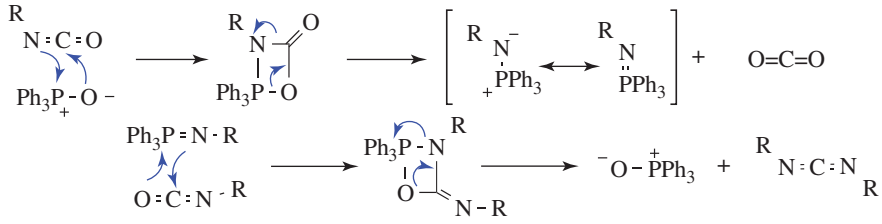


55

The treatment of isocyanates with 3-methyl-1-ethyl-3-phospholene-1-oxide (**55**) is a useful method for the synthesis of carbodiimides[2433] in good yields.[2434] The mechanism does not simply involve the addition of one molecule of isocyanate to another, since the kinetics

[2427] See Fry, A.J.; Simon, J.A. *J. Org. Chem.* ***1982***, *47*, 5032.
[2428] Anatol, J.; Berecoechea, J. *Bull. Soc. Chim. Fr.* ***1975***, 395; *Synthesis* ***1975***, 111.
[2429] See Bevington, J.C. *Q. Rev. Chem. Soc.* ***1952***, *6*, 141.
[2430] See Camarena, R.; Cano, A.C.; Delgado, F.; Zúñiga, N.; Alvarez, C. *Tetrahedron Lett.* ***1993***, *34*, 6857.
[2431] Barón, M.; de Manderola, O.B.; Westerkamp, J.F. *Can. J. Chem.* ***1963***, *41*, 1893.
[2432] Esfandiarfard, K.; Mai, J.; Ott, S. *J. Am. Chem. Soc.* ***2017***, *139*, 2940.
[2433] Williams, A.; Ibrahim, I.T. *Chem. Rev.* ***1981***, *81*, 589; Mikolajczyk, M.; Kielbasinski, P. *Tetrahedron* ***1981***, *37*, 233; Kurzer, F.; Douraghi-Zadeh, K. *Chem. Rev.* ***1967***, *67*, 107.
[2434] Campbell, T.W.; Monagle, J.J.; Foldi, V.S. *J. Am. Chem. Soc.* ***1962***, *84*, 3673.

are first order in isocyanate and first order in catalyst. The following mechanism has been proposed (the catalyst is here represented as $R_3P^+—O^-$:[2435]



According to this mechanism, one molecule of isocyanate undergoes addition to C═O, and the other addition to C═N. Evidence is that ^{18}O labeling experiments have shown that each molecule of CO_2 produced contains one oxygen atom derived from the isocyanate and one from **55**,[2436] precisely what is predicted by this mechanism. Certain other catalysts are also effective.[2437] High load, soluble oligomeric carbodiimides have been prepared.[2438]

The conversion of 1,3-diphenylthiourea into diphenylcarbodiimide was reported by reaction with [hydroxy(tosyloxy)iodo]benzene and an amine.[2439]

OS **V**, 501.

16-88 The Conversion of Carboxylic Acid Derivatives to Nitriles

$$RCOO^- + BrCN \xrightarrow{250–300\ ^\circ C} RCN + CO_2$$

Salts of aliphatic or aromatic carboxylic acids can be converted to the corresponding nitriles by heating with BrCN or ClCN. Heating with acetonitrile in sulfuric acid also gave the nitrile.[2440] Despite appearances, this is not a substitution reaction. When $R^{14}COO^-$ was used, the label appeared in the nitrile, not in the CO_2,[2441] and optical activity in the R group was retained.[2442] The acyl isocyanate RCON═C═O could be isolated from the reaction mixture and a cycloaddition mechanism was proposed.[2441]

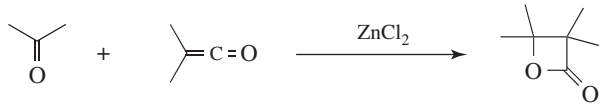
The reaction of *N*,*N*-dimethyl amides, *N*-methoxy-*N*-methyl amides, or isopropyl esters with dibalH, followed by treatment with I_2 in aqueous ammonia, gave the corresponding nitriles.[2443] Triflic anhydride and 2-fluoropyridine dehydrate secondary amides to give nitriles.[2444] The Fe-catalyzed dehydration of amides to the corresponding nitriles used *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide.[2445]

[2435] Monagle, J.J.; Campbell, T.W.; McShane Jr., H.F. *J. Am. Chem. Soc.* ***1962***, *84*, 4288.
[2436] Monagle, J.J.; Mengenhauser, J.V. *J. Org. Chem.* ***1966***, *31*, 2321.
[2437] See Ostrogovich, G.; Kerek, F.; Buzás, A.; Doca, N. *Tetrahedron* ***1969***, *25*, 1875.
[2438] Zhang, M.; Vedantham, P.; Flynn, D.L.; Hanson, P.R. *J. Org. Chem.* ***2004***, *69*, 8340.
[2439] Zhu, C.; Xu, D.; Wei, Y. *Synthesis* ***2011***, *43*, 711.
[2440] Mlinarić-Majerski, K.; Margeta, R.; Veljković, J. *Synlett* ***2005***, 2089.
[2441] Douglas, D.E.; Burditt, A.M. *Can. J. Chem.* ***1958***, *36*, 1256.
[2442] Barltrop, J.A.; Day, A.C.; Bigley, D.B. *J. Chem. Soc.* ***1961***, 3185.
[2443] Suzuki, Y.; Yoshino, T.; Moriyama, K.; Togo, H. *Tetrahedron* ***2011***, *67*, 3809.
[2444] Geng, H.; Huang, P.-Q. *Tetrahedron* ***2015***, *71*, 3795.
[2445] Enthaler, S. *Eur. J. Org. Chem.* ***2011***, 4760.

C. Carbon Adding to the Carbon

The reactions in this group are cycloadditions.

16-89 The Formation of β-Lactones and Oxetanes



Aldehydes, ketones, and quinones react with ketenes to give β-lactones,[2446] diphenylketene being used most often.[2447] The reaction is catalyzed by Lewis acids, and without them most ketenes do not give adducts because the adducts decompose at the high temperatures necessary when no catalyst is used. The phosphine-catalyzed reaction of disubstituted ketenes with aldehydes gave the β-lactone,[2448] and a chiral variation was reported using α-oxyaldehydes.[2449] The Rh-catalyzed intramolecular C—H insertion into the ester group of aryldiazoacetates led to the asymmetric synthesis of β-lactones.[2450]

When ketene was added to chloral (Cl_3CCHO) in the presence of the chiral catalyst (+)-quinidine, one enantiomer of the β-lactone was produced with excellent enantioselectivity.[2451] Enantioselective β-lactone formation was accomplished using chiral oxazaborolidines.[2452] The use of a chiral Al catalyst also led to β-lactones with good *syn* selectivity and good enantioselectivity.[2453] Other di- and trihalo aldehydes and ketones also give the reaction enantioselectively, with somewhat lower enantioselectivity.[2454] Dimerization of ketene leads to an alkylidene β-lactone, along with the isomeric conjugated β-lactone. This dimerization is so rapid that ketene does not form β-lactones with aldehydes or ketones, except at low temperatures. Other ketenes dimerize more slowly. In these cases the major dimerization product is not the β-lactone, but a cyclobutanedione (see **15-59**). However, the proportion of ketene that dimerizes to β-lactone can be increased by the addition of catalysts such as triethylamine or triethyl phosphite.[2455] Ketene acetals $R_2C{=}C(OR')_2$ add to aldehydes and ketones in the presence of $ZnCl_2$ to give the corresponding oxetanes.[2456]

The chemistry of β-thiolactones has been compared to that of β-lactones.[2457]

OS **III**, 508; **V**, 456. For the reverse reaction, see OS **V**, 679.

[2446] See Calter, M.A.; Tretyak, O.A.; Flaschenriem, C. *Org. Lett.* ***2005***, *7*, 1809.

[2447] Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***, pp. 139–168; Ulrich, H. *Cycloaddition Reactions of Heterocumulenes*, Academic Press, NY, ***1967***, pp. 39–45, 64–74.

[2448] Chen, S.; Mondal, M.; Ibrahim, A.A.; Wheeler, K.A.; Kerrigan, N.J. *J. Org. Chem.* ***2014***, *79*, 4920.

[2449] Mondal, M.; Chen, S.; Othman, N.; Wheeler, K.A.; Kerrigan, N.J. *J. Org. Chem.* ***2015***, *80*, 5789; Chen, S.; Mondal, M.; Adams, M.P.; Wheeler, K.A.; Kerrigan, N.J. *Tetrahedron Lett.* ***2015***, *56*, 6421.

[2450] Fu, L.; Wang, H.; Davies, H.M.L. *Org. Lett.* ***2014***, *16*, 3036.

[2451] See Wynberg, H.; Staring, E.G.J. *J. Chem. Soc., Chem. Commun.* ***1984***, 1181.

[2452] Gnanadesikan, V.; Corey, E.J. *Org. Lett.* ***2006***, *8*, 4943.

[2453] Nelson, S.G.; Zhu, C.; Shen, X. *J. Am. Chem. Soc.* ***2004***, *126*, 14.

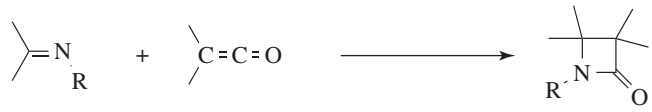
[2454] Wynberg, H.; Staring, E.G.J. *J. Org. Chem.* ***1985***, *50*, 1977.

[2455] Elam, E.U. *J. Org. Chem.* ***1967***, *32*, 215.

[2456] Aben, R.W.; Hofstraat, R.; Scheeren, J.W. *Recl. Trav. Chim. Pays-Bas* ***1981***, *100*, 355. For a discussion of oxetane cycloreversion, see Miranda, M.A.; Izquierdo, M.A.; Galindo, F. *Org. Lett.* ***2001***, *3*, 1965. For a review of the importance of oxetanes in medicinal chemistry, see Bull, J.A.; Croft, R.A.; Davis, O.A.; Doran, R.; Morgan, K.F. *Chem. Rev.* ***2016***, *116*, 12150.

[2457] Noel, A.; Delpech, B.; Crich, D. *J. Org. Chem.* ***2014***, *79*, 4068.

16-90 The Formation of β-Lactams



Ketenes add to imines to give β-lactams[2458] in a [2 + 2] cycloaddition product (see **15.54**, **15.55**). This reaction probably occurs by a different mechanism. This alternative mechanism probably involves a radical or dipolar intermediate or it occurs via by HOMO–HOMO or LUMO–LUMO interactions.[2459] The reaction is generally carried out with ketenes of the form $R_2C{=}C{=}O$. It has not been successfully applied to $RCH{=}C{=}O$, except when these are generated *in situ* by decomposition of a diazo ketone (the *Wolff rearrangement*, **18-8**) in the presence of the imine. Thioketenes[2460] ($R_2C{=}C{=}S$) give β-thiolactams.[2461] Imines also form β-lactams when treated with zinc (or another metal[2462]) and an α-bromo ester (*Reformatsky* conditions, **16-27**),[2463] or the chromium carbene complexes $(CO)_5Cr{=}C(Me)OMe$.[2464] Ketenes have also been added to certain hydrazones (e.g., $PhCH{=}NNMe_2$) to give *N*-amino β-lactams.[2465] A polymer-bound pyridinium salt facilitates β-lactam formation from carboxylic acids and imines.[2466] α-Chloroimines have been used as chiral inductors in this reaction.[2467] The synthesis of β-lactams with π-electron substituents has been reported.[2468] The cycloreversion of β-lactams is known via photoinduced electron transfer.[2469] The Pd-catalyzed intramolecular amination of aminoquinoline carboxamides using C_6F_5I generated the β-lactam.[2470] Organocatalysts have been used.[2471] An intramolecular version of this ketene imine reaction is known.[2472] Most of these reactions probably take place by a diionic mechanism (see **15-59**).[2473]

Enantioselective versions of this reaction have been reported.[2474] *N*-Tosyl imines react with ketenes (see **15-59**), Proton Sponge (Sec. 8.A.i), and a chiral amine to give the *N*-tosyl

[2458] For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1919–1921. See Fu, N.; Tidwell, T.T. *Tetrahedron* ***2008***, *64*, 10465; Isaacs, N.S. *Chem. Soc. Rev.* ***1976***, *5*, 181; Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***, pp. 173–206; Anselme, J. in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 305–309. See Pitts, C.R.; Lectka, T. *Chem. Rev.* ***2014***, *114*, 7930.

[2459] Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p 35.

[2460] See Schaumann, E. *Tetrahedron* ***1988***, *44*, 1827.

[2461] Schaumann, E. *Chem. Ber.* ***1976***, *109*, 906.

[2462] With indium: Banik, B.K.; Ghatak, A.; Becker, F.F. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 2179.

[2463] For a review, see Hart, D.J.; Ha, D. *Chem. Rev.* ***1989***, *89*, 1447.

[2464] Hegedus, L.S.; McGuire, M.A.; Schultze, L.M. *Org. Synth.* ***65***, 140. Hegedus, L.S.; Imwinkelried, R.; Alarid-Sargent, M.; Dvorak, D.; Satoh, Y. *J. Am. Chem. Soc.* ***1990***, *112*, 1109.

[2465] Sharma, S.D.; Pandhi, S.B. *J. Org. Chem.* ***1990***, *55*, 2196.

[2466] Donati, D.; Morelli, C.; Porcheddu, A.; Taddei, M. *J. Org. Chem.* ***2004***, *69*, 9316.

[2467] D'hooghe, M.; Brabandt, W.V.; Dekeukeleire, S.; Dejaegher, Y.; De Kimpe, N. *Chem. Eur. J.* ***2008***, *14*, 6336.

[2468] Xu, J. *Tetrahedron* ***2012***, *68*, 10696.

[2469] Pérez-Ruiz, R.; Sáez, J.A.; Jiménez, M.C.; Miranda, M.A. *Org. Biomol. Chem.* ***2014***, *12*, 8428.

[2470] Sun, W.-W.; Cao, P.; Mei, R.-Q.; Li, Y.; Ma, Y.-L.; Wu, B. *Org. Lett.* ***2014***, *16*, 480.

[2471] Pawar, S.A.; Alapour, S.; Khanyase, S.; Cele, Z.E.D.; Chitti, S.; Kruger, H.G.; Govender, T.; Arvidsson, P.I. *Org. Biomol. Chem.* ***2013***, *11*, 8294.

[2472] Clark, A.J.; Battle, G.M.; Bridge, A. *Tetrahedron Lett.* ***2001***, *42*, 4409.

[2473] See Brady, W.T.; Shieh, C.H. *J. Org. Chem.* ***1983***, *48*, 2499.

[2474] Chen, J.-H.; Liao, S.-H.; Sun, X.-L.; Shen, Q.; Tang, Y. *Tetrahedron* ***2012***, *68*, 5042; Grzeszczyk, B.; Poławska, K.; Shaker, Y.M.; Stecko, S.; Mames, A.; Woźnica, M.; Chmielewski, M.; Furman, B. *Tetrahedron* ***2012***, *68*, 10633; Chen, Z.; Lin, L.; Wang, M.; Liu, X.; Feng, X. *Chem. Eur. J.* ***2013***, *19*, 7561.

β-lactam with good enantioselectivity.[2475] Catalyzed by a chiral bis(phosphine), ketenes reacted with tosylimines to give the corresponding chiral *N*-tosyl β-lactam.[2476] A chiral ferrocenyl catalyst also gives good enantioselectivity,[2477] and chiral ammonium salts[2478] or chiral *Cinchona* alkaloids[2479] have been used as catalysts. A catalytic amount of benzoyl quinine gives β-lactams with good enantioselectivity.[2480] In a synthesis of β-lactams, LiHMDS and TMEDA reacted with a chiral 2-imidazolidinone auxiliary followed by addition of an aldimine to give the β-lactam.[2481]

The synthesis of spiro-fused β-lactams has been reviewed.[2482] A theoretical study[2483] of the Cu-catalyzed [2 + 2] cycloaddition of nitrones and alkynes to give β-lactams, called the *Kinusaga reaction*,[2484] has been reported. This reaction has been used for the synthesis of natural products.[2485]

The mechanical activation of a β-lactam mechanophore used ultrasound to induce a formal [2 + 2] cycloelimination reaction that gave a ketene and an imine,[2486] which is formally the reverse reaction of the *Staudinger cycloaddition* (**15-59**).

The reactive compound chlorosulfonyl isocyanate[2487] ($ClSO_2NCO$) forms β-lactams even with unactivated alkenes,[2488] as well as with imines,[2489] allenes,[2490] conjugated dienes,[2491] and cyclopropenes.[2492] With microwave irradiation, alkyl isocyanates also react.[2493] The preparation of *trans*-β-lactams by the reaction of imines and aryl-substituted acetic acids used T3P (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide solution) as an activating agent.[2494]

β-Lactams have also been prepared in the opposite manner by the addition of enamines to isocyanates.[2495] α-Diazo ketones react with imines and microwave irradiation to give β-lactams.[2496] A different approach to β-lactams involved heating aziridines with CO and

[2475] Taggi, A.E.; Hafez, A.M.; Wack, H.; Young, B.; Drury III, W.J.; Lectka, T. *J. Am. Chem. Soc.* ***2000***, *122*, 7831. See Magriotis, P.A. *Eur. J. Org. Chem.* ***2014***, 2647.
[2476] Chen, S.; Salo, E.C.; Wheeler, K.A.; Kerrigan, N.J. *Org. Lett.* ***2012***, *14*, 1784.
[2477] Hodous, B.L.; Fu, G.C. *J. Am. Chem. Soc.* ***2002***, *124*, 1578.
[2478] Taggi, A.E.; Hafez, A.M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* ***2002***, *124*, 6626.
[2479] France, S.; Shah, M.H.; Weatherwax, A.; Wack, H.; Roth, J.P.; Lectka, T. *J. Am. Chem. Soc.* ***2005***, *127*, 1206.
[2480] Shah, M.H.; France, S.; Lectka, T. *Synlett* ***2003***, 1937.
[2481] Goyal, S.; Pal, A.; Chouhan, M.; Gangar, M.; Sarak, S.; Nair, V.A. *Tetrahedron Lett.* ***2017***, *58*, 346.
[2482] Singh, G.S.; D'hooghe, M.; De Kimpe, N. *Tetrahedron* ***2011***, *67*, 1989.
[2483] Santoro, S.; Liao, R.-Z.; Marcelli, T.; Hammar, P.; Himo, F. *J. Org. Chem.* ***2015***, *80*, 2649.
[2484] Kinugasa, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun.* ***1972***, 466; Khangarot, R.K.; Kaliappan, K.P. *Eur. J. Org. Chem.* ***2013***, 7664. For reviews, see Stecko, S.; Furman, B.; Chmielewski, M. *Tetrahedron* ***2014***, *70*, 7817; Mandal, B.; Basu, B. *Top. Heterocycl. Chem.* ***2013***, *30*, 85; Pal, R.; Ghosh, S.C.; Chandra, K.; Basak, A. *Synlett* ***2007***, 2321; Marco-Contelles, J. *Angew. Chem. Int. Ed.* ***2004***, *43*, 2198.
[2485] Kabala, K.; Grzeszczyk, B.; Stecko, S.; Furman, B.; Chmielewski, M. *J. Org. Chem.* ***2015***, *80*, 12038.
[2486] Robb, M.J.; Moore, J.S. *J. Am. Chem. Soc.* ***2015***, *137*, 10946.
[2487] Kamal, A.; Sattur, P.B. *Heterocycles* ***1987***, *26*, 1051; Rasmussen, J.K.; Hassner, A. *Chem. Rev.* ***1976***, *76*, 389; Graf, R. *Angew. Chem. Int. Ed.* ***1968***, *7*, 172.
[2488] Bestian, H. *Pure Appl. Chem.* ***1971***, *27*, 611. See also, Barrett, A.G.M.; Betts, M.J.; Fenwick, A. *J. Org. Chem.* ***1985***, *50*, 169.
[2489] See McAllister, M.A.; Tidwell, T.T. *J. Chem. Soc., Perkin Trans. 2* ***1994***, 2239.
[2490] Moriconi, E.J.; Kelly, J.F. *J. Org. Chem.* ***1968***, *33*, 3036. See also, Martin, J.C.; Carter, P.L.; Chitwood, J.L. *J. Org. Chem.* ***1971***, *36*, 2225.
[2491] Malpass, J.R.; Tweddle, N.J. *J. Chem. Soc., Perkin Trans. 1* ***1977***, 874.
[2492] Moriconi, E.J.; Kelly, J.F.; Salomone, R.A. *J. Org. Chem.* ***1968***, *33*, 3448.
[2493] Taguchi, Y.; Tsuchiya, T.; Oishi, A.; Shibuya, I. *Bull. Chem. Soc. Jpn.* ***1996***, *69*, 1667.
[2494] Coulthard, G.; Unsworth, W.P.; Taylor, R.J.K. *Tetrahedron Lett.* ***2015***, *56*, 3113.
[2495] See Opitz, G.; Koch, J. *Angew. Chem. Int. Ed.* ***1963***, *2*, 152.
[2496] Linder, M.R.; Podlech, J. *Org. Lett.* ***2001***, *3*, 1849.

a Co catalyst.[2497] Aziridines also react with CO and a dendrimer catalyst to give a β-lactam.[2498]

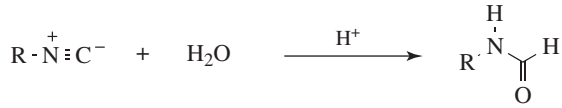
β-Thiolactams are prepared from aryl isothiocyanates.[2499] The reaction of imines and sulfonic acids was mediated by phosphonitrilic chloride to give β-sultams.[2500]

OS **V**, 673; **VIII**, 3, 216.

16.B.iv. Addition to Isocyanides[2501]

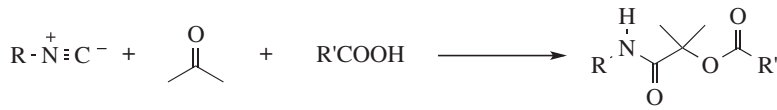
Addition to $R—^{+}N{\equiv}C^{-}$ is not a matter of a species with an electron pair adding to one atom and a species without a pair adding to the other, as is addition to the other types of double and triple bonds in this chapter and Chapter 15. The electrophile and the nucleophile *both add to the carbon*.

16-91 The Addition of Water to Isocyanides



Formamides can be prepared by the acid-catalyzed addition of water to isocyanides. The mechanism probably involves protonation of the isocyanide followed by addition of water.[2502] The reaction has also been carried out under alkaline conditions, with hydroxide in aqueous dioxane.[2503] The mechanism here involves nucleophilic attack by hydroxide at the carbon atom. An intramolecular addition of an alkyne (in an *ortho* alkynyl phenyl isonitrile) to the carbon of an isonitrile occurred with heating in methanol to give quinoline derivatives.[2504]

16-92 The Passerini and Ugi Reactions[2505]



When an isocyanide is treated with a carboxylic acid and an aldehyde or ketone, an α-acyloxy amide is the product in what is called the *Passerini reaction*.[2506] A $SiCl_4$-mediated

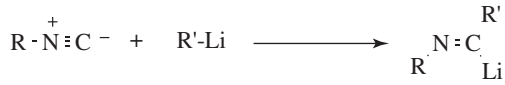
[2497] See Davoli, P.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *Tetrahedron* ***2001***, *57*, 1801.
[2498] Lu, S.-M.; Alper, H. *J. Org. Chem.* ***2004***, *69*, 3558.
[2499] Awasthi, C.; Yadav, L.D.S. *Synlett* ***2010***, 1783.
[2500] Zarei, M. *Tetrahedron Lett.* ***2013***, *54*, 1100.
[2501] Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, ***1971***; Walborsky, H.M.; Periasamy, M.P. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1983***, pp. 835–887; Hoffmann, P.; Marquarding, D.; Kliimann, H.; Ugi, I. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 853–883.
[2502] Lim, Y.Y.; Stein, A.R. *Can. J. Chem.* ***1971***, *49*, 2455.
[2503] Cunningham, I.D.; Buist, G.J.; Arkle, S.R. *J. Chem. Soc., Perkin Trans. 2* ***1991***, 589.
[2504] Suginome, M.; Fukuda, T.; Ito, Y. *Org. Lett.* ***1999***, *1*, 1977.
[2505] Ugi, I. *Angew. Chem. Int. Ed.* ***1982***, *21*, 810; Marquarding, D.; Gokel, G.W.; Hoffmann, P.; Ugi, I. in Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, ***1971***, pp. 133–143; Gokel, G.W.; Lüdke, G.; Ugi, I. in Ugi, I, *Isonitrile Chemistry*, Academic Press, NY, ***197***, pp. 145–199, 252–254.
[2506] Ramozzi, R.; Morokuma, K. *J. Org. Chem.* ***2015***, *80*, 5652. See Chandgude, A.L.; Dömling, A. *Org. Lett.* ***2016***, *18*, 6396.

reaction in the presence of a chiral bis-phosphoramide gives an α-hydroxy amide with good enantioselectivity.[2507] There is a solvent-free Passerini reaction[2508] and ionic liquids[2509] can be used. The mechanism involves a cyclic transition state and addition of the acid carbonyl oxygen to the isonitrile followed by an acyl rearrangement to give the α-acyloxy amide. The phosphoric acid-catalyzed Passerini reaction proceeds with good enantioselectivity.[2510]

If ammonia or an amine is also added to the mixture (in which case the reaction is known as the *Ugi reaction*[2511] or the *Ugi four-component condensation*),[2512] the product is R′(C═C)NH—C—(C═O)NHR (the corresponding bis(amide) from NH_3) or R′(C═C)NR′—C—(C═O)NHR (from a primary amine RNH_2).

There is a catalytic *three-component Ugi reaction*.[2513] Repetitive Ugi reactions are known.[2514] This product probably arises from a reaction between the carboxylic acid, the isocyanide, and the *imine* formed from the aldehyde or ketone and ammonia or the primary amine. "Isocyanide-free" Ugi reactions use alkyl halides/silver cyanide and KCN to generate the isocyanide *in situ*.[2515] The use of an *N*-protected amino acid[2516] or peptide as the carboxylic acid component and/or the use of an isocyanide containing a *C*-protected carboxyl group allows the reaction to be used for peptide synthesis.[2517] Rare earth metal triflates catalyze this reaction.[2518]

16-93 The Formation of Metalated Aldimines



Isocyanides that do not contain an α hydrogen react with alkyllithium compounds,[2519] as well as with Grignard reagents, to give lithium (or magnesium) aldimines.[2520] These metalated aldimines are versatile nucleophiles and react with various substrates. The reaction therefore constitutes a method for converting an organometallic compound R′M to an

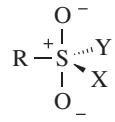
[2507] Denmark, S.E.; Fan, Y. *J. Org. Chem.* ***2005***, *70*, 9667.
[2508] Koszelewski, D.; Szymanski, W.; Krysiak, J.; Ostaszewski, R. *Synth. Commun.* ***2008***, *38*, 1120.
[2509] Fan, X.; Li, Y.; Zhang, X.; Qu, G.; Wang, J. *Can. J. Chem.* ***2006***, *84*, 794.
[2510] Zhang, J.; Lin, S.-X.; Cheng, D.-J.; Liu, X.-Y.; Tan, B. *J. Am. Chem. Soc.* ***2015***, *137*, 14039.
[2511] Chéron, N.; Ramozzi, R.; El Kaïm, L.; Grimaud, L.; Fleurat-Lessard, P. *J. Org. Chem.* ***2012***, *77*, 1361; Zhu, Z.; Seidel, D. *Org. Lett.* ***2016***, *18*, 631.
[2512] See Medeiros, G.A.; da Silva, W.A.; Batagion, G.A.; Ferreira, D.A.C.; de Oliveira, H.C.B.; Eberlin, M.N.; Neto, B.A.D. *Chem. Commun.* ***2014***, *50*, 338.
[2513] Katsuyama, A.; Matsuda, A.; Ichikawa, S. *Org. Lett.* ***2016***, *18*, 2552; Shaabani, A.; Keshipour, S.; Shaabani, S.; Mahyari, M. *Tetrahedron Lett.* ***2012***, *53*, 1641; Milen, M.; Dancsó, A.; Földesi, T.; Volk, B. *Tetrahedron* ***2017***, *73*, 70; Zhao, W.; Huang, L.; Gua, Y.; Wulff, W.D. *Angew. Chem. Int. Ed.* ***2014***, *53*, 3436.
[2514] Constabel, F.; Ugi, I. *Tetrahedron* ***2001***, *57*, 5785.
[2515] El Kaïm, L.; Grimaud, L.; Schiltz, A. *Org. Biomol. Chem.* ***2009***, *7*, 3024.
[2516] Godet, T.; Bovin, Y.; Vincent, G.; Merle, D.; Thozet, A.; Ciufolini, M.A. *Org. Lett.* ***2004***, *6*, 3281.
[2517] Ugi, I. in Gross, E.; Meienhofer, J. *The Peptides*, Vol. 2, Academic Press, NY, ***1980***, pp. 365–381, *Intra-Sci. Chem. Rep.* ***1971***, *5*, 229; Gokel, G.W.; Hoffmann, P.; Kleimann, H.; Klusacek, H.; Lüdke, G.; Marquarding, D.; Ugi, I. in Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, ***1971***, pp. 201–215. See also, Kunz, H.; Pfrengle, W. *J. Am. Chem. Soc.* ***1988***, *110*, 651.
[2518] Okandeji, B.O.; Gordon, J.R.; Sello, J.K. *J. Org. Chem.* ***2008***, *73*, 5595.
[2519] See Ito, Y.; Murakami, M. *Synlett* ***1990***, 245.
[2520] Walborsky, H.M. *J. Org. Chem.* ***1981***, *46*, 5405; ***1982***, *47*, 52. See also, Murakami, H.; Ito, H.; Ito, Y. *J. Org. Chem.* ***1988***, *53*, 4158.

aldehyde R′CHO (**12-32**), an α-keto acid,[2521] a ketone R′COR (**12-32**), an α-hydroxy ketone, or a β-hydroxy ketone. In each case the C═N bond is hydrolyzed to a C═O bond (**16-2**).

OS **VI**, 751.

16.B.v. Nucleophilic Substitution at a Sulfonyl Sulfur Atom[2522]

Nucleophilic substitution at RSO_2X is similar to attack at RCOX. Many of the reactions are essentially the same, though sulfonyl halides are less reactive than halides of carboxylic acids.[2523] The mechanisms[2524] are not identical, because a "tetrahedral" intermediate in this case (**56**) would have five groups on the central atom. This is possible since sulfur can accommodate up to 12 electrons in its valence shell, but it seems more likely that these mechanisms more closely resemble the S_N2 mechanism, with a trigonal-bipyramidal transition state (**57**).



56

57

There are two major experimental results leading to this conclusion.

1. The stereospecificity of this reaction is more difficult to determine than that of nucleophilic substitution at a saturated carbon, where chiral compounds are relatively easy to prepare. Recall (see Sec. 4.C, category 2) that optical activity is possible in a compound of the form RSO_2X if one oxygen is ^{16}O and the other ^{18}O. When a sulfonate ester possessing this type of chirality was converted to a sulfone by reaction with a *Grignard reagent* (**16-98**), inversion of configuration was found.[2525] This is not incompatible with an intermediate such as **56** but it is in good accord with an S_N2-like mechanism with back-side attack.
2. More direct evidence against **56** (though still not conclusive) was found in an experiment involving acidic and basic hydrolysis of aryl arenesulfonates, where it has been shown by the use of ^{18}O that an intermediate like **56** is not reversibly formed, since ester recovered when the reaction was stopped before completion contained no ^{18}O when the hydrolysis was carried out in the presence of labeled water.[2526]

Other evidence favoring the S_N2-like mechanism comes from kinetics and substituent effects.[2527] However, evidence for the mechanism involving **56** is that the rates did not

[2521] See Cooper, A.J.L.; Ginos, J.Z.; Meister, A. *Chem. Rev.* ***1983***, *83*, 321.
[2522] See Ciuffarin, E.; Fava, A. *Prog. Phys. Org. Chem.* ***1968***, *6*, 81.
[2523] See Hirata, R.; Kiyan, N.Z.; Miller, J. *Bull. Soc. Chim. Fr.* ***1988***, 694.
[2524] See Gordon, I.M.; Maskill, H.; Ruasse, M. *Chem. Soc. Rev.* ***1989***, *18*, 123.
[2525] Sabol, M.A.; Andersen, K.K. *J. Am. Chem. Soc.* ***1969***, *91*, 3603. See also, Jones, M.R.; Cram, D.J. *J. Am. Chem. Soc.* ***1974***, *96*, 2183.
[2526] Kaiser, E.T.; Zaborsky, O.R. *J. Am. Chem. Soc.* ***1968***, *90*, 4626.
[2527] Arcoria, A.; Ballistreri, F.P.; Spina, E.; Tomaselli, G.A.; Maccarone, E. *J. Chem. Soc., Perkin Trans. 2* ***1988***, 1793; Gnedin, B.G.; Ivanov, S.N.; Shchukina, M.V. *J. Org. Chem. USSR* ***1988***, *24*, 731.

change much with changes in the leaving group[2528] and the ρ values were large, indicating that a negative charge builds up in the transition state.[2529]

In certain cases in which the substrate carries an α hydrogen, there is strong evidence[2530] that at least some of the reaction takes place by an elimination–addition mechanism (E1cB, similar to the one shown in **16-68**) going through a *sulfene* intermediate ($CH_2{=}SO_2$),[2531] as in the reaction between methanesulfonyl chloride and aniline to give the sulfonamide.

In the special case of nucleophilic substitution at a sulfonic ester RSO_2OR', where R′ is alkyl, R′—O cleavage is much more likely than S—O cleavage because the OSO_2R group is such a good leaving group (Sec. 10.G.iii).[2532] Many of these reactions have been considered previously (e.g., **10-4**, **10-10**) as nucleophilic substitutions at an alkyl carbon atom and not at a sulfur atom. However, when R′ is aryl, then the S—O bond is much more likely to cleave because of the low tendency of aryl substrates to undergo nucleophilic substitution.[2533]

The order of nucleophilicity toward a sulfonyl sulfur has been reported as $OH^- > RNH_2 > N_3 > F^- > AcO^- > Cl^- > H_2O > I^-$.[2534] This order is similar to that at a carbonyl carbon (Sec. 10.G.ii). Both of these substrates can be regarded as relatively hard acids, compared to a saturated carbon which is considerably softer and which has a different order of nucleophilicity (Sec. 10.G.ii).

16-94 Attack by OH: Hydrolysis of Sulfonic Acid Derivatives and Phosphoric Acid Derivatives

$$RSO_2X \xrightarrow[H_2O+H^+]{H_2O \quad or} RSO_2OH \quad (X = Cl, OR', NR'_2)$$

Sulfonyl chlorides as well as esters and amides of sulfonic acids can be hydrolyzed to the corresponding acids. Sulfonyl chlorides can by hydrolyzed with water or with an alcohol in the absence of acid or base. Basic catalysis is also used, though of course the salt is the product obtained. Esters are readily hydrolyzed, many with water or dilute alkali. This is the same reaction as **10-4**, and usually involves R′—O cleavage, except when R′ is aryl. In some cases, retention of configuration has been shown at alkyl R′, indicating S—O cleavage.[2535] Sulfonamides are generally *not* hydrolyzed by alkaline treatment, not even with hot concentrated alkali. However, the alkaline hydrolysis of sulfonate esters has been discussed.[2536] Acids, however, do hydrolyze sulfonamides, but less readily than they do sulfonyl halides or sulfonic esters. Of course, ammonia or the amine appears as the salt. However, sulfonamides can be hydrolyzed with base if the solvent is HMPA.[2537]

OS **I**, 14; **II**, 471; **III**, 262; **IV**, 34; **V**, 406; **VI**, 652, 727. Also see, OS **V**, 673; **VI**, 1016.

[2528] Ciuffarin, E.; Senatore, L.; Isola, M. *J. Chem. Soc., Perkin Trans. 2* ***1972***, 468.
[2529] Ciuffarin, E.; Senatore, L. *Tetrahedron Lett.* ***1974***, 1635.
[2530] Opitz, G. *Angew. Chem. Int. Ed.* ***1967***, *6*, 107. See Pregel, M.J.; Buncel, E. *J. Chem. Soc., Perkin Trans. 2* ***1991***, 307.
[2531] King, J.F. *Acc. Chem. Res.* ***1975***, *8*, 10; Opitz, G. *Angew. Chem. Int. Ed.* ***1967***, *6*, 107; Wallace, T.J. *Q. Rev. Chem. Soc.* ***1966***, *20*, 67.
[2532] See Netscher, T.; Prinzbach, H. *Synthesis* ***1987***, 683.
[2533] See Tagaki, W.; Kurusu, T.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1969***, *42*, 2894.
[2534] Kice, J.L.; Legan, E. *J. Am. Chem. Soc.* ***1973***, *95*, 3912.
[2535] Chang, F.C. *Tetrahedron Lett.* ***1964***, 305.
[2536] Duarte, F.; Geng, T.; Marloie, G.; Al Hussain, A.O.; Williams, N.H.; Kamerlin, S.C.L. *J. Org. Chem.* ***2014***, *79*, 2816.
[2537] Cuvigny, T.; Larchevêque, M. *J. Organomet. Chem.* ***1974***, *64*, 315.

16-95 Attack by OR: Formation of Sulfonic Esters and Phosphoric Esters

$$RSO_2Cl + R'OH \xrightarrow{\text{Base}} RSO_2OR'$$

$$RSO_2NR''_2 + R'OH \xrightarrow{\text{Base}} RSO_2OR' + NHR''_2$$

Sulfonic esters (sulfonates) are most frequently prepared by treatment of the corresponding sulfonyl halides with alcohols in the presence of a base.[2538] This procedure is the most common method for the conversion of alcohols to tosylates, brosylates, and similar sulfonic esters. Both R and R′ may be alkyl or aryl. The base is often pyridine or another amine, which functions as a nucleophilic catalyst.[2539] Primary alcohols react the most rapidly, and it is often possible to sulfonate a primary OH group selectively in a molecule that also contains secondary or tertiary OH groups. The reaction with sulfonamides has been much less frequently used and is limited to *N*,*N*-disubstituted sulfonamides. The nucleophile in this case is actually RO^-. Acidic catalysts are used in this case.[2540] Sulfonic acids have been converted directly to sulfonates by treatment with triethyl or trimethyl orthoformate $HC(OR)_3$, without catalyst or solvent,[2541] and with a trialkyl phosphite, $P(OR)_3$.[2542]

Thiols were oxidized by reaction with $ZnCr_2O_7{\cdot}3H_2O$ to give thiosulfonates.[2543] Asymmetric thiosulfonates were prepared by the Fe-catalyzed reaction of thiols and sodium sulfinates.[2544]

The Cu-catalyzed reaction of dialkyl phosphonates with diaryliodonium salts gave monoarylated alkyl aryl phosphonates.[2545] Benzyl phosphonate esters were prepared by the reaction of benzylic alcohols with $P(OEt)_3$ and ZnI_2.[2546] The Zn-mediated reaction gave dialkyl and diaryl benzylphosphonates. The phosphorylation of alcohols to give the corresponding phosphate monoesters via reaction with trichloroacetonitrile gave the organophosphate as the ammonium salt.[2547] The phosphorylation of alcohols was reported by the reaction with triallyl phosphite and molecular iodine.[2548] The esterification of alkylphosphonic acids to give the phosphonate involved the reaction of primary alcohols, iodine, imidazole and polymer-bound triphenylphosphine.[2549]

The preparation of thiophosphates used diphenylphosphine oxide and sulfonyl chlorides.[2550]

Amines, alcohols, and sulfoximines reacted with phosphites with a molecular iodine catalyst and H_2O_2 as oxidant to give phosphoramidates, phosphorus triesters, and sulfoximine-derived phosphoramidites, respectively.[2551]

OS **I**, 145; **III**, 366; **IV**, 753; **VI**, 56, 482, 587, 652; **VII**, 117; **66**, 1; **68**, 188. Also see, OS **IV**, 529; **VI**, 324, 757; **VII**, 495; **VIII**, 568.

[2538] See Simpson, L.S.; Widlanski, T.S. *J. Am. Chem. Soc.* ***2006***, *128*, 1605.
[2539] Rogne, O. *J. Chem. Soc. B* ***1971***, 1334. See also, Litvinenko, M.; Shatskaya, V.A.; Savelova, V.A. *Dokl. Chem.* ***1982***, *265*, 199.
[2540] Klamann, D.; Fabienke, E. *Chem. Ber.* ***1960***, *93*, 252.
[2541] Padmapriya, A.A.; Just, G.; Lewis, N.G. *Synth. Commun.* ***1985***, *15*, 1057.
[2542] Karaman, R.; Leader, H.; Goldblum, A.; Breuer, E. *Chem. Ind. (London)* ***1987***, 857.
[2543] Sobhani, S.; Aryanejad, S.; Maleki, M.F. *Synlett* ***2011***, *22*, 319.
[2544] Keshari, T.; Kapoorr, R.; Yadav, L.D.S. *Synlett* ***2016***, *27*, 1878.
[2545] Fañanás-Mastral, M.; Feringa, B.L. *J. Am. Chem. Soc.* ***2014***, *136*, 9894.
[2546] See Richardson, R.M.; Barney, R.J.; Wiemer, D.F. *Tetrahedron Lett.* ***2012***, *53*, 6682.
[2547] Lira, L.M.; Vasilev, D.; Pilli, R.A.; Wessjohann, L.A. *Tetrahedron Lett.* ***2013***, *54*, 1690.
[2548] Li, S.Z.; Ahmar, M.; Queneau, Y.; Soulère, L. *Tetrahedron Lett.* ***2015***, *56*, 4694.
[2549] Purohit, A.K.; Pardasani, D.; Tak, V.; Kumar, A.; Jain, R.; Dubey, D.K. *Tetrahedron Lett.* ***2012***, *53*, 3795.
[2550] He, W.; Wang, Z.; Li, X.; Yu, Q.; Wang, Z. *Tetrahedron* ***2016***, *72*, 7594.
[2551] Dhineshkumar, J.; Prabhu, K.R. *Org. Lett.* ***2013***, *15*, 6062.

16-96 Attack by Nitrogen: Formation of Sulfonamides and Phosphoramides

$$RSO_2Cl + NH_3 \longrightarrow RSO_2NH_2$$

The reaction of amines with a sulfonation reagent leads to the sulfonamide,[2552] and the functionalization of sulfonamides has been reviewed.[2553] The treatment of sulfonyl chlorides with ammonia or amines is the usual way of preparing sulfonamides.[2554] Nonracemic sulfonamides have been prepared.[2555] Primary amines give *N*-alkyl sulfonamides, and secondary amines give *N*,*N*-dialkyl sulfonamides. The reaction is the basis of the *Hinsberg test* for distinguishing between primary, secondary, and tertiary amines. *N*-Alkyl sulfonamides, having an acidic hydrogen, are soluble in alkali, while *N*,*N*-dialkyl sulfonamides are not. Since tertiary amines are usually recovered unchanged, primary, secondary, and tertiary amines can be told apart. However, the test is limited for at least two reasons:[2556] (i) many *N*-alkyl sulfonamides in which the alkyl group has six or more carbons are insoluble in alkali, despite their acidic hydrogen,[2557] so that a primary amine may appear to be a secondary amine, and (ii) if the reaction conditions are not carefully controlled, tertiary amines may not be recovered unchanged.[2542] A primary or a secondary amine can be protected by reaction with phenacylsulfonyl chloride ($PhCOCH_2SO_2Cl$) to give a sulfonamide ($RNHSO_2CH_2COPh$ or $R_2NSO_2CH_2COPh$).[2558] The protecting group can be removed when desired with zinc and acetic acid.

The iodine-catalyzed reaction of amines with arylsulfonyl hydrazides in the presence of TBHP gave sulfonamides.[2559] Sulfonamides were prepared by the electrochemical oxidative amination of sodium sulfinates with amines using a substoichiometric amount of NH_4I.[2560] The reaction between *N*-tosylhydrazone, amines, and DABSO [DABCO-bis(sulfur dioxide)] as a SO_2 source gave alkyl sulfonamides.[2561] Arylboronic acids reacted with F_3SNEt_2 to give the sulfonamide, which was oxidized.[2562] The reaction of aryl sulfonyl chlorides and Ph_3SiNH_2 gave the primary sulfonamide, and reaction with $PhNHSiMe_3$ gave the *N*-aryl sulfonamide.[2563] The ultrasonic irradiation of methyl sulfinates and primary or secondary amines (neat) gave sulfinamides, and subsequent mcpba oxidation gave the corresponding sulfonamide.[2564] The reaction of $PhSO_2Na$, benzylamine, Bu_4NBr, and mcpba gave *N*-benzyl benzenesulfonamide.[2565]

An alternative synthesis of sulfonamides involved the reaction of allyltributyltin with PhI=NTs in the presence of copper (II) triflate.[2566] The Rh- and Ag-catalyzed reaction

[2552] See Yang, F.-L.; Tian, S.-K. *Tetrahedron Lett.* ***2017***, *58*, 487.
[2553] Chen, Y. *Synthesis* ***2016***, *48*, 2483.
[2554] See Kamal, A.; Reddy, J.S.; Bharathi, E.V.; Dastagiri, D. *Tetrahedron Lett.* ***2008***, *49*, 348.
[2555] Kamińska, K.; Wojaczyńska, E.; Skarżewski, J.; Kochel, A.; Wojaczyński, J. *Tetrahedron: Asymmetry* ***2017***, *28*, 561.
[2556] See Gambill, C.R.; Roberts, T.D.; Shechter, H. *J. Chem. Educ.* ***1972***, *49*, 287.
[2557] Fanta, P.E.; Wang, C.S. *J. Chem. Educ.* ***1964***, *41*, 280.
[2558] Hendrickson, J.B.; Bergeron, R. *Tetrahedron Lett.* ***1970***, 345.
[2559] Yotphan, S.; Sumunnee, L.; Beukeaw, D.; Buathongjan, C.; Retrakul, V. *Org. Biomol. Chem.* ***2016***, *14*, 590.
[2560] Jiang, Y.-y.; Wang, Q.-Q.; Liang, S.; Hu, L.-M.; Little, R.D.; Zeng, C.-C. *J. Org. Chem.* ***2016***, *81*, 4713.
[2561] Tsai, A.S.; Curto, J.M.; Rocke, B.N.; Dechert-Schmitt, A.-M.R.; Ingle, K.; Mascitti, V. *Org. Lett.* ***2016***, *18*, 508.
[2562] Wang, Q.; Tang, X.-Y.; Shi, M. *Angew. Chem. Int. Ed.* ***2016***, *55*, 10811.
[2563] Naredla, R.R.; Klumpp, D.A. *Tetrahedron Lett.* ***2013***, *54*, 5945.
[2564] Ruano, J.L.G.; Parra, A.; Marzo, L.; Yuste, F.; Mastranzo, V.M. *Tetrahedron* ***2011***, *67*, 2905.
[2565] Wu, S.; Zhang, Y.; Zhu, M.; Yan, J. *Synlett* ***2016***, *27*, 2699.
[2566] Kim, D.Y.; Kim, H.S.; Choi, Y.J.; Mang, J.Y.; Lee, K. *Synth. Commun.* ***2001***, *31*, 2463.

of 8-methylquinolines with sulfonylazides gave quinolin-8-ylmethane sulfonamide derivatives.[2567] The Fe-catalyzed reaction of arylnitro compounds with RSO_2Na, $NaHSO_3$, and DMDACH (*trans-N,N′*-dimethylcyclohexane-1,2-diamine) in DMSO gave the corresponding sulfonamide.[2568] Sulfonamides were prepared by the Cu-catalyzed coupling of sodium sulfinates and amines with 1 atm O_2 or DMSO as the oxidant.[2569] Aryl and heteroaryl sulfonamides were prepared by the reaction of 2,4,6-trichlorophenyl chlorosulfate with 2-pyridylzinc reagents and the resulting 2,4,6-trichlorophenyl pyridine-2-sulfonates reacted with amines.[2570]

OS **IV**, 34, 943; **V**, 39, 179, 1055; **VI**, 78, 652; **VII**, 501; **VIII**, 104. See also, OS **VI**, 788.

16-97 Attack by Halogen: Formation of Sulfonyl Halides and Phosphoryl Halides

$$RSO_2OH + SOCl_2 \longrightarrow RSO_2Cl$$

This reaction, parallel with **16-78**, is the standard method for the preparation of sulfonyl halides. Both PCl_3 and $SOCl_2$ have been used, and sulfonic acid salts can also serve as substrates. Cyanuric acid (2,4,6-trichloro[1,3,5]triazene) serves as a chlorinating agent.[2571] Sulfonyl bromides and iodides have been prepared from sulfonyl hydrazides ($ArSO_2NHNH_2$, themselves prepared by **16-96**) by treatment with bromine or iodine.[2572] Sulfonyl fluorides are generally prepared from the chlorides, by halogen exchange.[2573] Alkanesulfonyl chlorides were prepared by the reaction of *S*-alkyl isothiourea salts with aqueous bleach and 2 M HCl.[2574]

OS **I**, 84; **IV**, 571, 693, 846, 937; **V**, 196. See also, OS **VII**, 495.

16-98 Attack by Carbon: Preparation of Sulfones

$$ArSO_2Cl + Ar'MgX \longrightarrow ArSO_2Ar'$$

There are many methods for the synthesis of sulfones.[2575] *Grignard reagents* convert aromatic sulfonyl chlorides or aromatic sulfonates to sulfones. Organolithium reagents react with sulfonyl fluorides at −78 °C to give the corresponding sulfone.[2576] Aromatic sulfonates have been converted to sulfones with organolithium compounds,[2577] with aryltin compounds,[2578] with an Fe catalyst,[2579] and with alkyl halides and Zn metal.[2580] Vinylic and allylic sulfones have been prepared by treatment of sulfonyl chlorides with a vinylic

[2567] Wang, N.; Li, R.; Li, L.; Xu, S.; Song, H.; Wang, B. *J. Org. Chem.* ***2014***, *79*, 5379.
[2568] Zhang, W.; Xie, J.; Rao, B.; Luo, M. *J. Org. Chem.* ***2015***, *80*, 3504.
[2569] Tang, X.; Huang, L.; Qi, C.; Wu, X.; Wu, W.; Jiang, H. *Chem. Commun.* ***2013***, *49*, 6102.
[2570] Colombe, J.R.; DeBergh, J.R.; Buchwald, S.L. *Org. Lett.* ***2015***, *17*, 3170.
[2571] Blotny, G. *Tetrahedron Lett.* ***2003***, *44*, 1499.
[2572] Poshkus, A.C.; Herweh, J.E.; Magnotta, F.A. *J. Org. Chem.* ***1963***, *28*, 2766; Litvinenko, L.M.; Dadali, V.A.; Savelova, V.A.; Krichevtsova, T.I. *J. Gen. Chem. USSR* ***1964***, *34*, 3780.
[2573] See Bianchi, T.A.; Cate, L.A. *J. Org. Chem.* ***1977***, *42*, 2031, and references cited therein.
[2574] Yang, Z.; Zhou, B.; Xu, J. *Synthesis* ***2014***, *46*, 225.
[2575] Liu, N.-W.; Liang, S.; Manolikakes, G. *Synthesis* ***2016***, *48*, 1939.
[2576] Frye, L.L.; Sullivan, E.L.; Cusack, K.P.; Funaro, J.M. *J. Org. Chem.* ***1992***, *57*, 697.
[2577] Baarschers, W.H. *Can. J. Chem.* ***1976***, *54*, 3056.
[2578] Neumann, W.P.; Wicenec, C. *Chem. Ber.* ***1993***, *126*, 763.
[2579] Volla, C.M.R.; Vogel, P. *Angew. Chem. Int. Ed.* ***2008***, *47*, 1305.
[2580] Sun, X.; Wang, L.; Zhang, Y. *Synth. Commun.* ***1998***, *28*, 1785.

or allylic stannane and a Pd catalyst.[2581] Alkynyl sulfones can be prepared by treatment of sulfonyl chlorides with trimethylsilylalkynes with an $AlCl_3$ catalyst.[2582] Note that trifluoromethylsulfones were converted to methyl sulfones by reaction with methylmagnesium bromide.[2583]

The preparation of (*E*)-alkenyl sulfones by the Cu-catalyzed aerobic decarboxylative sulfonylation of alkenyl carboxylic acids with sodium sulfinates was reported.[2584] Lithium, Mg, and Zn aryl compounds reacted with SO_2 and then with diaryliodonium salts to give diaryl sulfones.[2585] The TBHP/TBAI-mediated reaction of propargyl alcohols and sulfonyl hydrazides in the presence of HOAc gave allenyl sulfones.[2586] The Cu-catalyzed reaction of 2-alkynylaryldiazonium tetrafluoroborate with sulfur dioxide in the presence of morpholin-4-amine, gave benzo[*b*]thiophene 1,1-dioxides.[2587] The reaction of aryldiazonium tetrafluoroborates, sulfur dioxide, and aryliodonium tetrafluoroborates in the presence of morpholin-4-amine and $NaHSO_3$ gave sulfones.[2588] The Pd-catalyzed coupling of arylboronic acids and alkynyl halides gave alkyl aryl sulfones.[2589] Sodium *p*-toluenesulfinate reacted with diaryliodium salts to give the diaryl sulfone.[2590]

Grignard reagents or organolithium reagents reacted with the SO_2-surrogate DABSO to give a metal sulfinate that reacted with alkyl, allyl, and benzyl halides, epoxides, and (hetero)aryliodoniums to give the sulfone.[2591] Organozinc reagents also reacted with DABSO and alkyl halides to give sulfones.[2592] Arylsulfonyl alkynes were prepared by the reaction of the palladium-catalyzed reaction of aryl Grignard reagents and aryl iodides in the presence of DABSO, followed by reaction with ethynyl benziodoxolone (EBX) reagents.[2593]

Arylboronic acids (**12-27**) react with sulfonyl chlorides in the presence of $PdCl_2$ to give the corresponding sulfone.[2594] Arylboronic acids also react with sulfinate anions (RSO_2Na) in the presence of $Cu(OAc)_2$ to give the sulfone.[2595] Aryl boronic acids reacted with the sodium salt of sulfinic acids using a Cu/Cu(II) catalyst to give diaryl sulfones.[2596]

OS **VIII**, 281.

[2581] Labadie, S.S. *J. Org. Chem.* ***1989***, *54*, 2496.
[2582] See Waykole, L.; Paquette, L.A. *Org. Synth.* ***67***, 149.
[2583] Steensma, R.W.; Galabi, S.; Tagat, J.R.; McCombie, S.W. *Tetrahedron Lett.* ***2001***, *42*, 2281.
[2584] Jiang, Q.; Xu, B.; Jia, J.; Zhao, A.; Zhao, Y.-R.; Li, Y.-Y.; He, N.-N.; Guo, C.-C. *J. Org. Chem.* ***2014***, *79*, 7372.
[2585] See Margraf, N.; Manolikakes, G. *J. Org. Chem.* ***2015***, *80*, 2582.
[2586] Yang, Z.; Hao,W.-J.; Wang, S.-L.; Zhang, J.-P.; Jiang, B.; Li, G.; Tu, S.-J. *J. Org. Chem.* ***2015***, *80*, 9224.
[2587] Luo, Y.; Pan, X.; Chen, C.; Yao, L.; Wu, J. *Chem. Commun.* ***2015***, *51*, 180.
[2588] Liu, X.; Li, W.; Zheng, D.; Fan, X.; Wu, J. *Tetrahedron* ***2015***, *71*, 3359.
[2589] Shavnya, A.; Hesp, K.D.; Mascitti, V.; Smith, A.C. *Angew. Chem. Int. Ed.* ***2015***, *54*, 13571.
[2590] Kumar, D.; Arun, V.; Pilania, M.; Shekar, K.P.C. *Synlett* ***2013***, *24*, 831.
[2591] Deeming, A.S.; Russell, C.J.; Hennessy, A.J.; Willis, M.C. *Org. Lett.* ***2014***, *16*, 150.
[2592] Rocke, B.N.; Bahnck, K.B.; Herr, M.; Lavergne, S.; Mascitti, V.; Perreault, C.; Polivkova, J.; Shavnya, A. *Org. Lett.* ***2014***, *16*, 154.
[2593] Chen, C.C.; Waser, J. *Org. Lett.* ***2015***, *17*, 736.
[2594] Bandgar, B.P.; Bettigeri, S.V.; Phopase, J. *Org. Lett.* ***2004***, *6*, 2105. See Zhu H.; Shen, Y.; Deng, Q.; Chen, J.; Tu, T. *Chem. Commun.* ***2017***, *54*, 12473.
[2595] Beaulieu, C.; Guay, D.; Wang, Z.; Evans, D.A. *Tetrahedron Lett.* ***2004***, *45*, 3233.
[2596] Nandi, G.C. *Synth. Commun.* ***2017***, *47*, 319.

CHAPTER 17

Elimination Reactions

A general feature of elimination rections is that the atom bearing a leaving group is the α atom and the adjacent atom is the β atom. A so-called β-*elimination* reaction occurs when two groups are lost from adjacent atoms so that a new double[1] (or triple) bond is formed.[2] In an α-elimination both groups are lost from the same atom to give a carbene (or a nitrene). In a γ-elimination, a three-membered ring is formed.

Some of these processes were discussed in Chapter 10. Another type of elimination involves the expulsion of a fragment from within a chain or ring (X—Y—Z → X—Z + Y). Such reactions are called *extrusion reactions*. This chapter discusses β-elimination and extrusion reactions (Sec. 2.F.vi), but β-elimination in which both X and Z are hydrogen atoms are oxidation reactions and are treated in Chapter 19.

17.A. MECHANISMS AND ORIENTATION

There are two β-elimination reactions that are categorized here. One type takes place largely in solution, while the other (pyrolytic elimination) takes place mostly in the gas phase. In the reactions, one group leaves with its electrons and the other without (i.e., it is pulled off), with the latter most often being hydrogen. In these cases, the former group is the *leaving group* or *nucleofuge*. Substitution reactions can sometimes compete with elimination reactions.[3] For pyrolytic eliminations, there are two principal mechanisms, one pericyclic and the other a free-radical pathway. A few photochemical eliminations are also known (the most important is Norrish type II cleavage of ketones, Sec. 7.A.vii), but these are not generally of synthetic importance[4] and will not be discussed further. In most β-eliminations the new bonds are C=C or C≡C; the discussion of mechanisms is largely confined to these cases.[5]

[1] See Williams, J.M.J. *Preparation of Alkenes, A Practical Approach*, Oxford University Press, Oxford, ***1996***.

[2] Graulich, N.; Hopf, H.; Schreiner, P.R. *Chem. Asian J.* ***2011***, *6*, 3180.

[3] Conner, K.M.; Gronert, S. *J. Org. Chem.* ***2013***, *78*, 8606.

[4] See Neckers, D.C.; Kellogg, R.M.; Prins, W.L.; Schoustra, B. *J. Org. Chem.* ***1971***, *36*, 1838.

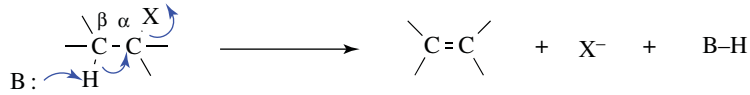
[5] Saunders Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***. For reviews, see Gandler, J.R. in Patai, S. *The Chemistry of Double-bonded Functional Groups*, Supplement A, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 733–797; Cockerill, A.F.; Harrison, R.G. in Patai, S. *The Chemistry of Functional Groups*, Supplement A, pt. 1, Wiley, NY, ***1977***, pp. 153–221; Cockerill, A.F. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 163–372; Saunders Jr., W.H. *Acc. Chem. Res.* ***1976***, *9*, 19; Bordwell, F.G. *Acc. Chem. Res.* ***1972***, *5*, 374; Fry, A. *Chem. Soc. Rev.* ***1972***, *1*, 163; in Patai, S. *The Chemistry of*

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

Mechanisms in solution (E2, E1)[6] and E1cB are discussed first. While standard methods are used to examine elimination reactions, new techniques such as the velocity map ion imaging technique have been used to study ultrafast elimination reactions.[7]

17.A.i. The E2 Mechanism

In the E2 mechanism (elimination, bimolecular), the proton on the β carbon is pulled off by a base, leading to near-simultaneous expulsion of the leaving group (known as a nucleofuge):



The mechanism takes place in one step and is kinetically is second order: first order in substrate and first order in base. An *ab initio* study has produced a model for the E2 transition state geometry.[8] The IUPAC designation is $A_{xH}D_HD_N$ or, more generally (to include cases where the electrofuge is not hydrogen), $A_nD_ED_N$. This type of elimination often competes with the S_N2 mechanism (Sec. 10.A.i).[9] With respect to the substrate, the difference between the two pathways is whether the species with the unshared pair attacks the carbon (and thus acts as a nucleophile) or attacks the hydrogen (and thus acts as a base).

Evidence for the existence of the E2 mechanism includes: (i) the reaction displays the proper second-order kinetics; and (ii) when the hydrogen is replaced by deuterium in second-order eliminations, there is an isotope effect of from 3 to 8, consistent with breaking of this bond in the rate-determining step.[10] However, neither of these results alone could prove an E2 mechanism, since both are compatible with other mechanisms also (e.g., see E1cB, Sec. 17.A.iii). The most compelling evidence for the E2 mechanism is found in stereochemical studies.[11]

As will be illustrated in the examples, the E2 mechanism is stereospecific: the five atoms involved (including the base) in the transition state must be in one plane. There are two ways for this to happen. The H and X may be *trans* to one another (**A**) with a dihedral angle of 180°, or they may be *cis* (**B**) with a dihedral angle of 0°.[12]

Alkenes, Vol. 1, Wiley, NY, ***1964***, see the articles by Saunders Jr., W.H. pp. 149–201 (eliminations in solution) and by Maccoll, A. pp. 203–240 (pyrolytic eliminations); Köbrich, G. *Angew. Chem. Int. Ed.* ***1965***, *4*, 49 (pp. 59–63, for the formation of triple bonds).

[6] Thibblin, A. *Chem. Soc. Rev.* ***1993***, *22*, 427.

[7] Roeterdink, W.G.; Rijs, A.M.; Janssen, M.H.M. *J. Am. Chem. Soc.* ***2006***, *128*, 576.

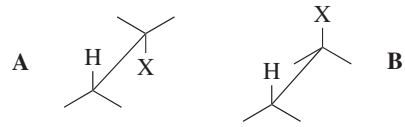
[8] Schrøder, S.; Jensen, F. *J. Org. Chem.* ***1997***, *62*, 253. See Wu, W.; Shaik, S.; Saunders, Jr., W.H. *J. Org. Chem.* ***2010***, *75*, 3722.

[9] For a review, see O'Reilly, M.E.; Dutta, S.; Veige, A.S. *Chem. Rev.* ***2016***, *116*, 8105; Rablen, P.R.; McLarney, B.D.; Karlow, B.J.; Schneider, J.E. *J. Org. Chem.* ***2014***, *79*, 867.

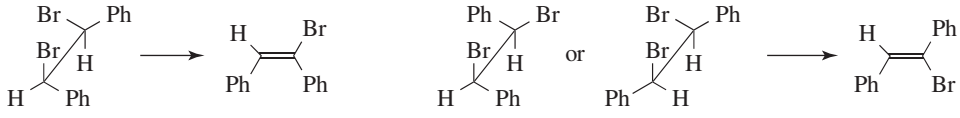
[10] See Shiner Jr., V.J.; Smith, M.L. *J. Am. Chem. Soc.* ***1961***, *83*, 593. For a review of isotope effects, see Fry, A. *Chem. Soc. Rev.* ***1972***, *1*, 163.

[11] Bartsch, R.A.; Závada, J. *Chem. Rev.* ***1980***, *80*, 453; Sicher, J. *Angew. Chem. Int. Ed.* ***1972***, *11*, 200; Saunders Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 105–163; Cockerill, A.F. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 217–235; More O'Ferrall, R.A. in Patai, S. *The Chemistry of the Carbon-Halogen Bond*, pt. 2, Wiley, NY, ***1973***, pp. 630–640.

[12] DePuy, C.H.; Morris, G.F.; Smith, J.S.; Smat, R.J. *J. Am. Chem. Soc.* ***1965***, *87*, 2421.

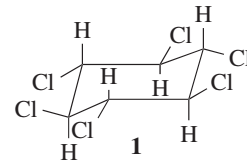


Conformation **A** is called *anti-periplanar*, and this type of elimination, in which H and X depart in opposite directions, is called *anti elimination*. Conformation **B** is *syn-periplanar*, and this type of elimination, with H and X leaving in the same direction, is called *syn elimination*. Many examples of both kinds have been discovered. If the reaction with base to remove the β-hydrogen atom is intermolecular, *anti* elimination is greatly favored over *syn* elimination, largely because the *anti* transition state molecule requires less energy and the molecule is expected to have a greater percentage of this conformation. If the base is "tethered" to the molecule such that approach to the β-hydrogen atom must be intramolecular, the higher energy eclipsed transition state **B** is required for reaction and much less of this conformation is expected. Solvent effects play an important role in the conformational preference. Several experimental details confirm these hypotheses.



1. The elimination is stereospecific. Elimination of HBr from *meso*-1,2-dibromo-1,2-diphenylethane gave *cis*-2-bromostilbene, while the (+) or (−) isomer gave the *trans* isomer. This stereospecific result was obtained in 1904,[13] and demonstrated that in this case elimination is *anti*. Many similar examples have been discovered since. *Anti* elimination requires that an *erythro dl* pair (or either isomer) give the *cis* alkene, and the *threo dl* pair (or either isomer) give the *trans* isomer, which has been confirmed many times. *Anti* elimination has also been demonstrated in cases where the electrofuge is not hydrogen. In the reaction of 2,3-dibromobutane with iodide ion, the two bromines are removed (**17-20**).[14]
2. In open-chain compounds, rotation about C—C bonds usually leads to a conformation in which H and X are anti-periplanar. However, in cyclic systems this is not always the case. There are nine stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane: seven *meso* forms and a *dl* pair (Sec. 4.G). Four of the *meso* compounds and the *dl* pair were treated with base to initiate elimination. Only one of these (**1**) has no Cl that is *trans* to an H. Of the other isomers, the fastest elimination rate was about three times as fast as the slowest, but the rate for **1** was 7000 times slower than that of the slowest of the other isomers.[15] This result demonstrates that *anti* elimination is greatly favored over *syn* elimination, although the latter must be taking place on **1**, but very slowly, to be sure.

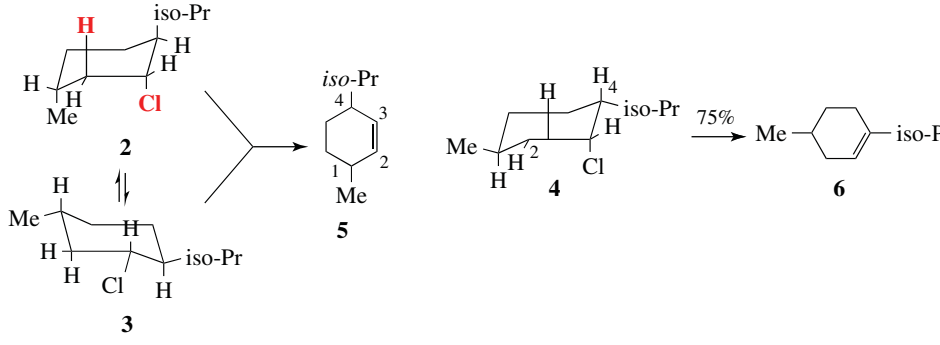
[13] Pfeiffer, P. *Z. Phys. Chem.* ***1904***, *48*, 40.
[14] Winstein, S.; Pressman, D.; Young, W.G. *J. Am. Chem. Soc.* ***1939***, *61*, 1645.
[15] Cristol, S.J.; Hause, N.L.; Meek, J.S. *J. Am. Chem. Soc.* ***1951***, *73*, 674.



1

3. The preceding result shows that elimination of HCl in a six-membered ring proceeds best when the H and X are *trans* and diaxial to each other. Adjacent *trans* groups on a six-membered ring can be diaxial or diequatorial (Sec. 4.O.ii) and the molecule will exist in both conformations. Barring special circumstances, the conformation with the most groups in the axial position will have a higher energy, and that with the most equatorial groups will have the lower energy. For an E2-type reaction, the β-hydrogen that is removed by the base must be anti-periplanar to the leaving group, which requires that the leaving group and the β-hydrogen atom be *trans* and diaxial, if this is the conformation of higher energy.

   The results with menthyl and neomenthyl chlorides are interpretable on the basis of a *trans* diaxial relationship of the β-hydrogen and the leaving group. Menthyl chloride has two chair conformations, **2** and **3**. Compound **3**, in which the three substituents are all equatorial, is the more stable and less reactive. The more stable chair conformation of neomenthyl chloride is **4**, in which the chlorine is axial, and there are axial hydrogen atoms on both C-2 and C-4. The results are: neomenthyl chloride gives rapid E2 elimination and the alkene produced is predominantly **6** (**6**/**5** ratio is ~3:1) in accord with *Zaitsev's rule* (see **12-2**, Sec. 17.B). Since an axial hydrogen is available on both sides, this factor does not control the direction of elimination and Zaitsev's rule is free to operate. In other words, the more substituted, and more stable, alkene (**5**) is the product. For menthyl chloride, elimination is much slower and the product is entirely the anti-Zaitsev alkene **5**. It is slow because the unfavorable conformation **2** must be achieved before elimination can take place. There an axial hydrogen only on this side so the product is **5**.[16]



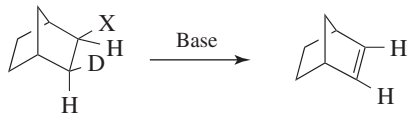
4. *Anti* elimination also occurs in the formation of triple bonds, as shown by elimination from *cis*- and *trans*-$HO_2C{-}CH{=}C(Cl)CO_2H$. In this case, the product in both

[16] Hughes, E.D.; Ingold, C.K.; Rose, J.B. *J. Chem. Soc.* ***1953***, 3839.

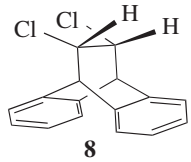
cases is $HO_2CC{\equiv}CCO_2H$, but the *trans* isomer reacts ~50 times faster than the *cis* compound.[17]

Some examples of *syn* elimination have been found in molecules where H and X could not achieve an anti-periplanar conformation.

1. The deuterated norbornyl bromide (**7**, X = Br) gave 94% of the product containing no deuterium.[18] Similar results were obtained with other leaving groups and with bicyclo[2.2.2] compounds.[19]



7



8

   In these cases the *exo* X group cannot achieve a dihedral angle of 180° with the *endo* β hydrogen because of the rigid structure of the molecule. The dihedral angle here is ~120°. *Syn* elimination with a dihedral angle of ~0° is clearly preferred to *anti* elimination where the angle is restricted to ~120°.
2. Molecule **8** is a particularly graphic example of the need for a planar transition state. In **8**, each Cl has an adjacent hydrogen *trans* to it, and if planarity of leaving groups were not required, *anti* elimination could easily take place. However, the crowding of the rest of the molecule forces the dihedral angle to be ~120°, and elimination of HCl from **8** is much slower than from corresponding nonbridged compounds.[20] Note that *syn* elimination from **8** is even less likely than *anti* elimination. *Syn* elimination can take place from the *trans* isomer of **8** (dihedral angle ~0°); this isomer reacted about eight times faster than **8**.[20]

The examples given so far illustrate two points. (i) *Anti* elimination *requires* a dihedral angle of 180°. When this angle cannot be achieved, *anti* elimination is greatly slowed or prevented entirely. (ii) For the simple systems so far discussed *syn* elimination is not found to any significant extent unless *anti* elimination is greatly diminished by failure to achieve the 180° angle.

The concept of vinylogy was introduced in Sec. 6.B and in **10-68**, category 4. Using this concept, a 1,2-elimination can be extended to give a 1,*x*-elimination when π bonds are incorporated between the carbon bearing the acidic proton and the leaving group: e.g., X–C–C=C–C, X–C–C=C–C=C–C, or X–C–C≡C–C.[21]

As noted in Sec. 4.Q.ii, six-membered rings are the only ones among rings of 4–13 members in which strain-free anti-periplanar conformations can be achieved. It is not surprising,

[17] Michael, A. *J. Prakt. Chem.* ***1895***, *52*, 308. See also, Marchese, G.; Naso, F.; Modena, G. *J. Chem. Soc. B* ***1968***, 958.
[18] Kwart, H.; Takeshita, T.; Nyce, J.L. *J. Am. Chem. Soc.* ***1964***, *86*, 2606.
[19] See Bartsch, R.A.; Lee, J.G. *J. Org. Chem.* ***1991***, *56*, 212, 2579.
[20] Cristol, S.J.; Hause, N.L. *J. Am. Chem. Soc.* ***1952***, *74*, 2193.
[21] See Werner, C.; Hopf, H.; Dix, I.; Bubenitschek, P.; Jone, P.G. *Chem. Eur. J.* ***2007***, *13*, 9462.

therefore, that *syn* elimination is least common in six-membered rings. Cycloalkyltrimethylammonium hydroxides were subjected to elimination (**17-6**) and the following percentages of *syn* elimination were found with each ring size: four-membered, 90%; five-membered, 46%; six-membered, 4%; seven-membered, 31–37%.[22] Note that the NMe_3^+ group has a greater tendency to *syn* elimination than do other common leaving groups, such as OTs, Cl, and Br.

Other examples of *syn* elimination have been found in medium-ring compounds, where both *cis* and *trans* alkenes are possible (Sec. 4.K.i). The elimination reaction of 1,1,4,4-tetramethyl-7-cyclodecyltrimethylammonium chloride,[23] for example, gave mostly *trans*- but also some *cis*-tetramethylcyclodecenes as products. Note that *trans*-cyclodecenes, although stable, are less stable than the *cis* isomers. In order to determine the stereochemistry of the reaction, the elimination was repeated, this time using deuterated substrates. When deuterated in the *trans* position, there was a substantial isotope effect in the formation of *both cis* and *trans* alkenes, but when deuterated in the *cis* position, there was *no* isotope effect in the formation of either alkene. Since an isotope effect is expected for an E2 mechanism,[24] these results indicated that *only* the *trans* hydrogen (H_t) was lost, whether the product was the *cis* or the *trans* isomer.[25] In turn, this result means that *the cis isomer must have been formed by anti elimination and the trans isomer by syn elimination*. *Anti* elimination could take place from approximately the *anti* conformation, but for *syn* elimination the molecule must twist into a conformation in which the C—H and C—NMe_3^+ bonds are syn-periplanar. Other types of evidence have also demonstrated this remarkable result, called the *syn*/*anti* dichotomy.[26] The fact that *syn* elimination in this case predominates over *anti* (as indicated by the formation of *trans* isomer in greater amounts than *cis*) has been explained by conformational factors.[27] The *syn*/*anti* dichotomy has also been found in other medium-ring systems (8- to 12-membered rings),[28] although the effect is greatest for 10-membered rings. With leaving groups,[29] the extent of this behavior decreases in the order $^+NMe_3 > OTs > Br > Cl$, which parallels steric requirements. When the leaving group is uncharged, *syn* elimination is favored by strong bases and by weakly ionizing solvents.[30]

Syn elimination and the *syn*/*anti* dichotomy have also been found in open-chain systems, although to a lesser extent than in medium-ring compounds. For example, in the conversion of 3-hexyl-4-*d*-trimethylammonium ion to hex-3-ene with potassium *sec*-butoxide, ~67% of the reaction followed the *syn*/*anti* dichotomy.[31] In general *syn* elimination in open-chain systems is only important in cases where certain types of steric effect are present. One such type is compounds in which substituents are found on both the β′ and the γ carbons

[22] Cooke Jr., M.P.; Coke, J.L. *J. Am. Chem. Soc.* ***1968***, *90*, 5556. See also, Coke, J.L.; Smith, G.D.; Britton Jr., G.H. *J. Am. Chem. Soc.* ***1975***, *97*, 4323.

[23] Závada, J.; Svoboda, M.; Sicher, J. *Collect. Czech. Chem. Commun.* ***1968***, *33*, 4027.

[24] Other possible mechanisms, such as E1cB (Sec. 17.A.iii) or α′,β elimination (**17-8**), were ruled out in all these cases by other evidence.

[25] This conclusion has been challenged by Coke, J.L. *Sel. Org. Transform* ***1972***, *2*, 269.

[26] For a review, see Bartsch, R.A.; Závada, J. *Chem. Rev.* ***1980***, *80*, 453.

[27] Bartsch, R.A.; Závada, J. *Chem. Rev.* ***1980***, *80*, 453; Sicher, J. *Angew. Chem. Int. Ed.* ***1972***, *11*, 200.

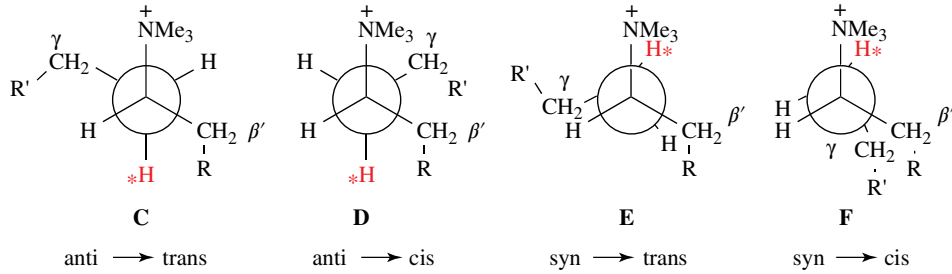
[28] See Coke, J.L.; Mourning, M.C. *J. Am. Chem. Soc.* ***1968***, *90*, 5561.

[29] See Sicher, J.; Jan, G.; Schlosser, M. *Angew. Chem. Int. Ed.* ***1971***, *10*, 926; Závada, J.; Pánková, M. *Collect. Czech. Chem. Commun.* ***1980***, *45*, 2171 and references cited therein.

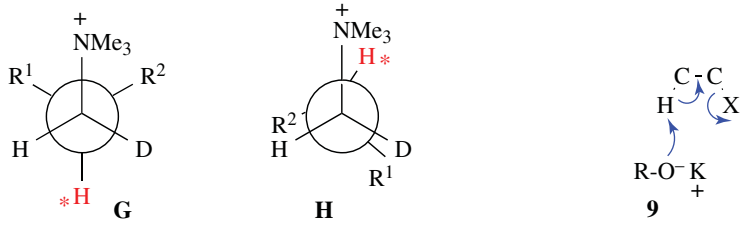
[30] See Sicher, J.; Závada, J. *Collect. Czech. Chem. Commun.* ***1968***, *33*, 1278.

[31] Bailey, D.S.; Saunders Jr., W.H. *J. Am. Chem. Soc.* ***1970***, *92*, 6904. See Pánková, M.; Kocián, O.; Krupicka, J.; Závada, J. *Collect. Czech. Chem. Commun.* ***1983***, *48*, 2944.

(the unprimed letter refers to the branch in which the elimination takes place). The factors that cause these results are not completely understood, but the following conformational effects have been proposed as a partial explanation.[32] The two anti-periplanar and two syn-periplanar conformations are, for a quaternary ammonium salt:



In order for an E2 mechanism to take place, a base must approach the proton marked*, which is anti-periplanar to the ammonium leaving group (**C**). In **C**, removal of this proton by *anti* elimination leads to the *trans* product. In **D**, *anti* elimination would give more *cis* product than *trans*. When *syn* elimination begins to appear, it seems clear that **E**, which has fewer eclipsing interactions than **F**, should be favored and *syn* elimination should generally give the *trans* isomer. Predominant *syn* elimination has also been found in compounds of the form $R^1R^2CHCHDNMe_3^+$, where R^1 and R^2 are both bulky.[33] In this case, the conformation leading to *syn* elimination (**H**) is also less strained than **G**, which gives *anti* elimination. The **G** compound has three bulky groups (including NMe_3^+) in the *gauche* position to each other.



It was mentioned above that weakly ionizing solvents promote *syn* elimination when the leaving group is uncharged. This is probably caused by ion pairing, which is greatest in non-polar solvents.[34] Ion pairing can cause *syn* elimination with an uncharged leaving group by means of the transition state shown in **9**. This effect was graphically illustrated by elimination from 1,1,4,4-tetramethyl-7-cyclodecyl bromide.[35] The ratio of *syn* to *anti* elimination when this compound was treated with *t*-BuOK in the nonpolar benzene was 55.0. When the crown ether dicyclohexano-18-crown-6 was added (this compound selectively removes K^+ from the *t*-BuO^- K^+ ion pair and thus leaves *t*-BuO^- as a free ion), the *syn*/*anti* ratio decreased to 0.12. Large decreases in the *syn*/*anti* ratio on addition of the crown ether were

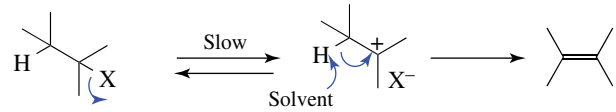
[32] Chiao, W.; Saunders Jr., W.H. *J. Am. Chem. Soc.* ***1977***, *99*, 6699.
[33] Dohner, B.R.; Saunders Jr., W.H. *J. Am. Chem. Soc.* ***1986***, *108*, 245.
[34] Bartsch, R.A.; Závada, J. *Chem. Rev.* ***1980***, *80*, 453; Bartsch, R.A. *Acc. Chem. Res.* ***1975***, *8*, 239.
[35] Svoboda, M.; Hapala, J.; Závada, J. *Tetrahedron Lett.* ***1972***, 265.

also found with the corresponding tosylate and with other nonpolar solvents.[36] However, with positively charged leaving groups the effect is reversed. Here, ion pairing *increases* the amount of *anti* elimination.[37] In this case, a relatively free base (e.g., PhO^-) can be attracted to the polar leaving group, putting it in a favorable position for attack on the *syn* β hydrogen, while ion pairing would reduce this attraction.

It can be concluded that *anti* elimination is generally favored in the E2 mechanism, but that steric (inability to form the anti-periplanar transition state), conformational, ion-pairing, and other factors cause *syn* elimination to intervene (and even predominate) in some cases.

17.A.ii. The E1 Mechanism

The E1 mechanism is a two-step process in which the rate-determining step is ionization of the substrate to give a carbocation that rapidly loses a β proton to a base, usually the solvent.



The IUPAC designation is $D_N + D_E$ (or $D_N + D_H$). This mechanism normally operates without an *added* base. Just as the E2 mechanism competes with the S_N2,[38] so the E1 mechanism competes with the S_N1. In fact, the first step of the E1 is exactly the same as that of the S_N1 mechanism. The second step differs in that the solvent pulls a proton from the β carbon of the carbocation rather than attacking it at the positively charged carbon, as in the S_N1 process. In a pure E1 reaction (without ion pairs, etc.), the product should be completely nonstereospecific, since a carbocation should be planar with no facial differentiation, and bond rotation is possible before deprotonation.

Some of the evidence for the E1 mechanism is as follows:

1. The reaction exhibits first-order kinetics (in substrate) as expected, since ionization to the carbocation is the slow step. Of course, the solvent is not expected to appear in the rate equation, even if it were involved in the rate-determining step (Sec. 6.J.vi), but this point can be easily checked by adding a small amount of the conjugate base of the solvent. It is generally found that such an addition does not increase the rate of the reaction. If this more powerful base does not enter into the rate-determining step, it is unlikely that the solvent does. An example of an E1 mechanism with a rate-determining second step (proton transfer) has been reported.[39]
2. If the reaction is performed on two molecules that differ only in the leaving group (e.g., *t*-BuCl and *t*-$BuSMe_2^+$), the rates should obviously be different, since they depend on the ionizing ability of the molecule. However, once the carbocation is formed, if the solvent and the temperature are the same, it should suffer the same

[36] See Croft, A.P.; Bartsch, R.A. *Tetrahedron Lett.* ***1983***, *24*, 2737; Kwart, H.; Gaffney, A.H.; Wilk, K.A. *J. Chem. Soc., Perkin Trans. 2* ***1984***, 565.
[37] Borchardt, J.K.; Saunders Jr., W.H. *J. Am. Chem. Soc.* ***1974***, *96*, 3912.
[38] Villano, S.M.; Eyet, N.; Lineberger, W.C.; Bierbaum, V.M. *J. Am. Chem. Soc.* ***2009***, *131*, 8227.
[39] Baciocchi, E.; Clementi, S.; Sebastiani, G.V.; Ruzziconi, R. *J. Org. Chem.* ***1979***, *44*, 32.

fate in both cases. This means that the nature of the leaving group does not affect the second step, and *the ratio of elimination to substitution should be the same*. The two compounds mentioned here were solvolyzed at 65.3 °C in 80% aqueous ethanol. *tert*-Butyl chloride gave 36.3% of 2-methylprop-1-ene and 63.7% of *tert*-butanol. *t*-$BuSMe_2^+$ gave 35.7% of 2-methylprop-1-ene and 64.3% of *tert*-butanol.[40] Although the rates were greatly different (as expected with such different leaving groups), the product ratios were the same, within 1%. If these reactions had taken place by a second-order mechanism, the nucleophile would not be expected to have the same ratio of preference for attack at the β hydrogen compared to attack at a *neutral* chloride as for attack at the β hydrogen compared to attack at a *positive* SMe_2 group.

3. Many reactions carried out under first-order conditions on systems where E2 elimination is *anti* proceed quite readily to give alkenes where a *cis* hydrogen must be removed, often in preference to the removal of a *trans* hydrogen. For example, menthyl chloride (**2**), which by the E2 mechanism gave only **5**, under E1 conditions gave 68% **6** and 32% **5**, since the steric nature of the hydrogen is no longer a factor here, and the more stable alkene (*Zaitsev's rule*, **12-2**) is predominantly formed.
4. If carbocations are intermediates, rearrangements should occur with suitable substrates. These have often been found in elimination reactions performed under E1 conditions.

E1 reactions can involve ion pairs, just as is true for S_N1 reactions (Sec. 10A.iii).[41] This effect is naturally greatest for nondissociating solvents: It is least in water, greater in ethanol, and greater still in acetic acid. It has been proposed that the ion-pair mechanism (Sec. 10.A.iii, category 1) extends to elimination reactions too, and that the S_N1, S_N2, E1, and E2 mechanisms possess an ion-pair intermediate in common, at least occasionally.[42]

17.A.iii. The E1cB Mechanism[43]

In the E1 mechanism, X leaves first and then H is removed. In the E2 mechanism, H is removed, which triggers the expulsion of X. However, there is a third possibility: the H is removed first to form a carbanion β to the leaving group (X), and then X is expelled. This is a two-step process, called the *E1cB mechanism*,[44] or the *carbanion mechanism*, since the intermediate is a carbanion that "kicks out" the leaving group. The name E1cB comes from the fact that it is the conjugate base of the substrate that is giving up the leaving group (see the S_N1cB mechanism, Sec. 10.G.iii, category 1). The IUPAC designation is $A_nD_E + D_N$ or $A_{xh}D_H + D_N$ (Sec. 9.F).

[40] Cooper, K.A.; Hughes, E.D.; Ingold, C.K.; MacNulty, B.J. *J. Chem. Soc.* ***1948***, 2038.
[41] See Thibblin, A. *J. Am. Chem. Soc.* ***1987***, *109*, 2071; *J. Phys. Org. Chem.* ***1989***, *2*, 15.
[42] Sneen, R.A. *Acc. Chem. Res.* ***1973***, *6*, 46; Thibblin, A.; Sidhu, H. *J. Chem. Soc., Perkin Trans. 2* ***1994***, 1423. See, however, McLennan, D.J. *J. Chem. Soc., Perkin Trans. 2* ***1972***, 1577.
[43] Cockerill, A.F.; Harrison, R.G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 158–178; Hunter, D.H. *Intra-Sci. Chem. Rep.* ***1973***, *7(3),* 19; McLennan, D.J. *Q. Rev. Chem. Soc.* ***1967***, *21*, 490. For a general discussion, see Koch, H.F. *Acc. Chem. Res.* ***1984***, *17*, 137.
[44] See Ryberg, P.; Matsson, O. *J. Org. Chem.* ***2002***, *67*, 811.

Three limiting cases can be distinguished:

1. The carbanion returns to starting material faster than it forms product: formation of the carbanion is reversible; expulsion of the leaving group is slow.
2. Formation of the carbanion is the slow step, and formation of product is faster than return of the carbanion to starting material. In this case formation of the carbanion is essentially irreversible.
3. Formation of the carbanion is rapid, and the carbanion goes slowly to product. This case occurs only with the most stable carbanions. Here, too, formation of the carbanion is essentially irreversible.

These cases have been given the designations: 1 as $(E1cB)_R$, 2 as $(E1cB)_I$ (or $E1cB_{irr}$), and 3 as $(E1)_{anion}$. Their characteristics are listed in Table 17.1.[45] Investigations of the reaction order are generally not very useful (except for case 3, which is first order), because cases 1 and 2 are second order and thus difficult or impossible to distinguish from the E2 mechanism by this procedure.[46] The greatest likelihood of finding the E1cB mechanism is expected in substrates that have (i) a poor nucleofuge and (ii) an acidic hydrogen. In addition, most investigations have concerned such substrates.

The following is some of the evidence in support of the E1cB mechanism.

1. The first step of the $(E1cB)_R$ mechanism involves a reversible exchange of protons between the substrate and the base. In that case, if deuterium is present in the base, recovered starting material should contain deuterium. This was found to be the case in the treatment of $Cl_2C{=}CHCl$ with NaOD to give $ClC{\equiv}CCl$. When the reaction was stopped before completion, there *was* deuterium in the recovered alkene.[47] A similar result was found for pentahaloethanes.[48] These substrates are relatively acidic. In both cases the electron-withdrawing halogens increase the acidity of the hydrogen, and in the case of trichloroethylene there is the additional factor that a hydrogen on an sp^2 carbon is more acidic than one on an sp^3 carbon (Sec. 8.F, category 7). Thus, the E1cB mechanism is more likely to be found in eliminations yielding triple bonds than in those giving double bonds. Another likely place for the E1cB mechanism should be in reaction of a substrate like $PhCH_2CH_2Br$, since the carbanion is stabilized by resonance with the phenyl group. Nevertheless, no deuterium exchange was found here.[49] If this type of evidence is a guide, then it may be inferred that the $(E1cB)_R$ mechanism is quite rare, at least for eliminations with common leaving groups such as Br, Cl, or OTs, which yield C=C double bonds.
2. When the elimination reaction was carried out in water containing acetohydroxamate buffers, a plot of the rate against the buffer concentration was curved and the

[45] This table, which appears in Cockerill, A.F.; Harrison, R.G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, p. 161, was adapted from a longer one in Bordwell, F.G. *Acc. Chem. Res.* ***1972***, *5*, 374 (see p. 375).

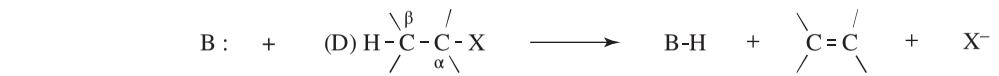
[46] $(E1cB)_I$ cannot be distinguished from E2 by this means, because it has the identical rate law: rate = k [substrate] [B^-]. The rate law for $(E1cB)_R$ is different: rate = k [substrate] [B^-]/[BH], but this is often not useful because the only difference is that the rate is also dependent (inversely) on the concentration of the conjugate acid of the base, and this is usually the solvent, so that changes in its concentration cannot be measured.

[47] Houser, J.J.; Bernstein, R.B.; Miekka, R.G.; Angus, J.C. *J. Am. Chem. Soc.* ***1955***, *77*, 6201.

[48] See Hine, J.; Wiesboeck, R.; Ramsay, O.B. *J. Am. Chem. Soc.* ***1961***, *83*, 1222.

[49] Skell, P.S.; Hauser, C.R. *J. Am. Chem. Soc.* ***1945***, *67*, 1661.

TABLE 17.1 Kinetic predictions for base-induced β-eliminations[45]



Mechanism	Kinetic[b] Order	β-Hydrogen Exchange Faster Than Elimination	General or Specific Base Catalysis	k_H/k_D	Electron Withdrawal at C_β[c]	Electron Release at C_α[c]	Leaving Group Isotope Effect or Element Effect
$(E1)_{anion}$	1	Yes	General[c]	1.0	Rate decrease	Rate increase	Substantial
$(E1cB)_R$	2	Yes	Specific	1.0	Small rate increase	Small rate increase	Substantial
$(E1cB)_{ip}$	2	No	General[e]	1.0-1.2	Small rate increase	Small rate increase	Substantial
$(E1cB)_l$	2	No	General	2-8	Rate increase	Little effect	Small to negligible
E2[b]	2	No	General	2-8	Rate increase	Small rate increase	Small

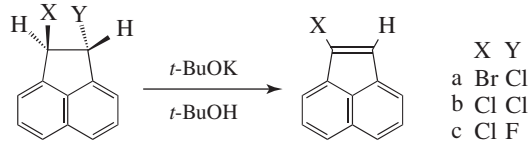
[a]Al mechanisms exhibit first-order kinetics in substrate.
[b]Only transition states with considerable carbanion character considered in this table.
[c]Specific base catalysis predicted if extent of substrate ionization reduced from almost complete.
[d]Effect on rate assuming no change in mechanism is caused; steric factors upon substitution at Cl γ and rise to Cl′ have not been considered. The rate reductions are geared to substituent effects such as those giving rise to Hammett reaction constants onl′- and l γ-aryl substitution.
[e]Depends on whether an ion pair assists in removal of leaving group.
Reprinted with permission Bordwell, F.G. *Acc. Chem. Res.* ***1972***, *5*, 374. Copyright 1972 American Chemical Society.

rate leveled off at high buffer concentrations, indicating a change in rate-determining step.[50] This rules out an E2 mechanism, which has only one step.[51] When D_2O was used instead of H_2O as solvent, there was an initial inverse solvent isotope effect of 7.7 (the highest inverse solvent isotope effect yet reported). In other words, the reaction took place faster in D_2O than in H_2O. This result is compatible only with an E1cB mechanism in which the proton-transfer step is not entirely rate determining. The isotope effect arises from a partitioning of a carbanion intermediate. This intermediate either can go to product or it can revert to starting compound, which requires taking a proton from the solvent. In D_2O the latter process is slower (because the O—D bond of D_2O cleaves less easily than the O—H bond of H_2O), reducing the rate at which a carbanion intermediate returns to starting compound. With the return reaction competing less effectively, the rate of conversion of a carbanion intermediate to product is increased.

3. Substrates containing acidic hydrogen atoms and poor leaving groups are most likely to proceed by the E1cB mechanism. Compounds of the type ZCH_2CH_2OPh, where Z is an electron-withdrawing group (e.g., NO_2, SMe_2^+, $ArSO_2$, CN, CO_2R), belong to this category, because OPh is a very poor leaving group (Sec. 10.A.iii, category 1). There is much evidence to show that the mechanism here is indeed E1cB.[52] Isotope effects, measured for $MeSOCD_2CH_2OPh$ and $Me_2S^+CD_2CH_2OPh$ with NaOD in D_2O, are ~0.7. This is compatible with an $(E1cB)_R$ mechanism, but not with an E2 mechanism for which an isotope effect of perhaps 5 might be expected (of course, an E1 mechanism is precluded by the extremely poor nucleofugal ability of OPh). The fact that k_H/k_D is less than the expected value of 1 is attributable to solvent and secondary isotope effects. Among other evidence for an E1cB mechanism in these systems is that changes in the identity of Z had a dramatic effect on the relative rates, with a span of 10^{11} between NO_2 and COO^-. Note that elimination from substrates of the type $RCOCH_2CH_2Y$ is the reverse of *Michael-type addition* to C=C bonds. Such addition involves initial attack by a nucleophile Y and subsequent protonation (Sec. 15.A.ii). Thus the initial loss of a proton from substrates of this type (i.e., an E1cB mechanism) is in accord with the principle of microscopic reversibility.[53] It may also be recalled that the benzyne formation (Sec. 13.A.iii) can occur by such a process. It has been suggested that all base-initiated eliminations wherein the proton is activated by a strong electron-withdrawing group are E1cB reactions.[54] However, there is evidence that this is not the case when there is a good nucleofuge; the mechanism is E2 even when strong electron-withdrawing groups are present.[55] On the other hand, Cl^- has been found to be a leaving group in an E1cB reaction.[56]

[50] Keeffe, J.R.; Jencks, W.P. *J. Am. Chem. Soc.* ***1983***, *105*, 265.
[51] For a borderline E1cB/E2 mechanism, see Jia, Z.S.; Rudzinsci, J.; Paneth, P.; Thibblin, A. *J. Org. Chem.* ***2002***, *67*, 177.
[52] Cann, P.F.; Stirling, C.J.M. *J. Chem. Soc., Perkin Trans. 2* ***1974***, 820. For other examples, see Kurzawa, J.; Leffek, K.T. *Can. J. Chem.* ***1977***, *55*, 1696.
[53] Patai, S.; Weinstein, S.; Rappoport, Z. *J. Chem. Soc.* ***1962***, 1741. See also, Hilbert, J.M.; Fedor, L.R. *J. Org. Chem.* ***1978***, *43*, 452.
[54] Bordwell, F.G. *Acc. Chem. Res.* ***1972***, *5*, 374.
[55] Banait, N.S.; Jencks, W.P. *J. Am. Chem. Soc.* ***1990***, *112*, 6950.
[56] Ölwegård, M.; McEwen, I.; Thibblin, A.; Ahlberg, P. *J. Am. Chem. Soc.* ***1985***, *107*, 7494.

Of the three cases of the E1cB mechanism, the one most difficult to distinguish from E2 is $(E1cB)_I$. One way to make this distinction is to study the effect of a change in leaving group. This was done in the case of the three acenaphthylenes **10**, where it was found that (i) the three rates were fairly similar, the largest being only about four times that of the smallest, and (ii) in compound c (X = Cl, Y = F), the only product contained Cl and no F, i.e., only the poorer nucleofuge F departed while Cl remained.[57]



10

Result (i) rules out all the E1cB mechanisms except $(E1cB)_I$, because the others should all have considerable leaving group effects (Table 17.1). An ordinary E2 mechanism should also have a large leaving group effect, but an E2 mechanism with substantial carbanionic character (see the next section) might not. However, no E2 mechanism can explain result (ii), which can be explained by the fact that an α Cl is more effective than an α F in stabilizing the planar carbanion that remains when the proton is lost. Thus (as in the somewhat similar case of aromatic nucleophilic substitution, Sec. 13.B.ii), when X^- leaves in the second step, the one that leaves is not determined by which is the better nucleofuge, but by which has had its β hydrogen removed.[58] Additional evidence for the existence of the $(E1cB)_I$ mechanism was the observation of a change in the rate-determining step in the elimination reaction of *N*-(2-cyanoethyl)pyridinium ion, treated with base, when X was changed to give acrylonitrile and a pyridine derivative.[59] Once again, the demonstration that two steps are involved precludes the one-step E2 mechanism. Note that pyridyl systems appear to be a borderline case, and it is not obvious if the reaction involves a carbanion intermediate (E1cb, $A_{xh}D_H + D_N$) or if the reaction proceeds by concerted loss of a proton and the halide (E2, ANDEDN) with attack by the base.[60]

4. An example of an $(E1)_{anion}$ mechanism has been found with the substrate 1-methoxy-1-phenyl-2-nitrocyclopentane, which when treated with methoxide ion gives nitro enolate anion. This nitro enolate anion undergoes elimination to 1-phenyl-2-nitrocyclopent-1-ene, which is unstable under the reaction conditions and rearranges to 1-phenyl-5-nitrocyclopent-1-ene.[61] Among the evidence for the proposed mechanism in this case were kinetic and isotope effect results, as well as the spectral detection of the nitro enolate anion.[62]

[57] Baciocchi, E.; Ruzziconi, R.; Sebastiani, G.V. *J. Org. Chem.* ***1982***, *47*, 3237.
[58] See Gandler, J.R.; Storer, J.W.; Ohlberg, D.A.A. *J. Am. Chem. Soc.* ***1990***, *112*, 7756.
[59] See Bunting, J.W.; Kanter, J.P. *J. Am. Chem. Soc.* ***1991***, *113*, 6950.
[60] See Mosconi, E.; De Angelis, F.; Belpassi, L.; Tarantelli, F.; Alunni, S. *Eur. J. Org. Chem.* ***2009***, 5501; Duarte, F.; Gronert, S.; Kamerlin, S.C.L. *J. Org. Chem.* ***2014***, *79*, 1280.
[61] Bordwell, F.G.; Yee, K.C.; Knipe, A.C. *J. Am. Chem. Soc.* ***1970***, *92*, 5945.
[62] See Albeck, M.; Hoz, S.; Rappoport, Z. *J. Chem. Soc., Perkin Trans. 2* ***1972***, 1248; ***1975***, 628.

5. In many eliminations to form C=O and C≡N bonds the initial step is loss of a positive group (normally a proton) from the oxygen or nitrogen. These may also be regarded as E1cB processes.

There is evidence that some E1cB mechanisms can involve ion pairs, as in the deprotonation of 1,2-dibromoethene with NEt_3 in DMF to give the anion with a triethylammonium countererion, which gives the 1-bromoalkyne.[63] This case is designated $(E1cB)_{ip}$; its characteristics are shown in Table 17.1.

17.A.iv. The E1-E2-E1cB Spectrum

In the three mechanisms so far considered, the similarities are greater than the differences. In each case, there is a leaving group that comes off with its pair of electrons and another group (usually hydrogen) that comes off without a pair of electrons. The only difference is in the order of the steps. It is now generally accepted that there is a spectrum of mechanisms ranging from one extreme, in which the leaving group departs well before the proton (pure E1), to the other extreme, in which the proton is removed first and then, after some time, the leaving group follows (pure E1cB). The *pure* E2 case would be somewhere in the middle, with both groups leaving simultaneously. However, most E2 reactions are not exactly in the middle, but somewhere to one side or the other. For example, the nucleofuge might depart just before the proton. This case may be described as an E2 reaction with a small amount of E1 character. The concept can be expressed by a question: "In the transition state, which bond (C—H or C—X) has undergone more cleavage?"[64]

Note that in both E1 and E2 reactions, removal of the hydrogen atom is an acid–base reaction, requiring a base. A stronger base is required for the E2 and a weaker base for E1. Further, the E1 reaction requires a solvent that facilitates ionization to a carbocation, such as aqueous media, whereas the E2 reaction is usually done in a protic solvent such as an alcohol.

One way to determine just where a given reaction stands on the E1-E2-E1cB spectrum is to study isotope effects, which ought to tell something about the behavior of bonds in the transition state.[65] For example, $CH_3CH_2NMe_3^+$ showed a nitrogen isotope effect (k^{14}/k^{15}) of 1.017, while $PhCH_2CH_2NMe_3^+$ gave a corresponding value of 1.009.[66] It would be expected that the phenyl group would move the reaction toward the E1cB side of the line, which means that for this compound the C—N bond is not as greatly broken in the transition state as it is for the unsubstituted one. The isotope effect bears this out, for it shows that in the phenyl compound, the mass of the nitrogen has less effect on the reaction rate than it does in the unsubstituted compound. Similar results have been obtained with SR_2^+

[63] Kwok, W.K.; Lee, W.G.; Miller, S.I. *J. Am. Chem. Soc.* ***1969***, *91*, 468. See also, Petrillo, G.; Novi, M.; Garbarino, G.; Dell'Erba, C.; Mugnoli, A. *J. Chem. Soc., Perkin Trans. 2* ***1985***, 1291.

[64] See Cockerill, A.F.; Harrison, R.G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 178–189; Saunders Jr., W.H. *Acc. Chem. Res.* ***1976***, *9*, 19; Saunders Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 47–104; Bordwell, F.G. *Acc. Chem. Res.* ***1972***, *5*, 374.

[65] Fry, A. *Chem. Soc. Rev.* ***1972***, *1*, 163. See also, Pulay, A.; Fry, A. *Tetrahedron Lett.* ***1986***, *27*, 5055.

[66] Ayrey, G.; Bourns, A.N.; Vyas, V.A. *Can. J. Chem.* ***1963***, *41*, 1759. Also see, Smith, P.J.; Bourns, A.N. *Can. J. Chem.* ***1970***, *48*, 125.

leaving groups by the use of $^{32}S/^{34}S$ isotope effects[67] and with Cl ($^{35}Cl/^{37}Cl$).[68] The position of reactions along the spectrum has also been studied from the other side of the newly forming double bond by the use of H/D and H/T isotope effects,[69] although interpretation of these results is clouded (i) by the fact that β hydrogen isotope effects are expected to change smoothly from small to large to small again as the degree of transfer of the β hydrogen from the β carbon to the base increases[70] (in Sec. 6.B, it was noted that isotope effects are greatest when the proton is half-transferred in the transition state), (ii) by the possibility of secondary isotope effects (e.g., the presence of a β deuterium or tritium may cause the leaving group to depart more slowly), and (iii) by the possibility of tunneling.[71] Other isotope-effect studies have involved labeled α or β carbon, labeled α hydrogen, or labeled base.[61]

Another way to study the position of a given reaction on the spectrum involves the use of β-aryl substitution. Since a positive *Hammett* ρ *value* is an indication of a negatively charged transition state, the ρ value for substituted β-aryl groups should increase as a reaction moves from E1-like to E1cB-like along the spectrum. This has been shown to be the case in a number of studies;[72] for example, ρ values of $ArCH_2CH_2X$ increase as the leaving-group ability of X decreases. A typical set of ρ values was: X = I, 2.07; Br, 2.14; Cl, 2.61; SMe_2^+, 2.75; F, 3.12.[73] As seen previously, decreasing leaving-group ability correlates with increasing E1cB character.

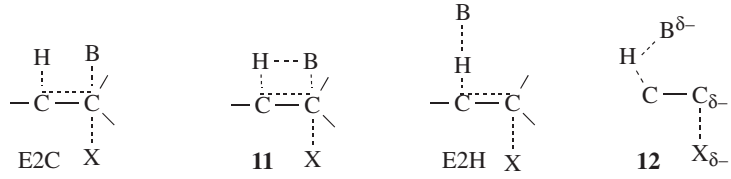
Still another method measures volumes of activation.[74] These are negative for E2 and positive for E1cB mechanisms. Measurement of the activation volume therefore provides a continuous scale for deciding just where a reaction lies on the spectrum.

17.A.v. The E2C Mechanism[75]

Certain alkyl halides and tosylates undergo E2 eliminations faster when treated with weak bases such as Cl^- in polar aprotic solvents or PhS^- than with the usual E2 strong bases such as RO^- in ROH.[76] In order to explain these results, it was proposed[77] that there is a spectrum[78] of E2 transition states in which the base can interact in the transition state with the α carbon, as well as with the β hydrogen. At one end of this spectrum is a mechanism (called E2C) in which, in the transition state, the base interacts mainly with the carbon. The E2C mechanism is characterized by strong nucleophiles that are weak bases. At the other extreme is the normal E2 mechanism, here called E2H to distinguish it from E2C, characterized by strong bases. Transition state **11** represents a transition state between these

[67] Wu, S.; Hargreaves, R.T.; Saunders Jr., W.H. *J. Org. Chem.* ***1985***, *50*, 2392 and references cited therein.
[68] Grout, A.; McLennan, D.J.; Spackman, I.H. *J. Chem. Soc., Perkin Trans. 2* ***1977***, 1758.
[69] See Thibblin, A. *J. Am. Chem. Soc.* ***1988***, *110*, 4582; Smith, P.J.; Amin, M. *Can. J. Chem.* ***1989***, *67*, 1457.
[70] However, see Blackwell, L.F. *J. Chem. Soc., Perkin Trans. 2* ***1976***, 488.
[71] See Miller, D.J.; Saunders Jr., W.H. *J. Org. Chem.* ***1981***, *46*, 4247 and previous papers in this series. See also, Amin, M.; Price, R.C.; Saunders Jr., W.H. *J. Am. Chem. Soc.* ***1990***, *112*, 4467.
[72] Smith, P.J.; Tsui, S.K. *J. Am. Chem. Soc.* ***1973***, *95*, 4760; *Can. J. Chem.* ***1974***, *52*, 749.
[73] DePuy, C.H.; Bishop, C.A. *J. Am. Chem. Soc.* ***1960***, *82*, 2532, 2535.
[74] Brower, K.R.; Muhsin, M.; Brower, H.E. *J. Am. Chem. Soc.* ***1976***, *98*, 779. For a review, see van Eldik, R.; Asano, T.; le Noble, W.J. *Chem. Rev.* ***1989***, *89*, 549.
[75] McLennan, D.J. *Tetrahedron* ***1975***, *31*, 2999; Ford, W.T. *Acc. Chem. Res.* ***1973***, *6*, 410.
[76] See Hayami, J.; Ono, N.; Kaji, A. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 1628.
[77] Parker, A.J.; Ruane, M.; Biale, G.; Winstein, S. *Tetrahedron Lett.* ***1968***, 2113.
[78] This is apart from the E1-E2-E1cB spectrum.

extremes. Additional evidence[79] for the E2C mechanism is derived from *Brønsted equation* considerations (Sec. 8.D), from substrate effects, from isotope effects, and from the effects of solvents on rates.



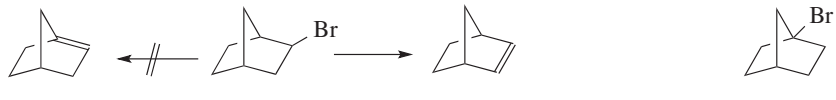
However, the E2C mechanism has been criticized, and it has been contended that all the experimental results can be explained by the normal E2 mechanism.[80] McLennan has suggested that the transition state is that shown as **12**.[81] An ion-pair mechanism has also been proposed.[82] Although the actual mechanisms involved may be a matter of controversy, there is no doubt that a class of elimination reactions exists that is characterized by second-order attack by weak bases.[83] These reactions also have the following general characteristics:[84] (i) they are favored by good leaving groups; (ii) they are favored by polar aprotic solvents; (iii) the reactivity order is tertiary > secondary > primary, which is the opposite of the normal E2 order (Sec. 17.D.i); (iv) the elimination is always *anti* (*syn* elimination is not found), but in cyclohexyl systems, a diequatorial *anti* elimination is about as favorable as a diaxial *anti* elimination (unlike the normal E2 reaction, Sec. 17.A.i, categories 2 and 3); and (v) they follow *Zaitsev's rule* (see Sec. 17.B below), where this does not conflict with the requirement for *anti* elimination.

17.B. REGIOCHEMISTRY OF THE DOUBLE BOND

With some substrates, a β hydrogen is present on only one carbon and (barring rearrangements) there is no doubt as to the identity of the product. For example, $PhCH_2CH_2Br$ can give only $PhCH{=}CH_2$. However, in many other cases two or three alkenyl products are possible. In the simplest such case, a *sec*-butyl compound can give either but-1-ene or but-2-ene. There are a number of rules that, in many instances, enable a prediction of which product will predominantly form.[85]

1. No matter the mechanism, a double bond does not go to a bridgehead carbon unless the ring sizes are large enough (*Bredt's rule*, Sec. 4.P.iii). This means, for example, not only that **13** gives only **14** and not **15** (indeed **15** is not a known compound), but also that **16** does *not* undergo elimination.

[79] See Kwart, H.; Wilk, K.A. *J. Org. Chem.* ***1985***, *50*, 3038.
[80] See Bunnett, J.F.; Migdal, C.A. *J. Org. Chem.* ***1989***, *54*, 3037, 3041 and references cited therein.
[81] McLennan, D.J.; Lim, G. *Aust. J. Chem.* ***1983***, *36*, 1821. For an opposing view, see Kwart, H.; Gaffney, A. *J. Org. Chem.* ***1983***, *48*, 4502.
[82] Ford, W.T. *Acc. Chem. Res.* ***1973***, *6*, 410.
[83] For convenience, these are called E2C reactions, although the actual mechanism is in dispute.
[84] See Beltrame, P.; Ceccon, A.; Winstein, S. *J. Am. Chem. Soc.* ***1972***, *94*, 2315.
[85] See Hückel, W.; Hanack, M. *Angew. Chem. Int. Ed.* ***1967***, *6*, 534.



15 **13** **14** **16**

2. No matter the mechanism, if there is a double bond (C═C or C═O) or an aromatic ring already in the molecule that can be in conjugation with the new double bond, the conjugated product usually predominates, sometimes even when the stereochemistry is unfavorable (for an exception, Sec. 17.C).
3. In the E1 mechanism the leaving group is gone before the choice is made as to which direction the new double bond takes. Therefore the direction is determined almost entirely by the relative stabilities of the two (or three) possible alkenes. In such cases *Zaitsev's rule*[86] operates. This rule states that *the double bond goes mainly toward the most highly substituted carbon*. That is, 3-bromo-2,3-dimethylpentane gives more 2,3-dimethylpent-2-ene than either 3,4-dimethylpent-2-ene or 2-ethyl-3-methylbut-1-ene. Thus Zaitsev's rule predicts that the alkene predominantly formed will be the one with the largest possible number of alkyl groups on the C═C carbons, and in most cases this is what is found. From heat of combustion data (Sec. 1.L), it is known that alkene stability increases with alkyl substitution, although just why this should be is a matter of conjecture. The most common explanation is hyperconjugation. For E1 eliminations, Zaitsev's rule governs the orientation whether the leaving group is neutral or positive, since, as already mentioned, the leaving group is not present when the choice of direction is made. This statement does not hold for E2 eliminations, and it may be mentioned here, for contrast with later results, that E1 elimination of $Me_2CHCHMeSMe_2^+$ gave 91% of the Zaitsev product and 9% of the other.[87] However, there *are* cases in which the leaving group affects the direction of the double bond in E1 eliminations.[88] This may be attributed to ion pairs; that is, the leaving group is not completely gone when the hydrogen departs. Zaitsev's rule breaks down in cases where the non-Zaitsev product is more stable for steric reasons. For example, E1 or E1-like eliminations of 1,2-diphenyl-2-X-propanes ($PhMeCXCH_2Ph$) were reported to give about 50% $CH_2{=}CPhCH_2Ph$, despite the fact that the double bond of the Zaitsev product (PhMeC═CHPh) is conjugated with two benzene rings.[89]
4. For the *anti* E2 mechanism a *trans* β proton is necessary; if this is available in only one direction, that is the way the double bond will form. Because of the free rotation in acyclic systems (except where steric hindrance is great), this is a factor only in cyclic systems. Where *trans* β hydrogen atoms are available on two or three carbons, two types of behavior are found, depending on substrate structure and the nature of the leaving group. Compounds either follow Zaitsev's rule and give predominant formation of the most highly substituted alkene, or they follow *Hofmann's rule: the double bond goes mainly toward the least highly substituted carbon*.

[86] Often given the German spelling: Saytzeff, or Saytseff, or Saytzev.
[87] de la Mare, P.B.D. *Prog. Stereochem.* ***1954***, *1*, 112.
[88] See Cram, D.J.; Sahyun, M.R.V. *J. Am. Chem. Soc.* ***1963***, *85*, 1257.
[89] Ho, I.; Smith, J.G. *Tetrahedron* ***1970***, *26*, 4277.

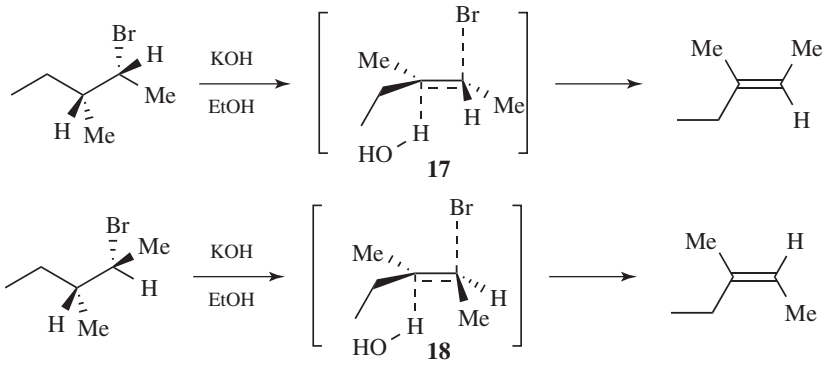
Since Zaitsev orientation almost always gives the thermodynamically more stable isomer, why in some cases the less stable Hofmann product predominates must be explained. *Hofmann orientation*[90] is caused by the fact that the acidity of the β hydrogen is decreased by the presence of the electron-donating alkyl groups. It is noted that in most cases, Hofmann elimination is an intramolecular acid–base reaction. Experiments showed that Hofmann elimination increases with the size of the leaving group.[91] Hofmann elimination was also shown to increase with increase in bulk of the substrate,[92] and steric factors operate in extreme cases.[93] In further experiments, a large series of bases of different kinds was shown to obey linear free-energy relationships between basicity and percentage of Hofmann elimination.[94]

5. Only a few investigations on the orientation of syn E2 eliminations have been carried out, but these show that Hofmann orientation is greatly favored over Zaitsev.[95]
6. In the E1cB mechanism, the question of orientation seldom arises because the mechanism is generally found only where there is an electron-withdrawing group in the β position, and that is where the double bond goes.
7. As already mentioned, E2C reactions show a strong preference for Zaitsev orientation.[96] The compound $PhCH_2CHOTsCHMe_2$ gave ~98% $PhCH{=}CHCHMe_2$ under the usual E2 reaction conditions (*t*-BuOK in *t*-BuOH). In this case the double bond goes to the side with more hydrogen atoms because on that side it will be able to conjugate with the benzene ring.

17.C. STEREOCHEMISTRY OF THE DOUBLE BOND

Several factors affect the stereochemistry of the product, including the nature of the leaving group, the base, the solvent, and the substrate. Not all these effects are completely understood.[97] If a chiral, nonracemic halide [e.g., (2*R*)-bromo-(3*R*)-methylpentane] is treated with KOH in ethanol then the more highly substituted product predicted by Zaitsev's rule is 3-methylpent-2-ene rather than 3-methylpent-1-ene, but there are *two* 3-methylpent-2-enes. Experimentally the E2 reaction is known to be *diastereospecific*. In other words, one diastereomeric alkyl halide will generate either the (*E*)-alkene or the (*Z*)-alkene and the other diastereomeric alkyl halide will give only the other alkene stereoisomer. The transition state for an E2 reaction of (2*R*)-bromo-(3*R*)-methylpentane is represented by **17**, where the bromine leaving group and the β hydrogen are anti-periplanar. This transition state can be formed only when one rotamer of (2*R*)-bromo-(3*R*)-methylpentane has the β hydrogen atom and the bromine leaving group *anti*. This *anti* rotamer leads to the requisite E2 transition state and the final product, 3-methylpent-(2*E*)-ene.

[90] See Ingold, C.K. *Proc. Chem. Soc.* ***1962***, 265.
[91] Brown, H.C.; Wheeler, O.H. *J. Am. Chem. Soc.* ***1956***, *78*, 2199.
[92] See Bartsch, R.A. *J. Org. Chem.* ***1970***, *35*, 1334; Charton, M. *J. Am. Chem. Soc.* ***1975***, *97*, 6159.
[93] See Banthorpe, D.V.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1960***, 4054.
[94] Bartsch, R.A.; Roberts, D.K.; Cho, B.R. *J. Org. Chem.* ***1979***, *44*, 4105.
[95] Sicher, J.; Svoboda, M.; Pánková, M.; Závada, J. *Collect. Czech. Chem. Commun.* ***1971***, *36*, 3633; Bailey, D.S.; Saunders Jr., W.H. *J. Am. Chem. Soc.* ***1970***, *92*, 6904.
[96] Muir, D.M.; Parker, A.J. *J. Org. Chem.* ***1976***, *41*, 3201.
[97] Alunni, S.; Baciocchi, E. *J. Chem. Soc., Perkin Trans. 2* ***1976***, 877; Saunders Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 165–193.



Once the *anti* rotamer is achieved in the presence of the hydroxide, the bond making–breaking process begins, and the stereochemical positions of all groups are essentially "locked" in position in transition state **17**. The two methyl groups in (2*R*)-bromo-(3*R*)-methylpentane are "on the same side" in transition state **17** and they will be on the same side in the alkene product, 3-methylpent-(2*E*)-ene. The requisite *anti* transition state dictates that an enantiopure halide will yield one and only one stereoisomeric alkene. The E2 reaction of (2*R*)-bromo-(3*R*)-methylpentane is diastereospecific, which means that the identical reaction of KOH with (2*S*)-bromo-(3*R*)-methylpentane [the diastereomer of (2*R*)-bromo-(3*R*)-methylpentane] will lead to transition state **18** and 3-methylpent-(2*Z*)-ene, as shown.

For E1 eliminations, if there is a free carbocation and rotation can occur about the C—C bond, then no matter the geometry of the original compound, the more stable situation will give the (*E*)-alkene. If the carbocation is not completely free, then to that extent, E2-type products are formed. Similar considerations apply in E1cB eliminations.[98]

17.D. REACTIVITY

In this section, the effects of changes in the substrate, base, leaving group, and medium on (i) overall reactivity, (ii) E1 versus E2 versus E1cB,[99] and (iii) elimination versus substitution will be examined.

17.D.i. Effect of Substrate Structure

1. *Effect on reactivity*. The carbon containing the nucleofuge (X) is referred to as the α carbon and the carbon that loses the positive species (usually a proton) is referred to as the β carbon. Groups attached to the α or β carbons can exert at least four kinds of influence:
   a. they can stabilize or destabilize the incipient double bond (both α and β groups);
   b. they can stabilize or destabilize an incipient negative charge, affecting the acidity of the proton (β groups only);
   c. they can stabilize or destabilize an incipient positive charge (α groups only);
   d. they can exert steric effects (e.g., eclipsing effects) (both α and β groups).

[98] See Redman, R.P.; Thomas, P.J.; Stirling, C.J.M. *J. Chem. Soc., Chem. Commun.* ***1978***, 43.
[99] See Cockerill, A.F.; Harrison, R.G. in Patai, S. *The Chemistry of Functional Groups*, Supplement A, pt. 1, Wiley, NY, ***1977***, pp. 178–189.

Effects a and d can apply in all three mechanisms, although steric effects are greatest for the E2 mechanism. Effect b does not apply in the E1 mechanism, and effect c does not apply in the E1cB mechanism. Groups such as Ar and C=C increase the rate by any mechanism, except perhaps when formation of the C=C bond is not the rate-determining step, whether they are α or β (effect a). Electron-withdrawing groups increase the acidity when in the β position, but have little effect in the α position unless they also conjugate with the double bond. Thus Br, Cl, CN, Ts, NO_2, CN, and SR in the β position all increase the rate of E2 eliminations.

2. *Effect on E1 versus E2 versus E1cB*. α-Alkyl and α-aryl groups stabilize the carbocation character of the transition state, shifting the spectrum toward the E1 end. β-Alkyl groups also shift the mechanism toward E1, since they *decrease* the acidity of the hydrogen. However, β-aryl groups shift the mechanism the other way (toward E1cB) by stabilizing the carbanion. Indeed, as seen in Sec. 17.A.iii, all electron-withdrawing groups in the β position shift the mechanism toward E1cB.[100] α-Alkyl groups also increase the extent of elimination with weak bases (E2C reactions).
3. *Effect on elimination versus substitution*. Under second-order conditions, increased branching increases elimination, to the point where tertiary substrates undergo few S_N2 reactions, as seen in Chapter 10. For example, Table 17.2 shows results on some simple alkyl bromides. Similar results were obtained with $^+SMe_2$ as the leaving group.[101] Two reasons can be presented for this trend. One is statistical: as α branching increases, there are usually more hydrogen atoms for the base to attack. The other is that α branching presents steric hindrance to attack of the base at the carbon. Under first-order conditions, increased α branching also increases the amount of elimination (E1 versus S_N1), although not so much, and usually the substitution product predominates.[102] β-Branching also increases the amount of E2 elimination with respect to S_N2 substitution (Table 17.2), not because elimination is faster but because the S_N2 mechanism is so greatly slowed (Sec. 10.G.i). Under first-order conditions too, β branching favors elimination over substitution, probably for steric reasons.[103] However, E2 eliminations from compounds with charged leaving groups are slowed by β branching, which is related to *Hofmann's rule* (Sec. 17.B, category 4). Electron-withdrawing groups in the β position not only increase the rate of E2 eliminations and shift the mechanisms toward the E1cB end of the spectrum but they also increase the extent of elimination as opposed to substitution.

Another method that compares E2 and S_N2 reactions is called the *activation-strain model*. In this model, the activation energy = activation strain + transition state interaction, and corresponds directly to the strength of the Lewis acid or base. A more basic nucleophile or base, with a higher energy HOMO, and a more acidic substrate, with a lower energy LUMO, interact more strongly.[104] Activation strain is connected with the strength of the bonds broken: a strong C leaving group bond has a higher activation strain and a higher barrier. Using this model, the E2 reaction has a higher activation strain than S_N2 because two bonds are broken, and with weak bases, S_N2 dominates E2 because S_N2 has less activation

[100] See Butskus, P.F.; Denis, G.I. *Russ. Chem. Rev.* ***1966***, *35*, 839.
[101] Dhar, M.L.; Hughes, E.D.; Ingold, C.K.; Masterman, S. *J. Chem. Soc.* ***1948***, 2055.
[102] Dhar, M.L.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1948***, 2058.
[103] Hughes, M.L.; Ingold, C.K.; Maw, G.A. *J. Chem. Soc.* ***1948***, 2065.
[104] See van Zeist, W.-J.; Bickelhaupt, F.M. *Org. Biomol. Chem.* ***2010***, *8*, 3118.

strain.[105] With strong bases, a favorable interaction of the more acidic transition state for the E2 reaction leads to a preference for E2.

TABLE 17.2 The effect of α and β branching on the rate of E2 elimination and the amount of alkene formed[a]

Substrate	Temperature, °C	Alkene, %	Rate of E2 reaction, $\times 10^5$	Reference
CH_3CH_2Br	55	0.9	1.6	106
$(CH_3)_2CHBr$	24	80.3	0.237	107
$(CH_3)_3Br$	25	97	4.17	101
$CH_3CH_2CH_2Br$	55	8.9	5.3	107
$(CH_3)_2CHCH_2Br$	55	59.5	8.5	107

[a]The reactions were between the alkyl bromide and ^-OEt. The rate for isopropyl bromide was actually greater than that for ethyl bromide, if the temperature difference is considered. Neopentyl bromide, the next compound in the β-branching series, cannot be compared because it has no β hydrogen and cannot give an elimination product without rearrangement.

17.D.ii. Effect of the Attacking Base

1. *Effect on E1 versus E2 versus E1cB*. In the E1 mechanism, an external base is generally not required: The solvent acts as the base. Hence, when external bases are added, the mechanism is shifted toward E2. Stronger bases and higher base concentrations cause the mechanism to move toward the E1cB end of the E1-E2-E1cB spectrum.[108] However, weak bases in polar aprotic solvents can also be effective in elimination reactions with certain substrates (the E2C reaction). Normal E2 elimination has been accomplished with the following bases:[109] H_2O, NR_3, ^-OH, ^-OAc, ^-OR, ^-OAr, $^-NH_2$, CO_3^{2-}, $LiAlH_4$, I^-, ^-CN, and organic bases. Weak bases effective in the E2C reaction are Cl^-, Br^-, F^-, ^-OAc, and RS^-. These bases are often used in the form of their R_4N^+ salts.
2. *Effect on elimination versus substitution*. Strong bases not only facilitate E2 rather than E1, but also benefit elimination rather than substitution. With a high concentration of strong base in a non-ionizing solvent, bimolecular mechanisms are favored and E2 predominates over S_N2. At low base concentrations, or in the absence of base altogether, in ionizing solvents, unimolecular mechanisms are favored, and the S_N1 mechanism predominates over the E1. In Chapter 10, it was pointed out that some species are strong nucleophiles but weak bases (Sec. 10.G.ii). The use of these obviously favors substitution, except that, as seen, elimination can predominate if polar aprotic solvents are used. It has been shown for the base cyanide that in polar aprotic

[105] See Bickelhaupt, F.M. *J. Comput. Chem.* ***1999***, *20*, 114. Prof. F.M. Bickelhaupt, Vrije Universiteit Amsterdam, personal communication.
[106] See Hughes, E.D.; Ingold, C.K.; Woolf, L.I. *J. Chem. Soc.* ***1948***, 2084.
[107] Brown, H.C.; Berneis, H.L. *J. Am. Chem. Soc.* ***1953***, *75*, 10.
[108] Baciocchi, E. *Acc. Chem. Res.* ***1979***, *12*, 430. See also, Baciocchi, E.; Ruzziconi, R.; Sebastiani, G.V. *J. Org. Chem.* ***1980***, *45*, 827.
[109] This list is from Banthorpe, D.V. *Elimination Reactions*, Elsevier, NY, ***1963***, p. 4.

solvents, the less the base is encumbered by its counterion in an ion pair (i.e., the freer the base), the more substitution is favored at the expense of elimination.[110]

17.D.iii. Effect of the Leaving Group

1. *Effect on reactivity*. The leaving groups in elimination reactions are similar to those in nucleophilic substitution. E2 eliminations have been performed with the following groups: $^{+}NR_3$, $^{+}PR_3$, $^{+}SR_2$, ^{+}OHR, SO_2R, OSO_2R, OCOR, OOH, OOR, NO_2,[111] F, Cl, Br, I, and CN (but *not* $^{+}OH_2$). E1 eliminations have been carried out with: $^{+}NR_3$, $^{+}SR_2$, $^{+}OH_2$, ^{+}OHR, OSO_2R, OCOR, Cl, Br, I, and $^{+}N_2$.[112] However, the major leaving groups for preparative purposes are $^{+}OH_2$ (always by E1) and Cl, Br, I, and $^{+}NR_3$ (usually by E2).
2. *Effect on E1 versus E2 versus E1cB*. Better leaving groups shift the mechanism toward the E1 end of the spectrum, *since they make ionization easier*. This effect has been studied in various ways. One way already mentioned was a study of ρ values (Sec. 17.A.iv). Poor leaving groups and positively charged leaving groups shift the mechanism toward the E1cB end of the spectrum because the strong electron-withdrawing field effects increase the acidity of the β hydrogen.[113] The E2C reaction is favored by good leaving groups.
3. *Effect on elimination versus substitution*. As seen previously (Sec. 17.A.ii), for first-order reactions the leaving group has nothing to do with the competition between elimination and substitution, since the leaving group is gone before the decision is made as to which path to take. However, this is not true where ion pairs are involved, and results have been found where the nature of the leaving group does affect the product.[114] In second-order reactions, the elimination/substitution ratio is not greatly dependent on a halide leaving group, although there is a slight increase in elimination in the order I > Br > Cl. When OTs is the leaving group, there is usually much more substitution. For example, *n*-$C_{18}H_{37}$Br treated with *t*-BuOK gave 85% elimination, while *n*-$C_{18}H_{37}$OTs gave, under the same conditions, 99% substitution.[115] On the other hand, positively charged leaving groups increase the amount of elimination.

17.D.iv. Effect of the Medium

1. *Effect of solvent on E1 versus E2 versus E1cB*. With any reaction a more polar environment enhances the rate of mechanisms that involve ionic intermediates. For neutral leaving groups, it is expected that E1 and E1cB mechanisms will be aided by

[110] Loupy, A.; Seyden-Penne, J. *Bull. Soc. Chim. Fr.* ***1971***, 2306.
[111] See Ono, N. in Feuer, H.; Nielsen, A.T. *Nitro Compounds; Recent Advances in Synthesis and Chemistry*, VCH, NY, ***1990***, pp. 1–135 (pp. 86–126).
[112] These lists are from Banthorpe, D.V. *Elimination Reactions*, Elsevier, NY, ***1963***, pp. 4, 7.
[113] See Stirling, C.J.M. *Acc. Chem. Res.* ***1979***, *12*, 198. See also, Varma, M.; Stirling, C.J.M. *J. Chem. Soc., Chem. Commun.* ***1981***, 553.
[114] See Wright, D.G. *J. Chem. Soc., Chem. Commun.* ***1975***, 776. See, however, Cavazza, M. *Tetrahedron Lett.* ***1975***, 1031.
[115] Veeravagu, P.; Arnold, R.T.; Eigenmann, E.W. *J. Am. Chem. Soc.* ***1964***, *86*, 3072.

increasing the polarity of the solvent and by increasing ionic strength. With certain substrates, polar aprotic solvents promote elimination with weak bases (the E2C reaction).

2. *Effect of solvent on elimination versus substitution*. Increasing polarity of solvent favors S_N2 reactions at the expense of E2. In the classical example, alcoholic KOH is used to effect elimination, while the more polar aqueous KOH is used for substitution. Charge-dispersal discussions, similar to those in Sec. 10.G.iv,[116] only partially explain this. In most solvents S_N1 reactions are favored over E1. The E1 reactions compete best in polar solvents that are poor nucleophiles, especially dipolar aprotic solvents[117] A study made in the gas phase, where there is no solvent, has shown that when 1-bromopropane reacts with MeO^- only elimination takes place (no substitution) even with this primary substrate.[118]
3. *Effect of temperature*. Elimination is favored over substitution by increasing temperature, whether the mechanism is first order or second order.[119] The reason is that the activation energies of eliminations are higher than those of substitutions (because eliminations have greater changes in bonding).

17.E. MECHANISMS AND ORIENTATION IN PYROLYTIC ELIMINATIONS

17.E.i. Mechanisms[120]

Several types of compounds undergo elimination on heating, with no other reagent present. Reactions of this type are often run in the gas phase. The mechanisms are obviously different from those already discussed, since all those mechanisms require an external base (which may be the solvent) in one of the steps, and there is no external base or solvent present in pyrolytic elimination. Two mechanisms have been found to operate. One involves a cyclic transition state, which may be four, five, or six membered. In this mechanism the two groups leave at about the same time and bond to each other as they are doing so. The designation is E^i in the Ingold terminology and *cyclo*-$D_ED_NA_n$ in the IUPAC system. The elimination must be *syn* and, for the four- and five-membered transition states, the four or five atoms making up the ring must be coplanar. Coplanarity is not required for the six-membered transition state, since there is room for the outside atoms when the leaving atoms are staggered.

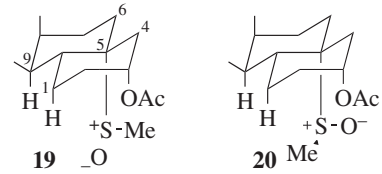
As in the E2 mechanism, it is not necessary that the C—H and C—X bonds be broken simultaneously in the transition state. In fact, there is also a spectrum of mechanisms here, ranging from a mechanism in which C—X bond breaking is a good deal more advanced

[116] Cooper, K.A.; Dhar, M.L.; Hughes, E.D.; Ingold, C.K.; MacNulty, B.J.; Woolf, L.I. *J. Chem. Soc.* ***1948***, 2043.
[117] Aksnes, G.; Stensland, P. *Acta Chem. Scand.* ***1989***, *43*, 893, and references cited therein.
[118] Jones, M.E.; Ellison, G.B. *J. Am. Chem. Soc.* ***1989***, *111*, 1645. For a different result with other reactants, see Lum, R.C.; Grabowski, J.J. *J. Am. Chem. Soc.* ***1988***, *110*, 8568.
[119] Cooper, K.A.; Hughes, E.D.; Ingold, C.K.; Maw, G.A.; MacNulty, B.J. *J. Chem. Soc.* ***1948***, 2049.
[120] Taylor, R. in Patai, S. *The Chemistry of Functional Groups*, Supplement B, pt. 2, Wiley, NY, ***1979***, pp. 860–914; Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* ***1971***, *8*, 75, pp. 76–143, 207–234; in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 5, Elsevier, NY, ***1972***, see the articles by Swinbourne, E.S. pp. 149–233 (pp. 158–188), and by Richardson, W.H.; O'Neal, H.E. pp. 381–565 (pp. 381–446); Maccoll, A. *Adv. Phys. Org. Chem.* ***1965***, *3*, 91. See Egger, K.W.; Cocks, A.T. in Patai, S. *The Chemistry of the Carbon-Halogen Bond*, pt. 2, Wiley, NY, ***1973***, pp. 677–745; Maccoll, A. *Chem. Rev.* ***1969***, *69*, 33.

than C—H bond breaking to one in which the extent of bond breaking is virtually identical for the two bonds. Evidence for the existence of the E^i mechanism includes the following:

1. The kinetics are first order, so only one molecule of the substrate is involved in the reaction (i.e., if one molecule attacked another, the kinetics would be second order in substrate).[121]
2. Free-radical inhibitors do not slow the reactions, so no free-radical mechanism is involved.[122]
3. The mechanism predicts exclusive *syn* elimination, and this behavior has been found in many cases.[123] The evidence is inverse to that for the *anti* E2 mechanism and generally involves the following facts: (i) an *erythro* isomer gives a *trans* alkene and a *threo* isomer gives a *cis* alkene; (ii) the reaction takes place only when a *cis* β hydrogen is available; (iii) if, in a cyclic compound, a *cis* hydrogen is available on only one side, the elimination goes in that direction.

   Another piece of evidence involves a pair of steroid molecules. In 3β-acetoxy-(*R*)-5α-methylsulfinylcholestane (structure **19** shows rings A and B of this compound) and in 3β-acetoxy-(*S*)-5α-methylsulfinylcholestane (**20**: rings A and B), the *only* difference is the configuration of oxygen and methyl about the sulfur. Yet pyrolysis of **19** gave only elimination to the 4 side (86% 4-ene), while **20** gave predominant elimination to the 6 side (65% 5-ene and 20% 4-ene).[124] Models show that interference from the 1 and 9 hydrogen atoms causes the two groups on the sulfur to lie *in front of it* with respect to the rings, rather than behind it. Since the sulfur is a stereogenic center, this means that in **19** the oxygen is near the 4 hydrogen, while in **20** it is near the 6 hydrogen. This experiment is compatible only with *syn* elimination.[125]



(17-12)

4. The ^{14}C isotope effects for the Cope elimination (**17-7**) show that both the C—H bond and the C—N bond have been extensively broken in the transition state.[126]
5. Some of these reactions have been shown to exhibit negative entropies of activation, indicating that the molecules are more restricted in geometry in the transition state than they are in the starting compound.

Where a pyrolytic elimination lies on the mechanistic spectrum seems to depend mostly on the leaving group. When the leaving group is halogen, all available evidence suggests

[121] O'Connor, G.L.; Nace, H.R. *J. Am. Chem. Soc.* ***1953***, *75*, 2118.
[122] Barton, D.H.R.; Head, A.J.; Williams, R.J. *J. Chem. Soc.* ***1953***, 1715.
[123] See, however, Briggs, W.S.; Djerassi, C. *J. Org. Chem.* ***1968***, *33*, 1625; Smissman, E.E.; Li, J.P.; Creese, M.W. *J. Org. Chem.* ***1970***, *35*, 1352.
[124] Jones, D.N.; Saeed, M.A. *Proc. Chem. Soc.* ***1964***, 81. See also, Goldberg, S.I.; Sahli, M.S. *J. Org. Chem.* ***1967***, *32*, 2059.
[125] See Bailey, W.J.; Bird, C.N. *J. Org. Chem.* ***1977***, *42*, 3895.
[126] Wright, D.R.; Sims, L.B.; Fry, A. *J. Am. Chem. Soc.* ***1983***, *105*, 3714.

that in the transition state the C—X bond is cleaved to a much greater extent than the C—H bond, that is, there is a considerable amount of carbocation character in the transition state. This observation is in accord with the fact that a completely nonpolar four-membered cyclic transition state violates the *Woodward-Hoffmann rules* (see the similar case of **15-59**). Evidence for the carbocation-like character of the transition state when halide is the leaving group is that relative rates are in the order I > Br > Cl[127] (Sec. 10.G.iii), and that the effects of substituents on reaction rates are in accord with such a transition state.[128] Rate ratios for pyrolysis of some alkyl bromides at 320 °C were ethyl bromide, 1; isopropyl bromide, 280; *tert*-butyl bromide, 78 000. Also, α-phenylethyl bromide had about the same rate as *tert*-butyl bromide. On the other hand, β-phenylethyl bromide was only slightly faster than ethyl bromide.[129] This result indicates that C—Br cleavage was much more important in the transition state than C—H cleavage, since the incipient carbocation was stabilized by α-alkyl and α-aryl substitution, while there was no incipient carbanion to be stabilized by β-aryl substitution. These substituent effects, as well as those for other groups, are very similar to the effects found for the S_N1 mechanism and are thus in very good accord with a carbocation-like transition state.

For carboxylic esters, the rate ratios were much smaller,[130] although still in the same order, so that this reaction is closer to a pure E^i mechanism, although the transition state still has some carbocationic character. Other evidence for a greater initial C—O cleavage with carboxylic esters is that a series of 1-arylethyl acetates followed σ^+ rather than σ, showing carbocationic character at the 1 position.[131] The extent of E1 character in the transition state increases in the following order of ester types: acetate < phenylacetate < benzoate < carbamate < carbonate.[132] Cleavage of xanthates (**17-5**), cleavage of sulfoxides (**17-10**), the *Cope reaction* (**17-7**), and reaction **17-2** are probably very close to straight E^i mechanisms.[133]

The second type of pyrolysis mechanism is completely different and involves free radicals. Initiation occurs by pyrolytic homolytic cleavage to give the alkyl radical and X•. The latter radical generates a new radical on the carbon β to the X group in a propagation step, and loss of X• gives the alkene. Free-radical mechanisms are mostly found in pyrolyses of polyhalides and of primary monohalides,[134] although they also have been postulated in pyrolysis of certain carboxylic esters.[135] β Elimination of tosyl radicals is known.[136] Much less is known about these mechanisms and we will not consider them further. Free-radical eliminations in solution are also known, but are rare.[137]

[127] Maccoll, A., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 215–216.
[128] For reviews of such studies, see Maccoll, A. *Chem. Rev.* ***1969***, *69*, 33.
[129] See Chuchani, G.; Rotinov, A.; Dominguez, R.M.; Martin, I. *Int. J. Chem. Kinet.* ***1987***, *19*, 781.
[130] Scheer, J.C.; Kooyman, E.C.; Sixma, F.L.J. *Recl. Trav. Chim. Pays-Bas* ***1963***, *82*, 1123. See also, Louw, R.; Vermeeren, H.P.W.; Vogelzang, M.W. *J. Chem. Soc., Perkin Trans. 2* ***1983***, 1875.
[131] August, R.; McEwen, I.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* ***1987***, 1683, and other papers in this series; Al-Awadi, N.A. *J. Chem. Soc., Perkin Trans. 2* ***1990***, 2187.
[132] Taylor, R. *J. Chem. Soc., Perkin Trans. 2* ***1975***, 1025.
[133] For a review of the mechanisms of **17-12**, **17-9**, and the pyrolysis of sulfilimines, see Oae, S.; Furukawa, N. *Tetrahedron* ***1977***, *33*, 2359.
[134] See Barton, D.H.R.; Howlett, K.E. *J. Chem. Soc.* ***1949***, 155, 165.
[135] See Louw, R.; Kooyman, E.C. *Recl. Trav. Chim. Pays-Bas* ***1965***, *84*, 1511.
[136] Timokhin, V.I.; Gastaldi, S.; Bertrand, M.P.; Chatgilialoglu, C. *J. Org. Chem.* ***2003***, *68*, 3532.
[137] See Boothe, T.E.; Greene Jr., J.L.; Shevlin, P.B. *J. Org. Chem.* ***1980***, *45*, 794; Kochi, J.K. *Organic Mechanisms and Catalysis*, Academic Press, NY, ***1978***, pp. 346–349; Kamimura, A.; Ono, N. *J. Chem. Soc., Chem. Commun.* ***1988***, 1278.

17.E.ii. Orientation in Pyrolytic Eliminations

As in the E1-E2-E1cB mechanistic spectrum, *Bredt's rule* applies; and if a double bond is present, a conjugated system will be preferred, if sterically possible. Apart from these considerations, the following statements can be made for E^i eliminations:

1. In the absence of considerations mentioned below, orientation is statistical and is determined by the number of β hydrogen atoms available (therefore *Hofmann's rule* is followed). For example, *sec*-butyl acetate gives 55–62% but-1-ene and 38–45% but-2-ene,[138] which is close to the 3:2 distribution predicted by the number of hydrogen atoms available.[139]
2. A *cis* β hydrogen is required. Therefore in cyclic systems, if there is a *cis* hydrogen on only one side, the double bond will go that way. However, when there is a six-membered transition state, this does not necessarily mean that the leaving groups must be *cis* to each other, since such transition states need not be completely coplanar. If the leaving group is axial, then the hydrogen obviously must be equatorial (and consequently *cis* to the leaving group), since the transition state cannot be realized when the groups are both axial. But if the leaving group is equatorial, it can form a transition state with a β hydrogen that is either axial (hence, *cis*) or equatorial (hence, *trans*). Thus ethyl (1*S*,2*R*)-2-acetoxycyclohexane-1-carboxylate, in which the leaving group is most likely axial, does not form a double bond in the direction of the carbethoxyl group, even although that would be conjugated, because there is no equatorial hydrogen on that side. Instead it gives 100% ethyl cyclohex-2-ene-1-carboxylate.[140] On the other hand, *S*-methyl *O*-((1*S*,2*R*)-2-methylcyclohexyl) carbonodithioate, with an equatorial leaving group, gave a 56:44 mixture of 3-methylcyclohex-1-ene and 1-methylcyclohex-1-ene but in only 31% yield, even though for elimination to 3-methylcyclohex-1-ene, the leaving group must depart with a *trans* hydrogen.[141]
3. In some cases, especially with cyclic compounds, the more stable alkene forms and *Zaitsev's rule* applies. For example, menthyl acetate gives 35% of the Hofmann product and 65% of the Zaitsev, even although a *cis* β hydrogen is present on both sides and the statistical distribution is the other way. A similar result was found for the pyrolysis of menthyl chloride.[142]
4. There are also steric effects. In some cases the direction of elimination is determined by the need to minimize steric interactions in the transition state or to relieve steric interactions in the ground state.

17.E.iii. 1,4 Conjugate Eliminations[143]

1,4 eliminations of the type H—C—C=C—C—X → C=C—C=C are much rarer than conjugate additions (Chapter 15), but some examples are known.[144]

[138] Froemsdorf, D.H.; Collins, C.H.; Hammond, G.S.; DePuy, C.H. *J. Am. Chem. Soc.* ***1959***, *81*, 643; Haag, W.O.; Pines, H. *J. Org. Chem.* ***1959***, *24*, 877.
[139] DePuy, C.H.; King, R.W. *Chem. Rev.* ***1960***, *60*, 431, with tables showing product distributions.
[140] Bailey, W.J.; Baylouny, R.A. *J. Am. Chem. Soc.* ***1959***, *81*, 2126.
[141] Botteron D.G.; Shulman, G.P. *J. Org. Chem.* ***1962***, *27*, 2007.
[142] See Bamkole, T.; Maccoll, A. *J. Chem. Soc. B* ***1970***, 1159.
[143] Taylor, R. in Patai, S. *The Chemistry of Functional Groups*, Supplement B, pt. 2, Wiley, NY, ***1979***, pp. 885–890; Smith, G.G.; Mutter, L.; Todd, G.P. *J. Org. Chem.* ***1977***, *42*, 44; Chuchani, G.; Dominguez, R.M. *Int. J. Chem. Kinet.* ***1981***, *13*, 577; Hernández, A.; Chuchani, G. *Int. J. Chem. Kinet.* ***1983***, *15*, 205.
[144] See Ölwegård, M.; Ahlberg, P. *Acta Chem. Scand.* ***1990***, *44*, 642.

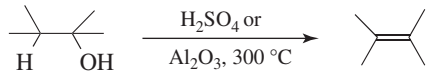
17.F. REACTIONS

17.F.i. Reactions in Which C=C and C≡C Bonds Are Formed

A. Reactions in Which Hydrogen Is Removed from One Side

In **17-1** to **17-5** the other leaving atom is oxygen. In **17-6** to **17-9**, it is nitrogen. For reactions in which hydrogen is removed from both sides, see **19-1** to **19-6**.

17-1 Dehydration of Alcohols



Dehydration of alcohols can be accomplished in several ways.[145] Both H_2SO_4 and H_3PO_4 are common reagents, but formation of an intermediate carbocation can lead to rearrangement products and to ether formation (**10-12**). If the alcohol is volatile, vapor-phase elimination over Al_2O_3 is an excellent method since side reactions are greatly reduced. This method has even been applied to such high molecular weight alcohols as dodecan-1-ol.[146] The presence of an electron-withdrawing group usually facilitates elimination of water, as in dehydration observed with the *aldol condensation* (**16-34**). Treating a 4-hydroxy lactam with DMAP and Boc anhydride leads to the conjugated lactam.[147] Elimination of serine derivatives to α-alkylidene amino acid derivatives was accomplished with $(EtO)_2POCl$.[148] The ease of dehydration increases with α branching, and tertiary alcohols are dehydrated so easily with only a trace of acid that it sometimes happens spontaneously. Dehydration is almost always spontaneous when the new double bond can be in conjugation with one already there.

Many other dehydrating agents[149] have been used on occasion: P_2O_5, I_2, PPh_3/I_2,[150] BF_3-etherate, DMSO, $KHSO_4$, anhydrous $CuSO_4$, and phthalic anhydride, among others. Secondary and tertiary alcohols can also be dehydrated, without rearrangement, simply by heating in HMPA at reflux,[151] or by mixing with Amberlyst-15.[152] With nearly all reagents, dehydration follows *Zaitsev's rule.* An exception involves the passage of hot alcohol vapors over thorium oxide at 350–450 °C, under which conditions *Hofmann's rule* is followed.[153]

[145] Mane, M.V.; Rizvi, M.A.; Vanka, K. *J. Org. Chem.* ***2015***, *80*, 2081.
[146] Spitzin, V.I.; Michailenko, I.E.; Pirogowa, G.N. *J. Prakt. Chem.* ***1964***, *[4] 25*, 160; Bertsch, H.; Greiner, A.; Kretzschmar, G.; Falk, F. *J. Prakt. Chem.* ***1964***, *[4] 25*, 184.
[147] Mattern, R.-H. *Tetrahedron Lett.* ***1996***, *37*, 291.
[148] Berti, F.; Ebert, C.; Gardossi, L. *Tetrahedron Lett.* ***1992***, *33*, 8145.
[149] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 291–294.
[150] Alvarez-Manzaneda, E.J.; Chahboun, R.; Torres, E.C.; Alvarez, E.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos, J. *Tetrahedron Lett.* ***2004***, *45*, 4453.
[151] See Lomas, J.S.; Sagatys, D.S.; Dubois, J.E. *Tetrahedron Lett.* ***1972***, 165.
[152] Frija, L.M.T.; Afonso, C.A.M. *Tetrahedron* ***2012***, *68*, 7414.
[153] Lundeen, A.J.; van Hoozer, R. *J. Org. Chem.* ***1967***, *32*, 3386. See also, Davis, B.H. *J. Org. Chem.* ***1982***, *47*, 900; Iimori, T.; Ohtsuka, Y.; Oishi, T. *Tetrahedron Lett.* ***1991***, *32*, 1209.

Alcohols were converted to the alkene via a dehydration protocol in which the alcohol is first converted to the alkoxide with NaH, and subsequent reaction with phenyl isothiocyanate gave the sodium carboimidothioate salt, which was heated overnight at 200 °C to give the alkene.[154] The 1,2,3-traizole-promoted, iron-catalyzed dehydration of propargyl alcohols gave conjugated enynes.[155] Simple aliphatic alcohols were dehydrated to the corresponding alkene by heating on mesoporous silica MCM-41 catalyst, with high reaction rates.[156] Heating over Sc_2O_3 has also been used for the dehydration of diols in the allylic alcohols.[157]

Transition metals can induce the dehydration of certain alcohols. β-Hydroxy ketones are converted to conjugated ketones by treatment with $CeCl_3$ and NaI.[158] A δ-hydroxy-α,β-unsaturated aldehyde was converted to a dienyl aldehyde with a Hf catalyst.[159] β-Hydroxy esters are converted to conjugated esters when treated with 2 molar equivalents of SmI_2.[160] In another variation of the dehydration reaction, vicinal bromohydrins are converted to alkenes upon treatment with In, $InCl_3$, and a Pd catalyst.[161] Chlorohydrins react similarly when treated first with Sm and then diiodomethane.[162]

When proton acids catalyze alcohol dehydration, the mechanism is E1.[163] The principal process involves conversion of ROH to ROH_2^+ and cleavage of the latter to R^+ and H_2O, although with some acids a secondary process probably involves conversion of the alcohol to an inorganic ester followed by ionization.

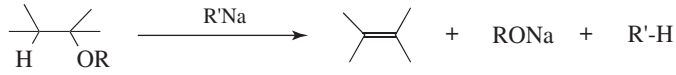
Note that these mechanisms are the reverse of those involved in the acid-catalyzed hydration of double bonds (**15-3**), in accord with the principle of microscopic reversibility. With anhydrides (e.g., P_2O_5, phthalic anhydride), as well as with some other reagents, such as HMPA,[164] it is likely that an ester is formed, and the leaving group is the conjugate base of the corresponding acid. In these cases, the mechanism can be E1 or E2. The mechanism with Al_2O_3 and other solid catalysts has been studied extensively, but is poorly understood.[165]

The dehydration of *vic*-diols[166] gives either conjugated dienes or they lose only 1 equivalent of water to give an aldehyde or ketone. Dienes can be prepared, however, by heating alkynyl alcohols with triphenylphosphine.[167]

[154] Majetich, G.; Irvin, T.C.; Thompson, S.B. *Tetrahedron Lett.* ***2015***, *56*, 3326.
[155] Yan, W.; Ye, X.; Akhmedov, N.G.; Petersen, J.L.; Shi, X. *Org. Lett.* ***2012***, *14*, 2358.
[156] Haishi, T.; Kasai, K.; Iwamoto, M. *Chem. Lett.* ***2011***, *40*, 614.
[157] Duan, H.; Yamada, Y.; Sato, S. *Chem. Lett.* ***2014***, *43*, 1773.
[158] Bartoli, G.; Bellucci, M.C.; Petrini, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Org. Lett.* ***2000***, *2*, 1791.
[159] Saito, S.; Nagahara, T.; Yamamoto, H. *Synlett* ***2001***, 1690.
[160] Concellón, J.M.; Pérez-Andrés, J.A.; Rodríguez-Solla, H. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2773.
[161] Cho, S.; Kang, S.; Keum, G.; Kang, S.B.; Han, S.-Y.; Kim, Y. *J. Org. Chem.* ***2003***, *68*, 180.
[162] Concellón, J.M.; Rodríguez-Solla, H.; Huerta, M.; Pérez-Andrés, J.A. *Eur. J. Org. Chem.* ***2002***, 1839.
[163] Vinnik, M.I.; Obraztsov, P.A. *Russ. Chem. Rev.* ***1990***, *59*, 63; Saunders Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 221–274, 317–331.
[164] See Kawanisi, M.; Arimatsu, S.; Yamaguchi, R.; Kimoto, K. *Chem. Lett.* ***1972***, 881.
[165] Beránek, L.; Kraus, M. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 20, Elsevier, NY, ***1978***, pp. 274–295; Noller, H.; Andréu, P.; Hunger, M. *Angew. Chem. Int. Ed.* ***1971***, *10*, 172; Berteau, P.; Ruwet, M.; Delmon, B. *Bull. Soc. Chim. Belg.* ***1985***, *94*, 859.
[166] See Bartók, M.; Molnár, A. in Patai, S. *The Chemistry of Functional Groups*, Supplement E, pt. 2, Wiley, NY, ***1980***, pp. 721–760.
[167] Guo, C.; Lu, X. *J. Chem. Soc., Chem. Commun.* ***1993***, 394.

OS **I**, 15, 183, 226, 280, 345, 430, 473, 475; **II**, 12, 368, 408, 606; **III**, 22, 204, 237, 312, 313, 353, 560, 729, 786; **IV**, 130, 444, 771; **V**, 294; **VI**, 307, 901; **VII**, 210, 241, 363, 368, 396; **VIII**, 210, 444. See also, OS **VII**, 63; **VIII**, 306, 474.

17-2 Cleavage of Ethers to Alkenes



Alkenes can be formed by the treatment of ethers with very strong bases, such as alkylsodium or alkyllithium[168] compounds, sodium amide,[169] or LDA,[170] although there are side reactions with many of these reagents. The reaction is aided by electron-withdrawing groups in the β position, and, for example, $EtOCH_2CH(COOEt)_2$ can be converted to $CH_2{=}C(COOEt)_2$ without any base at all, simply by heating.[171] *tert*-Butyl ethers are cleaved more easily than others. Several mechanisms are possible. In many cases, the mechanism is probably E1cB or on the E1cB side of the mechanistic spectrum,[172] since the base required is so strong, but it has been shown (by the use of $PhCD_2OEt$) that $PhCH_2OEt$ reacts by the five-membered E^i mechanism.[173] Propargylic benzyl ethers are converted to conjugated dienes by heating with a Ru catalyst.[174]

Cyclic ethers, such as THF, react slowly with organolithium reagents with cleavage that produces a C=C unit.[175] Fragmentation of 2,5-dihydrofuran with ethylmagnesium chloride and a chiral Zr catalyst leads to a chiral, homoallylic alcohol.[176] Acetals can be converted to enol ethers in this manner. When ketals react with 2 molar equivalents of triisobutylaluminum, the product is a vinyl ether.[177] This transformation can also be done at room temperature by treatment with trimethylsilyl triflate and a tertiary amine[178] or with Me_3SiI in the presence of hexamethyldisilazane.[179]

Conversion of a carbonyl compound to an enol phosphate[180] or triflate[181] allows a subsequent elimination reaction to give an alkyne. Conversion of an aldehyde to the vinyl nonaflate (nonafluorobutane-1-sulfonyl) was followed by reaction with a phosphazene base to give the alkyne.[182]

OS **IV**, 298, 404; **V**, 25, 642, 859, 1145; **VI**, 491, 564, 584, 606, 683, 948; **VIII**, 444.

[168] Tayama, E.; Sugai, S. *Synlett* ***2006***, 849.
[169] For a review, see Maercker, A. *Angew. Chem. Int. Ed.* ***1987***, *26*, 972.
[170] Fleming, F.F.; Wang, Q.; Steward, O.W. *J. Org. Chem.* ***2001***, *66*, 2171.
[171] Feely, W.; Boekelheide, V. *Org Synth.* ***IV***, 298.
[172] In the gas phase, see DePuy, C.H.; Bierbaum, V.M. *J. Am. Chem. Soc.* ***1981***, *103*, 5034.
[173] Letsinger, R.L.; Pollart, D.F. *J. Am. Chem. Soc.* ***1956***, *78*, 6079.
[174] Yeh, K.-L.; Liu, B.; Lo, C.-Y.; Huang, H.-L.; Liu, R.-S. *J. Am. Chem. Soc.* ***2002***, *124*, 6510.
[175] See Cohen, T.; Stokes, S. *Tetrahedron Lett.* ***1993***, *34*, 8023.
[176] Morken, J.P.; Didiuk, M.T.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1993***, *115*, 6997.
[177] Cabrera, G.; Fiaschi, R.; Napolitano, E. *Tetrahedron Lett.* ***2001***, *42*, 5867.
[178] Gassman, P.G.; Burns, S.J. *J. Org. Chem.* ***1988***, *53*, 5574.
[179] Miller, R.D.; McKean, D.R. *Tetrahedron Lett.* ***1982***, *23*, 323. For another method, see Marsi, M.; Gladysz, J.A. *Organometallics* ***1982***, *1*, 1467.
[180] Negishi, E.; King, A.O.; Klima, W.L.; Patterson, W.; Silveira, A. *J. Org. Chem.* ***1980***, *45*, 2526.
[181] Clasby, M.C.; Craig, D. *Synlett* ***1992***, 825.
[182] Lyapkalo, I.M.; Vogel, M.A.K.; Boltukhina, E.V.; Vavřík, J. *Synlett* ***2009***, 55.

17-3 The Conversion of Epoxides and Episulfides to Alkenes

Epoxides can be converted to alkenes[183] by treatment with triphenylphosphine[184] or triethyl phosphite $P(OEt)_3$.[185] The first step of the mechanism is nucleophilic substitution (**10-34**) to give a betaine, and a four-center elimination gives the alkene. Since inversion accompanies the substitution, the overall elimination is *anti*, that is, if two groups are *cis* in the epoxide, they will be *trans* in the alkene. Alternatively, the epoxide can be treated with lithium diphenylphosphide Ph_2PLi, and the product is quaternized with methyl iodide.[186] Alkenes have also been obtained from epoxides by reaction with a large number of reagents,[187] among them Li in THF,[188] trimethylsilyl iodide,[189] and compounds of Sm,[190] Mo, In,[191] and the W reagents mentioned in **17-16**. Some of these methods give *syn* elimination. Sodium amalgam with a Co salen complex converted epoxides to alkenes.[192]

Epoxides can be converted to allylic alcohols[193] by treatment with several reagents, including *sec*-butyllithium,[194] and *i*-Pr_2NLi-*t*-BuOK (the *LIDAKOR reagent*).[195] These bases remove the proton from the adjacent carbon, leading to formation of a C=C unit and opening of the epoxide to give an alkoxide. Phenyllithium reacts with epoxides in the presence of lithium 2,2,6,6-tetramethylpiperidide (LTMP) to give a *trans* alkene.[196] Sulfur ylids such as $Me_2S{=}CH_2$ also convert epoxides to allylic alcohols.[197] α,β-Epoxy ketones are converted to conjugated ketones by treatment with NaI in acetone in the presence of Amberlyst 15,[198] or with 2.5 molar equivalents of SmI_2.[199] The deoxygenation of epoxides to the alkene was catalyzed by oxo-rhenium(V) and (VII) complexes.[200] A mixture of Sn/NaI was used to deoxygenate epoxides to give the alkene.[201] Alkenes were prepared via electrolysis of epoxides with a pair of zinc electrodes, in a mixture of saturated aqueous

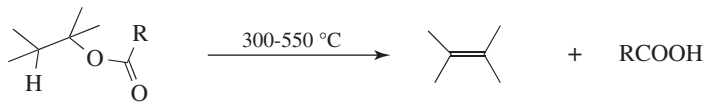
[183] For reviews, see Wong, H.N.C.; Fok, C.C.M.; Wong, T. *Heterocycles* ***1987***, *26*, 1345; Sonnet, P.E. *Tetrahedron* ***1980***, *36*, 557 (p. 576).
[184] Wittig, G.; Haag, W. *Chem. Ber.* ***1955***, *88*, 1654.
[185] Scott, C.B. *J. Org. Chem.* ***1957***, *22*, 1118.
[186] Vedejs, E.; Fuchs, P.L. *J. Am. Chem. Soc.* ***1971***, *93*, 4070; ***1973***, *95*, 822.
[187] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 272–277.
[188] Gurudutt, K.N.; Ravindranath, B. *Tetrahedron Lett.* ***1980***, *21*, 1173.
[189] Denis, J.N.; Magnane, R.; van Eenoo, M.; Krief, A. *Nouv. J. Chim.* ***1979***, *3*, 705. See Caputo, R.; Mangoni, L.; Neri, O.; Palumbo, G. *Tetrahedron Lett.* ***1981***, *22*, 3551.
[190] Matsukawa, M.; Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* ***1987***, 2101.
[191] Mahesh, M.; Murphy, J.A.; Wessel, H.P. *J. Org. Chem.* ***2005***, *70*, 4118.
[192] Isobe, H.; Branchaud, B.P. *Tetrahedron Lett.* ***1999***, *40*, 8747.
[193] Smith, J.G. *Synthesis* ***1984***, 629 (pp. 637–642); Crandall, J.K.; Apparu, M. *Org. React.* ***1983***, *29*, 345. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 231–233. See also, Okovytyy, S.; Gorb, L.; Leszczynski, J. *Tetrahedron* ***2001***, *57*, 1509.
[194] Doris, E.; Dechoux, L.; Mioskowski, C. *Tetrahedron Lett.* ***1994***, *35*, 7943.
[195] Thurner, A.; Faigl, F.; Töke, L.; Mordini, A.; Valacchi, M.; Reginato, G.; Czira, G. *Tetrahedron* ***2001***, *57*, 8173.
[196] Hodgson, D.M.; Fleming, M.J.; Stanway, S.J. *J. Org. Chem.* ***2007***, *72*, 4763.
[197] Alcaraz, L.; Cridland, A.; Kinchin, E. *Org. Lett.* ***2001***, *3*, 4051.
[198] Righi, G.; Bovicelli, P.; Sperandio, A. *Tetrahedron* ***2000***, *56*, 1733.
[199] Concellón, J.M.; Bardales, E. *J. Org. Chem.* ***2003***, *68*, 9492. In a similar manner, epoxy amides are converted to conjugated amides, see Concellón, J.M.; Bardales, E. *Eur. J. Org. Chem.* ***2004***, 1523.
[200] Sousa, S.C.A.; Fernandes, A.C. *Tetrahedron Lett.* ***2011***, *52*, 6960.
[201] Pathe, G.K.; Ahmed, N. *Synthesis* ***2015***, *47*, 3542.

NH_4Br and tetrahydrofuran.[202] The reaction of aliphatic epoxides with a catalytic amount of Re_2O_7 and triphenyl phosphite give the alkene with good stereoselectivity.[203] A 30 mol% solution of polyphosphoric acid (PPA) promoted the conversion of aliphatic and aromatic epoxides to alkenes.[204]

When an optically active reagent is used, optically active allylic alcohols can be produced from achiral epoxides.[205] Sparteine and *sec*-butyllithium generate a chiral base that leads to the formation of chiral allylic alcohols.[206] Chiral diamines react with organolithium reagents to produce chiral bases that convert epoxides to allylic alcohols with good enantioselectivity.[207] Chiral diamines with a mixture of LDA and DBU (**15-28**, **17-11**) give similar results.[208]

Episulfides[209] can be converted to alkenes.[210] However, in this case the elimination is *syn*, so the mechanism cannot be the same as that for conversion of epoxides. The phosphite attacks sulfur rather than carbon. Among other reagents that convert episulfides to alkenes are certain Rh complexes.[211] Episulfoxides can be converted to alkenes and sulfur monoxide simply by heating.[212]

17-4 Pyrolysis of Carboxylic Acids and Esters of Carboxylic Acids To Form Alkenes



Functional groups can be incorporated into a molecule that will facilitate *syn* elimination via intramolecular removal of a β hydrogen.[213] A simple example is an acetoxy group (—OCOMe), where the carbonyl oxygen of the ester functions as a tethered base.[214] The oxygen is a weak base and loss of the acetoxy group leads to loss of acetic acid. Such a *syn* elimination of acetic acid requires higher reaction temperatures, typically 300–550 °C. However, acetates are readily available by reaction of an alcohol with acetic anhydride or acetyl chloride and pyridine (or another base). The acetoxy unit at a tertiary carbon is usually eliminated in preference to an acetoxy at the secondary carbon. The reaction of SmI_2

[202] Huang, J.-M.; Lin, Z.-Q.; Chen, D.-S. *Org. Lett.* ***2012***, *14*, 22.
[203] Nakagiri, T.; Murai, M.; Takai, K. *Org. Lett.* ***2015***, *17*, 3346.
[204] Pathe, G.K; Ahmed, N. *Tetrahedron Lett.* ***2015***, *56*, 6202.
[205] Su, H.; Walder, L.; Zhang, Z.; Scheffold, R. *Helv. Chim. Acta* ***1988***, *71*, 1073, and references cited therein. See, Brookes, P.C.; Milne, D.J.; Murphy, P.J.; Spolaore, B. *Tetrahedron* ***2002***, *58*, 4675.
[206] Alexakis, A.; Vrancken, E.; Mangeney, P. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 3354.
[207] Equey, O.; Alexakis, A. *Tetrahedron: Asymmetry* ***2004***, *15*, 1069.
[208] Bertilsson, S.K.; Södergren, M.J.; Andersson, P.G. *J. Org. Chem.* ***2002***, *67*, 1567; Bertilsson, S.K.; Andersson, P.G. *Tetrahedron* ***2002***, *58*, 4665.
[209] See Sonnet, P.E. *Tetrahedron* ***1980***, *36*, 557 (see p. 587); Goodman, L.; Reist, E.J. in Kharasch, N.; Meyers, C.Y. *The Chemistry of Organic Sulfur Compounds*, Vol. 2, Pergamon, Elmsford, NY, ***1966***, pp. 93–113.
[210] Neureiter, N.P.; Bordwell, F.G. *J. Am. Chem. Soc.* ***1959***, *81*, 578.
[211] Calet, S.; Alper, H. *Tetrahedron Lett.* ***1986***, *27*, 3573.
[212] Aalbersberg, W.G.L.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* ***1977***, *99*, 2792.
[213] See DePuy, C.H.; King, R.W. *Chem. Rev.* ***1960***, *60*, 431 (pp. 432); Jenneskens, L.W.; Hoefs, C.A.M.; Wiersum, U.E. *J. Org. Chem.* ***1989***, *54*, 5811, and references cited therein.
[214] Alexander, E.R.; Mudrak, A. *J. Am. Chem. Soc.* ***1950***, *72*, 1810, 3194; Curtin, C.Y.; Kellom, D.B. *J. Am. Chem. Soc.* ***1953***, *75*, 6011.

and aromatic allylic benzoates gave the alkene, with high selectivity for the nonconjugated alkene.[215]

No solvent is required for the decarboxylation. Since rearrangement and other side reactions are few, the reaction is synthetically very useful and is often carried out as an indirect method of accomplishing **17-1**. The yields are excellent and the workup is easy. Many alkenes have been prepared in this manner. For longer carbon chains (greater than around C_{10}), pyrolysis of the alcohol in the presence of acetic anhydride is a better method.[216] Direct elimination of a carboxylic acid (decarboxylation) to an alkene has been accomplished by heating in the presence of Pd catalysts.[217] Allylic acetates give dienes when heated with certain Pd[218] or Mo[219] compounds.

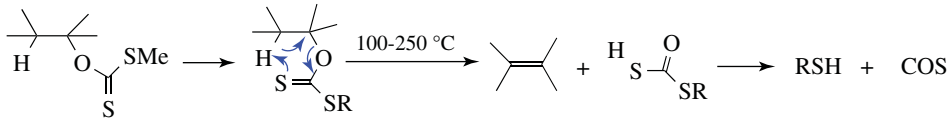
The mechanism is E^i (Sec. 17.E.i). Lactones can be pyrolyzed to give unsaturated acids, provided that the six-membered transition state required for E^i reactions is available (it is not for five- and six-membered lactones, but it is for larger rings[220]). Amides give a similar reaction, but require higher temperatures.

Carboxylic acids can be dehydrated by pyrolysis to give a ketene: $RCH_2CO_2H \rightarrow RCH{=}C{=}O$. Ketene itself is commercially prepared in this manner. Carboxylic acids have been converted to ketenes by treatment with certain reagents, including TsCl,[221] dicyclohexylcarbodiimide,[222] and 1-methyl-2-chloropyridinium iodide (*Mukaiyama's reagent*).[223] Analogously, amides can be dehydrated with P_2O_5, pyridine, and Al_2O_3 to give keteneimines.[224]

The dehydrosulfenylation of 2-arylsulfinyl esters to give the alkene followed a homolytic cleavage mechanism.[225]

OS **III**, 30; **IV**, 746; **V**, 235; **IX**, 293.

17-5 Decomposition of Other Esters: The Chugaev Reaction



Methyl xanthates are prepared by treatment of alcohols with NaOH and CS_2 to give RO–C(=S)–SNa, followed by treatment of this with iodomethane.[226] Pyrolysis of the

[215] Schaefer, S.L.; Roberts, C.L.; Volz, E.O.; Grasso, M.R.; O'Neil, G.W. *Tetrahedron Lett.* ***2013***, *54*, 6125.
[216] Aubrey, D.W.; Barnatt, A.; Gerrard, W. *Chem. Ind. (London)* ***1965***, 681.
[217] Gooßen, L.J.; Rodríguez, N. *Chem. Commun.* ***2004***, 724.
[218] Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 172–178. See Cheng, H.-Y.; Sun, C.-S.; Hou, D.-R. *J. Org. Chem.* ***2007***, *72*, 2674.
[219] Trost, B.M.; Lautens, M.; Peterson, B. *Tetrahedron Lett.* ***1983***, *24*, 4525.
[220] See Bailey, W.J.; Bird, C.N. *J. Org. Chem.* ***1977***, *42*, 3895.
[221] See Brady, W.T.; Marchand, A.P.; Giang, Y.F.; Wu, A. *J. Org. Chem.* ***1987***, *52*, 3457.
[222] Olah, G.A.; Wu, A.; Farooq, O. *Synthesis* ***1989***, 568.
[223] Brady, W.T.; Marchand, A.P.; Giang, Y.F.; Wu, A. *J. Org. Chem.* ***1987***, *52*, 3457; Funk, R.L.; Abelman, M.M.; Jellison, K.M. *Synlett* ***1989***, 36.
[224] Stevens, C.L.; Singhal, G.H. *J. Org. Chem.* ***1964***, *29*, 34.
[225] Latorre, A.; López, I.; Ramírez, V.; Rodríguez, S.; Izquierdo, J.; González, F.V.; Vicent, C. *J. Org. Chem.* ***2012***, *77*, 5191.
[226] See Nagle, A.S.; Salvataore, R.N.; Cross, R.M.; Kapxhiu, E.A.; Sahab, S.; Yoon, C.H.; Jung, K.W. *Tetrahedron Lett.* ***2003***, *44*, 5695.

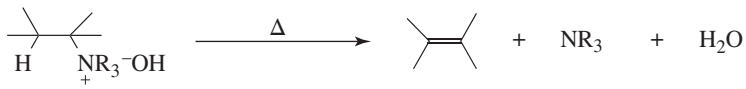
xanthate occurs via a *syn* elimination to give the alkene and RS(C=O)SH, which decomposes to O=C=S and the thiol. This reaction is called the *Chugaev reaction*.[227] The temperatures required with xanthates are lower than with ordinary esters, which is advantageous because possible isomerization of the resulting alkene is minimized. The mechanism is E^i, similar to that of **17-4**. For a time there was doubt as to which sulfur atom closed the ring, but now there is much evidence, including the study of ^{34}S and ^{13}C isotope effects, to show that it is the C=S sulfur.[228] In a structural variation of this reaction, heating a propargylic xanthate with 2,4,6-trimethylpyridinium trifluoromethyl sulfonate leads to formation of an alkene.[229]

OS **VII**, 139.

Several types of inorganic ester can be cleaved to alkenes by treatment with bases. Esters of sulfuric, sulfurous, and other acids undergo elimination in solution by E1 or E2 mechanisms, as do tosylates and other esters of sulfonic acids.[230] Esters of 2-pyridinesulfonic acid and 8-quinolinesulfonic acid gave alkenes in high yields simply on heating, without a solvent.[231] Phosphonate esters have been cleaved to alkenes by treatment with *Lawesson's reagent*[232] (see **16-10**).

OS, **VI**, 837; **VII**, 117.

17-6 Elimination of Quaternary Ammonium Hydroxides



Another example of *syn* elimination is the cleavage of quaternary ammonium hydroxides as the final step of the process known as *Hofmann exhaustive methylation* or *Hofmann degradation* or just *Hofmann elimination.*[233] In general, the less-substituted alkene is the major product. In the first step, a primary, secondary, or tertiary amine is treated with enough iodomethane to convert it to the quaternary ammonium iodide (**10-30**). In the second step, the iodide counterion is converted to the hydroxide counterion by treatment with silver oxide. In the cleavage step an aqueous or alcoholic solution of the ammonium hydroxide is distilled, often under reduced pressure. The decomposition generally takes place between 100 and 200 °C. Alternatively, the solution can be concentrated to a syrup by distillation or freeze-drying.[234] When the syrup is heated at low pressures, the cleavage reaction takes

[227] DePuy, C.H.; King, R.W. *Chem. Rev.* ***1960***, *60*, 431 (see p. 444); Nace, H.R. *Org. React.* ***1962***, *12*, 57.
[228] Bader, R.F.W.; Bourns, A.N. *Can. J. Chem.* ***1961***, *39*, 348.
[229] Fauré-Tromeur, M.; Zard, S.Z. *Tetrahedron Lett.* ***1999***, *40*, 1305.
[230] For a list of reagents used for sulfonate cleavages, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 294–295.
[231] Corey, E.J.; Posner, G.H.; Atkinson, R.F.; Wingard, A.K.; Halloran, D.J.; Radzik, D.M.; Nash, J.J. *J. Org. Chem.* ***1989***, *54*, 389.
[232] Shimagaki, M.; Fujieda, Y.; Kimura, T.; Nakata, T. *Tetrahedron Lett.* ***1995***, *36*, 719.
[233] Bentley, K.W. in Bentley, K.W.; Kirby, G.W. *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), pt. 2, Wiley, NY, ***1973***, pp. 255–289; White, E.H.; Woodcock, D.J. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 409–416; Cope, A.C.; Trumbull, E.R. *Org. React.* ***1960***, *11*, 317.
[234] Archer, D.A. *J. Chem. Soc. C* ***1971***, 1327.

place at lower temperatures than are required for the reaction in the ordinary solution, probably because the base (HO^- or RO^-) is less solvated.[235]

A side reaction involving nucleophilic substitution to give an alcohol ($R_4N^+ \ ^-OH \rightarrow ROH + R_3N$) often accompanies the normal elimination reaction,[236] but seldom causes trouble. However, when none of the four groups on the nitrogen has a β hydrogen, substitution is the only reaction possible. On heating $Me_4N^+ \ ^-OH$ in water, methanol is obtained, although without a solvent the product is not methanol, but dimethyl ether.[237]

The mechanism of elimination is usually E2 in protic solvents. *Hofmann's rule* is generally obeyed by acyclic substrates and *Zaitsev's rule* by cyclohexyl substrates (Sec. 17.B, category 4). In certain cases, where the molecule is highly hindered or if the ammonium hydroxide is heated without solvent (neat), a five-membered E^i mechanism, that is, the hydroxide in these cases, removes one of the methyl hydrogen atoms, which removes a proton from the less-substituted β carbon atom to give the less-substituted alkene with loss of the amine. It is also possible that the hydroxide (rather than the N-ylid) removes the β hydrogen atom via an eclipsed rotamer in which the hydroxide is tethered to the ammonium unit and a *syn* transition state is lower in energy.

The obvious way to distinguish between this mechanism and the ordinary E2 mechanism is by the use of deuterium labeling. For example, if the reaction is carried out on a quaternary hydroxide deuterated on the β carbon ($R_2CDCH_2NMe_3^+ \ ^-OH$), the fate of the deuterium indicates the mechanism. If the E2 mechanism were in operation, the trimethylamine produced would contain no deuterium (which would be found only in the water). But if the mechanism is E^i, the amine would contain deuterium. In the case of the highly hindered compound $(Me_3C)_2CDCH_2NMe_3^+ \ ^-OH$, the deuterium did appear in the amine, demonstrating an E^i mechanism for this case.[238] With simpler compounds, the mechanism is E2, since here the amine was deuterium free.[239]

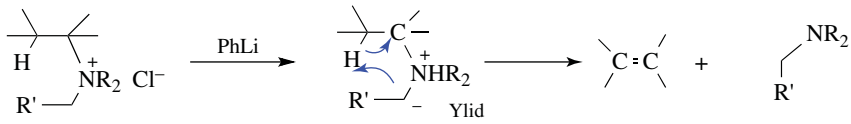
When the nitrogen bears more than one group possessing a β hydrogen, which group cleaves? The *Hofmann rule* says that *within* a group the hydrogen on the least alkylated carbon cleaves. This tendency is also carried over to the choice of which group cleaves: thus ethyl with three β hydrogen atoms cleaves more readily than any longer *n*-alkyl group, all of which have two β hydrogen atoms. "The β hydrogen is removed most readily if it is located on a methyl group, next from RCH_2, and least readily from R_2CH."[240] In fact, the *Hofmann rule* as first stated[241] in 1851 applied only to which group cleaved, not to the orientation within a group; the latter could not have been specified in 1851, since the structural theory of organic compounds was not formulated until 1857–1860. Of course, the *Hofmann rule* (applied to which group cleaves *or* to orientation within a group) is superseded by conjugation possibilities. Thus $PhCH_2CH_2N^+Me_2Et \ ^-OH$ gives mostly styrene instead of ethylene.

Triple bonds have been prepared by pyrolysis of 1,2-bis(ammonium) salts.[242]

OS **IV**, 980; **V**, 315, 608; **VI**, 552. Also see, OS **V**, 621, 883; **VI**, 75.

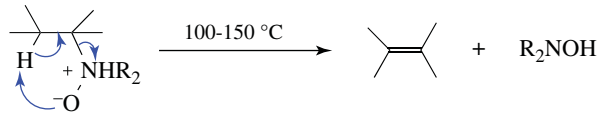
[235] Saunders Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 4–5.
[236] Baumgarten, R.J. *J. Chem. Educ.* ***1968***, *45*, 122.
[237] See Musker, W.K.; Stevens, R.R. *J. Am. Chem. Soc.* ***1968***, *90*, 3515.
[238] Cope, A.C.; Mehta, A.S. *J. Am. Chem. Soc.* ***1963***, *85*, 1949. See also, Baldwin, M.A.; Banthorpe, D.V.; Loudon, A.G.; Waller, F.D. *J. Chem. Soc. B* ***1967***, 509.
[239] Cope, A.C.; LeBel, N.A.; Moore, P.T.; Moore, W.R. *J. Am. Chem. Soc.* ***1961***, *83*, 3861.
[240] Cope, A.C.; Trumbull, E.R. *Org. React.* ***1960***, *11*, 317 (see p. 348).
[241] Hofmann, A.W. *Liebigs Ann. Chem.* ***1851***, *78*, 253.
[242] See Franke, W.; Ziegenbein, W.; Meister, H. *Angew. Chem.* ***1960***, *72*, 391 (see pp. 397–398).

When quaternary ammonium halides are treated with strong bases (e.g., PhLi, KNH_2 in liquid NH_3[243]), an elimination can occur that gives an alkene, although not by the mechanism discussed above. This reaction is done on the quaternary ammonium halide, so that it is not necessary to convert this to the hydroxide. The mechanism is E^i via ylid formation and subsequent fragmentation.



An α′ hydrogen is obviously necessary in order for the ylid to be formed. This type of mechanism is called α′,β elimination, since a β hydrogen is removed by the α′ carbon of the ylid. The mechanism has been confirmed by labeling experiments similar to those described above,[244] and by isolation of the intermediate ylids.[245] An important synthetic difference between this base-induced elimination via an ylid and other base-induced eliminations is that *syn* elimination is observed here, so products of opposite configuration are formed when the alkene exhibits *cis-trans* isomerism.

17-7 Cleavage of Amine Oxides



Cleavage of amine oxides to produce an alkene and a hydroxylamine is called the *Cope reaction* or *Cope elimination*[246] (not to be confused with the Cope *rearrangement*, **18-32**).[247] The reaction is usually performed with a mixture of amine and oxidizing agent (see **19-28**) without isolation of the amine oxide. Side reactions are few because of the mild conditions, and the alkenes do not usually rearrange. The reaction is thus very useful for the preparation of many alkenes. A limitation is that it does not open six-membered rings containing nitrogen, although it does open rings of 5 and 7–10 members.[248] Rates of the reaction increase with increasing size of α and β substituents.[249] The reaction can be carried out at room temperature in dry Me_2SO or THF.[250] The influence of solvent effects has been examined.[251] The elimination is a stereoselective *syn* process,[252] and the five-membered E^i mechanism operates. Almost all evidence indicates that the transition state must be planar. Deviations from planarity are not found here, and indeed this is why six-membered

[243] See Bach, R.D.; Bair, K.W.; Andrzejewski, D. *J. Chem. Soc., Chem. Commun.* ***1974***, 819.
[244] Bach, R.D.; Knight, J.W. *Tetrahedron Lett.* ***1979***, 3815.
[245] Wittig, G.; Burger, T.F. *Liebigs Ann. Chem.* ***1960***, *632*, 85.
[246] Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 131–132.
[247] See Cope, A.C.; Trumbull, E.R. *Org. React.* ***1960***, *11*, 317 (see p. 361); DePuy, C.H.; King, R.W. *Chem. Rev.* ***1960***, *60*, 431 (see pp. 448–451).
[248] See Cope, A.C.; Ciganek, E.; Howell, C.F.; Schweizer, E.E. *J. Am. Chem. Soc.* ***1960***, *82*, 4663.
[249] Závada, J.; Pánková, M.; Svoboda, M. *Collect. Czech. Chem. Commun.* ***1973***, *38*, 2102.
[250] Cram, D.J.; Sahyun, M.R.V.; Knox, G.R. *J. Am. Chem. Soc.* ***1962***, *84*, 1734.
[251] Acevedo, O.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***2006***, *128*, 6141.
[252] See, for example, Bach, R.D.; Andrzejewski, D.; Dusold, L.R. *J. Org. Chem.* ***1973***, *38*, 1742.

heterocyclic nitrogen compounds do not react. Because of the stereoselectivity of this reaction and the lack of rearrangement of the products, it is useful for the formation of *trans* cycloalkenes (eight-membered and higher). A polymer-bound Cope elimination reaction has been reported.[253]

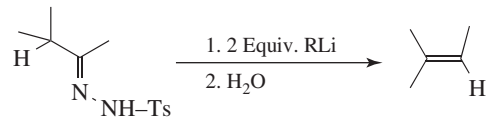
The Ir-catalyzed asymmetric allylation of imines gave 1,4-disubstituted homoallylic amines via an intermolecular regioselective allylation of 2-azaallyl anions and a subsequent 2-aza-Cope rearrangement.[254] The reaction of *N*-oxoammonium salts within the presence of DBU cycloalkenes followed by Cope elimination gave cycloalkadienes.[255] A reverse Cope elimination of hydroxylamines and alkenes or alkynes has been studied.[256]

OS **IV**, 612.

17-8 Pyrolysis of Keto Ylids

Phosphorus ylids are quite common (see **16-44**) and keto-phosphorus ylids [$RCOCH{=}PPh_3$] are also known. When these compounds are heated (flash vacuum pyrolysis, FVP) to > 500 °C, alkynes are formed. Simple alkynes[257] can be formed as well as keto-alkynes[258] and enynes.[259] Rearrangement from ylids derived from tertiary amines and α-diazo ketones is also known.[260]

17-9 Decomposition of Toluene-*p*-sulfonylhydrazones

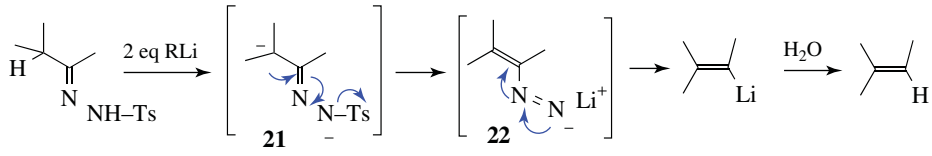


Treatment of the tosylhydrazone of an aldehyde or a ketone with a strong base leads to the formation of an alkene, the reaction being formally an elimination accompanied by a hydrogen shift.[261] The reaction (called the *Shapiro reaction*) has been applied to tosylhydrazones[262] of many aldehydes and ketones. The most useful synthetic method involves

[253] Sammelson, R.E.; Kurth, M.J. *Tetrahedron Lett.* ***2001***, *42*, 3419.
[254] Liu, J.; Cao, C.-G.; Sun, H.-B.; Zhang, X.; Niu, D. *J. Am. Chem. Soc.* ***2016***, *138*, 13103.
[255] Nagasawa, S.; Sasano, Y.; Iwabuchi, Y. *Angew. Chem. Int. Ed.* ***2016***, *55*, 13189.
[256] Krenske, E.H.; Davison, E.C.; Forbes, I.T.; Warner, J.A.; Smith, A.L.; Holmes, A.B.; Houk, K.N. *J. Am. Chem. Soc.* ***2012***, *134*, 2434.
[257] Aitken, R.A.; Atherton, J.I. *J. Chem. Soc., Perkin Trans. 1* ***1994***, 1281.
[258] Aitken, R.A.; Hérion, H.; Janosi, A.; Karodia, N.; Raut, S.V.; Seth, S.; Shannon, I.J.; Smith, F.C. *J. Chem. Soc., Perkin Trans. 1* ***1994***, 2467.
[259] Aitken, R.A.; Boeters, C.; Morrison, J.J. *J. Chem. Soc., Perkin Trans. 1* ***1994***, 2473.
[260] DelZotto, A.; Baratta, W.; Miani, F.; Verardo, G.; Rigo, P. *Eur. J. Org. Chem.* ***2000***, 3731.
[261] See Adlington, R.M.; Barrett, A.G.M. *Acc. Chem. Res.* ***1983***, *16*, 55; Shapiro, R.H. *Org. React.* ***1976***, *23*, 405.
[262] See Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem. Int. Ed.* ***2007***, *46*, 5587.

treatment of the substrate with at least 2 molar equivalents of an organolithium compound[263] (usually MeLi) in ether, hexane, or tetramethylenediamine.[264] This procedure gives good yields of alkenes without side reactions and, where a choice is possible, predominantly gives the less highly substituted alkene. Tosylhydrazones of α,β-unsaturated ketones give conjugated dienes.[265] A modified Shapiro reaction was reported that used bis(mesitoyl)magnesium as the base.[266]

The mechanism[267] has been formulated as that shown.

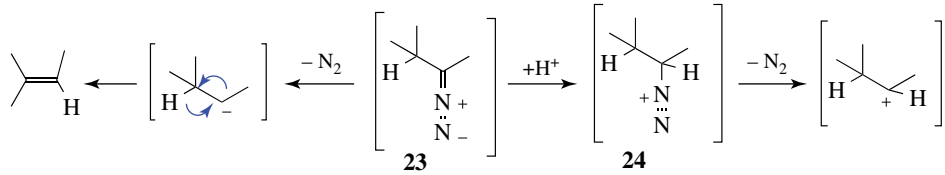


Evidence for this mechanism is: (i) 2 molar equivalents of RLi are required; (ii) the hydrogen in the product comes from the water and not from the adjacent carbon, as shown by deuterium labeling;[268] and (iii) the intermediates **21** and **22** have been trapped, along with the vinyllithium product.[269] This reaction, when performed in tetramethylenediamine, can be a synthetically useful method[270] of generating vinylic lithium compounds, which can be trapped by various electrophiles[271] such as D_2O (to give deuterated alkenes), CO_2 (to give α,β-unsaturated carboxylic acids, **16-30**), or DMF (to give α,β-unsaturated aldehydes, **16-29**). Treatment of *N*-aziridino hydrazones with LDA leads to alkenes with high *cis* selectivity.[272]

The reaction also takes place with other bases (e.g., NaH, LiH,[273] Na in ethylene glycol, $NaNH_2$) or with smaller amounts of RLi, but in these cases side reactions are common and the orientation of the double bond is in the other direction (to give the more highly substituted alkene). The reaction with Na in ethylene glycol is called the *Bamford-Stevens reaction*.[274] For these reactions two mechanisms are possible: a carbenoid mechanism and a carbocation mechanism.[275] The side reactions found are those expected of carbenes and carbocations. In general, the carbocation mechanism is chiefly found in protic solvents and the carbenoid mechanism in aprotic solvents. Both routes involve formation of a diazo compound (**23**), which is formed by base-induced deprotonation of the tosyl hydrazone to give an anion and loss of the tosyl group gives **23**. In fact, this reaction has been

[263] Shapiro, R.H. *Tetrahedron Lett.* ***1968***, 345; Meinwald, J.; Uno, F. *J. Am. Chem. Soc.* ***1968***, *90*, 800.
[264] Stemke, J.E.; Bond, F.T. *Tetrahedron Lett.* ***1975***, 1815.
[265] See Dauben, W.G.; Rivers, G.T.; Zimmerman, W.T. *J. Am. Chem. Soc.* ***1977***, *99*, 3414.
[266] Kerr, W.J.; Morrison, A.J.; Pazicky, M.; Weber, T. *Org. Lett.* ***2012***, *14*, 2250.
[267] For a review of the mechanism, see Casanova, J.; Waegell, B. *Bull. Soc. Chim. Fr.* ***1975***, 922.
[268] Ref. 263; Shapiro, R.H.; Hornaman, E.C. *J. Org. Chem.* ***1974***, *39*, 2302.
[269] Lipton, M.F.; Shapiro, R.H. *J. Org. Chem.* ***1978***, *43*, 1409.
[270] See Traas, P.C.; Boelens, H.; Takken, H.J. *Tetrahedron Lett.* ***1976***, 2287; Stemke, J.E.; Chamberlin, A.R.; Bond, F.T. *Tetrahedron Lett.* ***1976***, 2947.
[271] For a review, see Chamberlin, A.R.; Bloom, S.H. *Org. React.* ***1990***, *39*, 1.
[272] Maruoka, K.; Oishi, M.; Yamamoto, H. *J. Am. Chem. Soc.* ***1996***, *118*, 2289.
[273] Biellmann, J.F.; Pète, J. *Bull. Soc. Chim. Fr.* ***1967***, 675.
[274] Bamford, W.R.; Stevens, R.R. *J. Chem. Soc.* ***1952***, 4735. For a tandem *Bamford-Stevens-Claisen rearrangement*, see May, J.A.; Stoltz, B.M. *J. Am. Chem. Soc.* ***2002***, *124*, 12426.
[275] See Nickon, A.; Werstiuk, N.H. *J. Am. Chem. Soc.* ***1972***, *94*, 7081.

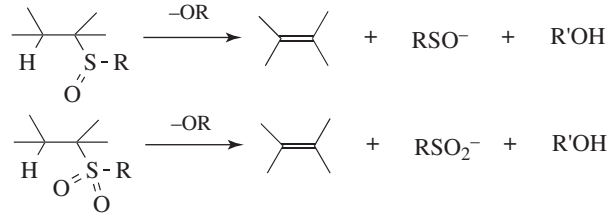
used as a synthetic method for the preparation of diazo compounds.[276] In the absence of protic solvents, **23** loses N_2 and hydrogen migrates to give the alkene product. The migration of hydrogen may immediately follow, or be simultaneous with, the loss of N_2. In a protic solvent, **23** becomes protonated to give the diazonium ion **24**, which loses N_2 to give the corresponding carbocation, that may then undergo elimination or give other reactions characteristic of carbocations.



A diazo compound is an intermediate in the formation of alkenes by treatment of *N*-nitrosoamides with a Rh catalyst.[277]

OS **VI**, 172; **VII**, 77; **IX**, 147. For the preparation of a diazo compound, see OS **VII**, 438.

17-10 Cleavage of Sulfoxides, Selenoxides, and Sulfones



Sulfonium compounds (—C—$^+SR_2$) undergo elimination similar to that of their ammonium counterparts (**17-6**) in scope and mechanism but this reaction is not of great synthetic importance and proceeds by *syn* elimination[278] to give the less-substituted alkene.

Sulfones and sulfoxides[279] with a β hydrogen, on the other hand, undergo elimination on treatment with an alkoxide or, for sulfones,[280] even with hydroxide.[281] Sulfones also eliminate in the presence of an organolithium reagent and a Pd catalyst.[282] Mechanistically, these reactions belong on the E1-E2-E1cB spectrum.[283] Although the leaving groups are uncharged, the orientation follows *Hofmann's rule*, not *Zaitsev's*. Sulfoxides (but not sulfones) also undergo elimination upon pyrolysis at ~80 °C in a manner analogous to

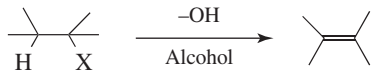
[276] See Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 257–295. For an improved procedure, see Wulfman, D.S.; Yousefian, S.; White, J.M. *Synth. Commun.* ***1988***, *18*, 2349.
[277] Godfrey, A.G.; Ganem, B. *J. Am. Chem. Soc.* ***1990***, *112*, 3717.
[278] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 129–131.
[279] See Cubbage, J.W.; Guo, Y.; McCulla, R.D.; Jenks, W.S. *J. Org. Chem.* ***2001***, *66*, 8722; Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 134–136.
[280] See Yoshida, T.; Saito, S. *Chem. Lett.* ***1982***, 165.
[281] Hofmann, J.E.; Wallace, T.J.; Argabright, P.A.; Schriesheim, A. *Chem. Ind. (London)* ***1963***, 1234.
[282] Gai, Y.; Jin, L.; Julia, M.; Verpeaux, J.-N. *J. Chem. Soc., Chem. Commun.* ***1993***, 1625.
[283] Hofmann, J.E.; Wallace, T.L.; Schriesheim, A. *J. Am. Chem. Soc.* ***1964***, *86*, 1561.

17-7. The mechanism is also analogous, being the five-membered E^i mechanism with *syn* elimination.[284]

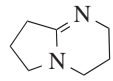
Selenoxides[285] and sulfinate esters $R_2CH—CHR—SO—OMe$[286] also undergo elimination by the E^i mechanism, and the selenoxide reaction takes place at room temperature. The reaction with selenoxides has been extended to the formation of triple bonds.[287] Both α-keto selenoxides[288] and α-keto sulfoxides[289] have been used in a method for the conversion of ketones, aldehydes, and carboxylic esters to their α,β-unsaturated derivatives. Allylic sulfoxides undergo 1,4 elimination to give dienes.[290]

OS **VI**, 23, 737; **VIII**, 543; **IX**, 63.

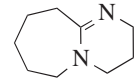
17-11 Dehydrohalogenation of Alkyl Halides



The elimination of HX from an alkyl halide is a very general reaction and can be accomplished with chlorides, fluorides, bromides, and iodides, usually by an E2 mechanism.[291] In other words, the more-substituted alkene is the major product. Hot alcoholic KOH is the most frequently used base, although stronger bases[292] (^-OR, $^-NH_2$, etc.) or weaker ones (e.g., amines) are used when feasible.[293] The bicyclic amidines 1,5-diazabicyclo[3.4.0]non-5-ene (DBN)[294] and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[295] are good reagents for difficult cases[296] and can convert primary halides to the corresponding alkene.



DBN



DBU

[284] Schmitz, C.; Harvey, J.N.; Viehe, H.G. *Bull. Soc. Chim. Belg.* ***1994***, *103*, 105.

[285] Back, T.G. in Patai, S. *The Chemistry of Organic Selenium and Telurium Compounds*, Vol. 2, Wiley, NY, ***1987***, pp. 91–213 (pp. 95–109); Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon, Elmsford, NY, ***1986***, pp. 132–143; Reich, H.J. *Acc. Chem. Res.* ***1979***, *12*, 22. See Liotta, D. *Organoselenium Chemistry*, Wiley, NY, ***1987***; Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 134–136.

[286] Jones, D.N.; Higgins, W. *J. Chem. Soc. C* ***1970***, 81.

[287] Reich, H.J.; Willis Jr., W.W. *J. Am. Chem. Soc.* ***1980***, *102*, 5967.

[288] Reich, H.J.; Renga, J.M.; Reich, I.L. *J. Am. Chem. Soc.* ***1975***, *97*, 5434 and references cited therein; Crich, D.; Barba, G.R. *Org. Lett.* ***2000***, *2*, 989. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 287–290.

[289] For a review of this and related methods, see Trost, B.M. *Acc. Chem. Res.* ***1978***, *11*, 453.

[290] de Groot, A.; Jansen, B.J.M.; Reuvers, J.T.A.; Tedjo, E.M. *Tetrahedron Lett.* ***1981***, *22*, 4137.

[291] See Baciocchi, E. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, Supplement D, pt. 2, Wiley, NY, ***1983***, pp. 1173–1227.

[292] See Anton, D.R.; Crabtree, R.H. *Tetrahedron Lett.* ***1983***, *24*, 2449.

[293] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 256–258.

[294] Vogel, E.; Klärner, F. *Angew. Chem. Int. Ed.* ***1968***, *7*, 374.

[295] Oediger, H.; Möller, F. *Angew. Chem. Int. Ed.* ***1967***, *6*, 76; Wolkoff, P. *J. Org. Chem.* ***1982***, *47*, 1944.

[296] See Oediger, H.; Möller, F.; Eiter, K. *Synthesis* ***1972***, 591.

Solvation by HMPA promotes LDA-mediated dehydrobromination.[297] An ionic liquid-dependent mechanism has been examined.[298] The decomposition kinetics of ethyl halides, phenethyl halides, and methoxyphenethyl halides were investigated using high level computational chemistry methods.[299]

Dehydrohalogenation with the nonionic base $(Me_2N)_3P{=}N{-}P(NMe_3)_2{=}NMe$ is even faster.[300] A Co catalyst with dimethylphenylsilylmethylmagnesium chloride leads to the formation of terminal alkenes from secondary alkyl bromides.[301] Phase-transfer catalysis has been used with hydroxide as base.[302] As previously mentioned (Sec. 17.A.v), certain weak bases in dipolar aprotic solvents are effective reagents for dehydrohalogenation. Among those most often used for synthetic purposes are LiCl or $LiBr/LiCO_3$ in DMF.[303] Dehydrohalogenation occurs by simply heating the alkyl halide in HMPA with no other reagent present.[304] As in nucleophilic substitution (Sec. 10.G.iii), the order of leaving group reactivity is I > Br > Cl > F.[305] Tertiary halides undergo elimination most easily. Eliminations of chlorides, bromides, and iodides follow *Zaitsev's rule,* except for a few cases where steric effects are important (for an example, see Sec. 17.B, category 4). Elimination of fluorides follow *Hofmann's rule* (Sec. 17.B, category 4).

Mechanistic studies have been carried out for the Pd-catalyzed base-induced dehydrohalogenation of primary allyl bromides to terminal alkenes.[306] The In- and Zn-mediated dehalogenation reaction of 1-bromo-2-iodo alkenes in an aqueous solvent gave allenes.[307] The Cu-catalyzed enantioselective reaction of propargylic dichlorides in the presence of a Grignard reagent gave axially chiral chloroallenes.[308] The elimination rate of base-induced alkyl iodides, including primary, secondary, and tertiary iodides in water, was enhanced with irradiation by ultraviolet (UV) light.[309] The reaction of *vic*-dibromides containing α-bromocarbonyl or α-bromoaromatic moieties with *o*- and *m*-anisidines gave the (*E*) alkene.[310] Heating 1,1-dibromo-1-alkenes with Cs_2CO_3 in DMSO gave the corresponding terminal alkyne.[311] The phase-transfer catalyzed synthesis of terminal alkynes from the corresponding vicinal dibromo compounds used anhydrous potassium phosphate as the base in aqueous PEG-900.[312]

[297] Clayden, J. *Organolithiums: Selectivity for Synthesis*, Pergamon, New York, ***2002***; for a mechanistic evaluation and an analysis of the influence of HMPA, see Ma, Y.; Ramirez, A.; Singh, K.J.; Keresztes, I.; Collum, D.B. *J. Am. Chem. Soc.* ***2006***, *128*, 15399.

[298] Allen, C.; Sambasivarao, S.V.; Acevedo, O. *J. Am. Chem. Soc.* ***2013***, *135*, 1065.

[299] Ahubelem, N.; Altarawneh, M.; Dlugogorski, B.Z. *Tetrahedron Lett.* ***2014***, *55*, 4860.

[300] Schwesinger, R.; Schlemper, H. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1167.

[301] Kobayashi, T.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* ***2008***, *130*, 11276.

[302] Halpern, M.; Zahalka, H.A.; Sasson, Y.; Rabinovitz, M. *J. Org. Chem.* ***1985***, *50*, 5088. See also, Barry, J.; Bram, G.; Decodts, G.; Loupy, A.; Pigeon, P.; Sansoulet, J. *J. Org. Chem.* ***1984***, *49*, 1138.

[303] See Fieser, L.F.; Fieser, M. *Reagents for Organic Syntheses*, Vol. 1, Wiley, NY, ***1967***, pp. 606–609; Yakobson, G.G.; Akhmetova, N.E. *Synthesis* ***1983***, 169 (see pp. 170–173).

[304] See Hoye, T.R.; van Deidhuizen, J.J.; Vos, T.J.; Zhao, P. *Synth. Commun.* ***2001***, *31*, 1367.

[305] Matsubara, S.; Matsuda, H.; Hamatani, T.; Schlosser, M. *Tetrahedron* ***1988***, *44*, 2855.

[306] Bissember, A.C.; Levina, A.; Fu, G.C. *J. Am. Chem. Soc.* ***2012***, *134*, 14232.

[307] Lin, M.-H.; Tsai, W.-S.; Lin, L.-Z.; Hung, S.-F.; Chuang, T.-H.; Su, Y.-J. *J. Org. Chem.* ***2011***, *76*, 8518.

[308] Li, H.; Müller, D.; Guénée, L.; Alexakis, A. *Org. Lett.* ***2012***, *14*, 5880.

[309] Liu, W.; Li, C.-J. *Tetrahedron Lett.* ***2015***, *56*, 1699.

[310] McGraw, K.M.; Bowler, J.T.; Ly, Vy.T.; Erden, I.; Wu, W. *Tetrahedron Lett.* ***2016***, *57*, 285.

[311] Zhao, M.; Kuang, C.; Yang, Q.; Cheng, X. *Tetrahedron Lett.* ***2011***, *52*, 992.

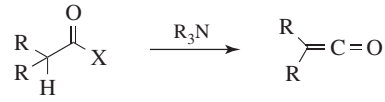
[312] Shenawi-Khalil, S.; Sonavane, S.U.; Sasson, Y. *Tetrahedron Lett.* ***2012***, *53*, 2295.

This reaction is by far the most important way of introducing a triple bond into a molecule.[313] Alkyne formation can be accomplished with 1,1-dihalo, 1,2-dihalo, and vinyl halides.[314] When the base is $NaNH_2$, 1-alkynes predominate (where possible), because this base is strong enough to form the salt of the alkyne, shifting any equilibrium between 1-alkynes and 2-alkynes. When the base is ^-OH or ^-OR, the equilibrium tends to be shifted to the internal alkyne, which is thermodynamically more stable. If another hydrogen is suitably located (e.g., —CRH—CX_2—CH_2—), allene formation can compete, although alkynes are usually more stable. Tetrabutylammonium fluoride mediates the dehydrobromination of vinyl bromides to terminal alkynes.[315] Treatment of 1,1-dibromo-1-alkenes with a Pd catalyst, followed by reaction with tetrabutylammonium hydroxide, gives an internal alkyne.[316] 1,1-Dibromoalkenes are converted to alkynes when treated with *n*-butyllithium.[317] This transformation is a modification of the *Fritsch-Buttenberg-Wiechell rearrangement* in which a 1,1-diaryl vinyl bromide gives a diaryl alkyne upon treatment with base.[318] Vinyl sulfoxides that contain a leaving group such as chloride on the double bond react with *tert*-butyllithium to give a lithio alkyne, and hydrolysis leads to the final product, an alkyne.

Dehydrohalogenation is generally carried out in solution, with a base, and the mechanism is usually E2, although the E1 mechanism has been demonstrated in some cases. However, elimination of HX can be accomplished by pyrolysis of the halide, in which case the mechanism is E^i (Sec. 17.E.i) or, in some instances, the free-radical mechanism (Sec. 17.E.i). Pyrolysis is normally performed without a catalyst at ~400 °C. The pyrolysis reaction is not generally useful synthetically, because of its reversibility. Less work has been done on pyrolysis with a catalyst[319] (usually a metallic oxide or salt), but the mechanisms here are probably E1 or E2.

OS **I**, 191, 205, 209, 438; **II**, 10, 17, 515; **III**, 125, 209, 270, 350, 506, 623, 731, 785; **IV**, 128, 162, 398, 404, 555, 608, 616, 683, 711, 727, 748, 755, 763, 851, 969; **V**, 285, 467, 514; **VI**, 87, 210, 327, 361, 368, 427, 462, 505, 564, 862, 883, 893, 954, 991, 1037; **VII**, 126, 319, 453, 491; **VIII**, 161, 173, 212, 254; **IX**, 191, 656, 662. Also see, OS **VI**, 968.

17-12 Dehydrohalogenation of Acyl Halides and Sulfonyl Halides



Ketenes can be prepared by treatment of acyl halides with tertiary amines[320] or with NaH and a crown ether.[321] The scope is broad, and most acyl halides possessing an α hydrogen

[313] Ben-Efraim, D.A. in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 2, Wiley, NY, ***1978***, p. 755; Köbrich, G.; Buck, P. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 100–134; Köbrich, G. *Angew. Chem. Int. Ed.* ***1965***, *4*, 49 (see pp. 50–53).

[314] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 569–571.

[315] See Okutani, M.; Mori, Y. *J. Org. Chem.* ***2009***, *74*, 442.

[316] Chelucci, G.; Capitta, F.; Baldino, S. *Tetrahedron* ***2008***, *64*, 10250.

[317] Chernick, E.T.; Eisler, S.; Tykwinski, R.R. *Tetrahedron Lett.* ***2001***, *42*, 8575.

[318] Fritsch, P. *Ann.* ***1894***, *279*, 319; Buttenberg, W.P. *Ann.* ***1894***, *279*, 324; Wiechell, H. *Ann.* ***1894***, *279*, 337. For a review, see Stang, P.J. *Chem. Rev.* ***1978***, *78*, 383. See Jahnke, E.; Tykwinski, R.R. *Chem. Commun.* ***2010***, 3235; Pratt, L.M.; Nguyen, N.V.; Kwon, O. *Chem. Lett.* ***2009***, *38*, 574.

[319] For a review, see Noller, H.; Andréu, P.; Hunger, M. *Angew. Chem. Int. Ed.* ***1971***, *10*, 172.

[320] See Tidwell, T.T. *Ketenes*, Wiley, NY, ***1995***.

[321] Taggi, A.E.; Wack, H.; Hafez, A.M.; France, S.; Lectka, T. *Org. Lett.* ***2002***, *4*, 627.

give the reaction, but if at least one R is hydrogen, only the ketene dimer, not the ketene, is isolated. However, if a reactive ketene must be used in a reaction with a given compound, the ketene can be generated *in situ* in the presence of the given compound.[322]

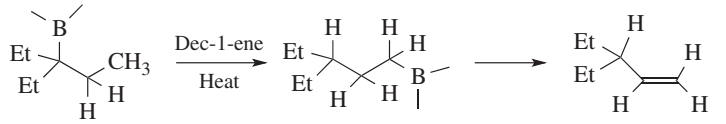
Closely related is the reaction of tertiary amines with sulfonyl halides that contain an α hydrogen. In this case the initial product is the highly reactive sulfene ($RCH{=}SO_2$), which cannot be isolated but reacts further to give products, one of which may be the alkene that is the dimer of RCH.[323] Reactions of sulfenes *in situ* are also common (e.g., see **16-48**).

OS **IV**, 560; **V**, 294, 877; **VI**, 549, 1037; **VII**, 232; **VIII**, 82.

17-13 Elimination of Boranes

$$(R_2CH{-}CH_2)_3B \;+\; 3\ \text{Dec-1-ene} \rightleftharpoons 3\ R_2C{=}CH_2 \;+\; [CH_3(CH_2)_8CH_2]_3B$$

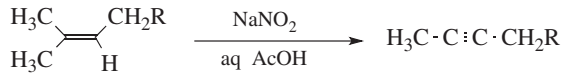
Trialkylboranes are formed from an alkene and BH_3 (**15-11**). When the resulting borane is treated with another alkene, an exchange reaction occurs,[324] which is an equilibrium process. This equilibrium can be shifted by using a large excess of an unusually reactive alkene, or by using an alkene with a higher boiling point than the displaced alkene and removing the latter by distillation. The reaction is useful for shifting a double bond in the direction opposite to that resulting from normal isomerization methods (**12-2**). Therefore, heating borane **25** leads to **26** (**18-11**) and when **26** is heated with a higher boiling alkene (e.g., dec-1-ene), the exchange reaction gives 3-ethylpent-1-ene.



25 **26** 3-Ethylpent-1-ene

These isomerizations proceed essentially without rearrangement. The mechanism is probably the reverse of borane addition (**15-11**).

17-14 Conversion of Alkenes to Alkynes



Alkenes of the form shown lose the elements of methane when treated with sodium nitrite in acetic acid and water, to form alkynes in moderate to high yields.[325] The R may contain additional unsaturation, as well as OH, OR, OAc, C=O, and other groups, but the $Me_2C{=}CHCH_2{-}$ portion of the substrate is necessary for the reaction to take place. The

[322] See Luknitskii, F.I.; Vovsi, B.A. *Russ. Chem. Rev.* ***1969***, *38*, 487.

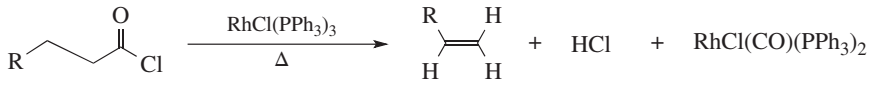
[323] See King, J.F. *Acc. Chem. Res.* ***1975***, *8*, 10; Nagai, T.; Tokura, N. *Int. J. Sulfur Chem. Part B* ***1972***, 207; Truce, W.E.; Liu, L.K. *Mech. React. Sulfur Compd.* ***1969***, *4*, 145.

[324] Brown, H.C.; Bhatt, M.V.; Munekata, T.; Zweifel, G. *J. Am. Chem. Soc.* ***1967***, *89*, 567; Taniguchi, H. *Bull. Chem. Soc. Jpn.* ***1979***, *52*, 2942.

[325] Abidi, S.L. *Tetrahedron Lett.* ***1986***, *27*, 267; *J. Org. Chem.* ***1986***, *51*, 2687.

mechanism is complex, beginning with a nitration that takes place with allylic rearrangement [$Me_2C{=}CHCH_2R \rightarrow H_2C{=}CMeCH(NO_2)CH_2R$], and involving several additional intermediates.[326] The CH_3 lost from the substrate appears as CO_2, as demonstrated by the trapping of this gas.[326]

17-15 Decarbonylation of Acyl Halides or Aldehydes

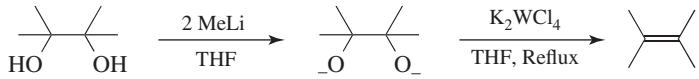


Acyl chlorides containing an α hydrogen are smoothly converted to alkenes, with loss of HCl and CO, upon heating with chlorotris(triphenylphosphine)rhodium, with metallic Pt, or with certain other catalysts.[327] The mechanism probably involves conversion of RCH_2CH_2COCl to $RCH_2CH_2{-}RhCO(Ph_3P)_2Cl_2$ followed by a concerted *syn* elimination of Rh and H[328] (see also, **14-26** and **19-12**).

Aldehydes are decarbonylated to give the corresponding hydrocarbon in the presence of an Ir catalyst and triphenylphosphine.

B. Reactions in Which Neither Leaving Atom is Hydrogen

17-16 Deoxygenation of Vicinal Diols



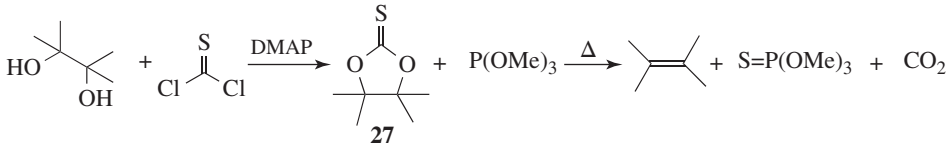
vic-Diols can be deoxygenated by treatment of the dilithium dialkoxide with a tungsten halide (e.g., K_2WCl_6), or with certain other tungsten reagents, in THF at reflux.[329] Tetrasubstituted diols react most rapidly. The elimination is largely, but not entirely, *syn*. Several other methods have been reported,[330] in which the diol is deoxygenated directly, without conversion to the dialkoxide. These include treatment with Ti metal,[331] with TsOH/NaI,[332] and by heating with $CpReO_3$,[333] where Cp is cyclopentadienyl.

vic-Diols can also be deoxygenated indirectly, through sulfonate ester derivatives. For example, *vic*-dimesylates and *vic*-ditosylates have been converted to alkenes by treatment with naphthalene/sodium[334] and NaI in DMF,[335] respectively. In another procedure, the

[326] Corey, E.J.; Seibel, W.L.; Kappos, J.C. *Tetrahedron Lett.* ***1987***, *28*, 4921.
[327] For a review, see Tsuji, J.; Ohno, K. *Synthesis* ***1969***, 157. For extensions to certain other acid derivatives, see Minami, I.; Nisar, M.; Yuhara, M.; Shimizu, I.; Tsuji, J. *Synthesis* ***1987***, 992.
[328] Lau, K.S.Y.; Becker, Y.; Huang, F.; Baenziger, N.; Stille, J.K. *J. Am. Chem. Soc.* ***1977***, *99*, 5664.
[329] Sharpless, K.B.; Umbreit, M.A.; Nieh, T.; Flood, T.C. *J. Am. Chem. Soc.* ***1972***, *94*, 6538.
[330] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 297–299.
[331] McMurry, J.E. *Acc. Chem. Res.* ***1983***, *16*, 405 and references cited therein.
[332] Sarma, J.C.; Sharma, R.P. *Chem. Ind. (London)* ***1987***, 96.
[333] Cook, G.K.; Andrews, M.A. *J. Am. Chem. Soc.* ***1996***, *118*, 9448.
[334] Carnahan Jr., J.C.; Closson, W.D. *Tetrahedron Lett.* ***1972***, 3447.
[335] Dafaye, J. *Bull. Soc. Chim. Fr.* ***1968***, 2099.

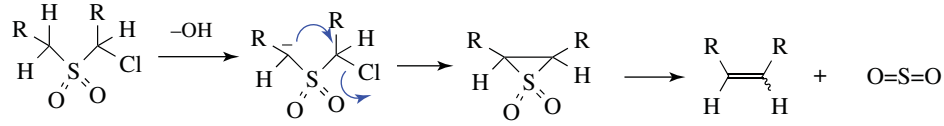
diols are converted to bisdithiocarbonates (bis xanthates), which undergo elimination (probably by a free-radical mechanism) when treated with tri-*n*-butylstannane in toluene or benzene.[336] *vic*-Diols can also be deoxygenated through cyclic derivatives (**17-19**).

17-17 Cleavage of Cyclic Thionocarbonates



Cyclic thionocarbonates (**27**) can be cleaved to alkenes (the *Corey-Winter reaction*)[337] by heating with trimethyl phosphite[338] or other trivalent phosphorus compounds[339] or by treatment with bis(1,5-cyclooctadiene)nickel.[340] The thionocarbonates such as **27** can be prepared by treatment of 1,2-diols with thiophosgene and 4-dimethylaminopyridine (DMAP).[341] The elimination is of course *syn*, so the product is sterically controlled. Alkenes that are not sterically favored can be made this way in high yield (e.g., *cis*-$PhCH_2CH{=}CHCH_2Ph$).[342]

17-18 The Ramberg-Bäcklund Reaction



The reaction of an α-halo sulfone with a base to give an alkene is called the *Ramberg-Bäcklund reaction*.[343] The reaction is quite general for α-halo sulfones with an α′ hydrogen, despite the unreactive nature of α-halo sulfones in normal S_N2 reactions (Sec. 10.G.i, category 6). Halogen reactivity is in the order I > Br ≫ Cl. Phase-transfer catalysis has been used.[344] In general, mixtures of *cis* and *trans* isomers are obtained, but usually the less stable *cis* isomer predominates. The mechanism involves formation of an episulfone, and then elimination of SO_2. There is much evidence for this mechanism,[345] including the

[336] Barrett, A.G.M.; Barton, D.H.R.; Bielski, R. *J. Chem. Soc., Perkin Trans. 1* ***1979***, 2378.

[337] See Block, E. *Org. React.* ***1984***, *30*, 457; Sonnet, P.E. *Tetrahedron* ***1980***, *36*, 557 (pp. 593–598); Mackie, R.K. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 354–359.

[338] Corey, E.J.; Winter, R.A.E. *J. Am. Chem. Soc.* ***1963***, *85*, 2677.

[339] Corey, E.J. *Pure Appl. Chem.* ***1967***, *14*, 19 (see pp. 32–33).

[340] Semmelhack, M.F.; Stauffer, R.D. *Tetrahedron Lett.* ***1973***, 2667. For another method, see Vedejs, E.; Wu, E.S.C. *J. Org. Chem.* ***1974***, *39*, 3641.

[341] Corey, E.J.; Hopkins, P.B. *Tetrahedron Lett.* ***1982***, *23*, 1979.

[342] Corey, E.J.; Carey, F.A.; Winter, R.A.E. *J. Am. Chem. Soc.* ***1965***, *87*, 934.

[343] Paquette, L.A. *Org. React.* ***1977***, *25*, 1; *Acc. Chem. Res.* ***1968***, *1*, 209; Meyers, C.Y.; Matthews, W.S.; Ho, L.L.; Kolb, V.M.; Parady, T.E. in Smith, G.V. *Catalysis in Organic Synthesis*, Academic Press, NY, ***1977***, pp. 197–278; Rappe, C. in Patai, S. *The Chemistry of the Carbon-Halogen Bond*, pt. 2, Wiley, NY, ***1973***, pp. 1105–1110; Bordwell, F.G. *Acc. Chem. Res.* ***1970***, *3*, 281.

[344] Hartman, G.D.; Hartman, R.D. *Synthesis* ***1982***, 504.

[345] See Bordwell, F.G.; Doomes, E. *J. Org. Chem.* ***1974***, *39*, 2526, 2531.

isolation of the episulfone intermediate,[346] and also the preparation of episulfones in other ways and the demonstration that they give alkenes under the reaction conditions faster than the corresponding α-halo sulfones.[347] Episulfones synthesized in other ways (e.g., **16-48**) are reasonably stable compounds, but eliminate SO_2 to give alkenes when heated or treated with base.

If the reaction is run on the unsaturated bromosulfones $RCH_2CH{=}CHSO_2CH_2Br$ (prepared by reaction of $BrCH_2SO_2Br$ with $RCH_2CH{=}CH_2$ followed by treatment with Et_3N), $RCH{=}CHCH{=}CH_2$ is produced in moderate to good yields.[348] The compound mesyltriflone $CF_3SO_2CH_2SO_2CH_3$ can be used as a synthon for the tetra ion $^{2-}C{=}C^{2-}$.

2,5-Dihydrothiophene-1,1-dioxides (**28**) and 2,7-dihydrothiepin-1,1-dioxides (**29**) undergo analogous 1,4 and 1,6 eliminations, respectively (see also **17-34**). These are concerted reactions and, as predicted by the orbital-symmetry rules (**15-46**.A, and immediately preceding pages), the former[349] is a suprafacial process and the latter[350] an antarafacial process. The rules also predict that elimination of SO_2 from episulfones cannot take place by a concerted mechanism (except antarafacially, which is unlikely for such a small ring), and the evidence shows that this reaction occurs by a nonconcerted pathway.[351] The eliminations of SO_2 from **28** and **29** are examples of *cheletropic reactions*,[352] which are defined as reactions in which two σ bonds that terminate at a single atom (in this case the sulfur atom) are made or broken in concert.[353]

28 **29**

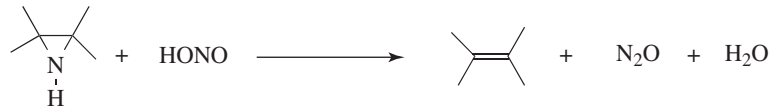
α,α-Dichlorobenzyl sulfones react with an excess of the base triethylenediamine (TED) in DMSO at room temperature to give 2,3-diarylthiiren-1,1-dioxides, which can be isolated.[354] Thermal decomposition gives the alkyne.[355] A Ramberg-Bäcklund-type reaction has been carried out on the α-halo *sulfides* ($ArCHClSCH_2Ar$), which react with *t*-BuOK and PPh_3 in refluxing THF to give the alkenes ($ArCH{=}CHAr$).[356] Cyclic sulfides lead to

[346] Sutherland, A.G.; Taylor, R.J.K. *Tetrahedron Lett.* ***1989***, *30*, 3267.
[347] See Bordwell, F.G.; Williams Jr., J.M. *J. Am. Chem. Soc.* ***1968***, *90*, 435.
[348] Block, E.; Aslam, M.; Eswarakrishnan, V.; Gebreyes, K.; Hutchinson, J.; Iyer, R.; Laffitte, J.; Wall, A. *J. Am. Chem. Soc.* ***1986***, *108*, 4568.
[349] Mock, W.L. *J. Am. Chem. Soc.* ***1966***, *88*, 2857; McGregor, S.D.; Lemal, D.M. *J. Am. Chem. Soc.* ***1966***, *88*, 2858.
[350] Mock, W.L. *J. Am. Chem. Soc.* ***1969***, *91*, 5682.
[351] Bordwell, F.G.; Williams Jr., J.M.; Hoyt Jr., E.B.; Jarvis, B.B. *J. Am. Chem. Soc.* ***1968***, *90*, 429; Bordwell, F.G.; Williams Jr., J.M. *J. Am. Chem. Soc.* ***1968***, *90*, 435. See also, Vilsmaier, E.; Tropitzsch, R.; Vostrowsky, O. *Tetrahedron Lett.* ***1974***, 3987.
[352] See Mock, W.L. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 141–179.
[353] Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***, pp. 152–163.
[354] Philips, J.C.; Swisher, J.V.; Haidukewych, D.; Morales, O. *Chem. Commun.* ***1971***, 22.
[355] Philips, J.C.; Morales, O. *J. Chem. Soc., Chem. Commun.* ***1977***, 713.
[356] Mitchell, R.H. *Tetrahedron Lett.* ***1973***, 4395. For a similar reaction without base treatment, see Pommelet, J.; Nyns, C.; Lahousse, F.; Merényi, R.; Viehe, H.G. *Angew. Chem. Int. Ed.* ***1981***, *20*, 585.

ring-contracted cyclic alkenes upon treatment with NCS in CCl_4 followed by oxidation with *m*-chloroperoxybenzoic acid.[357]

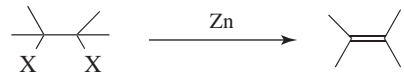
OS **V**, 877; **VI**, 454, 555; **VIII**, 212.

17-19 The Conversion of Aziridines to Alkenes



Aziridines not substituted on the nitrogen atom react with nitrous acid to produce alkenes.[358] A *N*-nitroso compound is an intermediate (**12-49**); other reagents that produce such intermediates also give alkenes. The reaction is stereospecific: *cis*-aziridines give *cis*-alkenes and *trans*-aziridines give *trans*-alkenes.[359] Aziridines carrying *N*-alkyl substituents can be converted to alkenes by treatment with ferrous iodide[360] or with *m*-chloroperoxybenzoic acid.[361] An *N*-oxide intermediate (**19-28**) is presumably involved in the latter case. *N*-Tosyl aziridnes give allylic sulfonamides when treated with butyllithium.[362] *N*-Tosyl aziridines are converted to *N*-tosyl imines when treated with boron trifluoride.[363] 2-Tosylmethyl *N*-tosyl aziridines react with Te^{2-} in the presence of Adogen 464 to give allylic *N*-tosyl amines.[364] 2-Halomethyl *N*-tosyl aziridines also react with In metal in methanol to give *N*-tosyl allylic amines.[365]

17-20 Elimination of Vicinal Dihalides



Dehalogenation has been accomplished with many reagents, the most common being Zn, Mg, and iodide ion.[366] Heating in HMPA is often enough to convert a *vic*-dibromide to an alkene.[367] When the reagent is Zn, *anti* stereospecificity has been observed in some cases,[368] but not in others.[369] Electrochemical reduction has also been used,[370] as has treatment with

[357] MacGee, D.I.; Beck, E.J. *J. Org. Chem.* ***2000***, *65*, 8367.

[358] See Sonnet, P.E. *Tetrahedron* ***1980***, *36*, 557 (see p. 591); Dermer, O.C.; Ham, G.E. *Ethylenimine and other Aziridines*, Academic Press, NY, ***1969***, pp. 293–295.

[359] See Carlson, R.M.; Lee, S.Y. *Tetrahedron Lett.* ***1969***, 4001.

[360] Imamoto, T.; Yukawa, Y. *Chem. Lett.* ***1974***, 165.

[361] Heine, H.W.; Myers, J.D.; Peltzer III, E.T. *Angew. Chem. Int. Ed.* ***1970***, *9*, 374.

[362] Hodgson, D.M.; Štefane, B.; Miles, T.J.; Witherington, J. *J. Org. Chem.* ***2006***, *71*, 8510.

[363] Sugihara, Y.; Iimura, S.; Nakayama, J. *Chem. Commun.* ***2002***, 134.

[364] Chao, B.; Dittmer, D.C. *Tetrahedron Lett.* ***2001***, *42*, 5789.

[365] Yadav, J.S.; Bandyapadhyay, A.; Reddy, B.V.S. *Synlett* ***2001***, 1608.

[366] Baciocchi, E. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, Supplement D, pt. 1, Wiley, NY, ***1983***, pp. 161–201. See Bosser, G.; Paris, J. *J. Chem. Soc., Perkin Trans. 2* ***1992***, 2057.

[367] Khurana, J.M.; Bansal, G.; Chauhan, S. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 1089.

[368] See Gordon, M.; Hay, J.V. *J. Org. Chem.* ***1968***, *33*, 427.

[369] See Sicher, J.; Havel, M.; Svoboda, M. *Tetrahedron Lett.* ***1968***, 4269.

[370] Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*, Springer, NY, ***1984***, pp. 145–147; Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 151–154.

In[371] or Sm[372] metal in methanol, $InCl_3/NaBH_4$,[373] or heating with Zn in acetic acid.[374] Microwave irradiation of a *vic*-dibromide in an ionic liquid leads to the alkene.[375] The reaction of a vicinal dibromide with triethylamine and DMF with microwave irradiation leads to vinyl bromide.[376] α,β-Dibromo amides are converted to conjugated amides upon photolysis in methanol.[377]

One useful feature of this reaction is that there is no doubt about the *position* of the new double bond, so that it can be used to give double bonds exactly where they are wanted. For example, allenes, which are not easily prepared by other methods, can be prepared from X—C—CX_2—C—X or X—C—CX=C— systems.[378] Cumulenes have been obtained from 1,4 elimination, as in the reaction of Zn and 1,4-dibromobut-2-yne to give buta-1,2,3-triene. Cumulenes have also been prepared by treating alkynyl epoxides with boron trifluoride.[379]

Allylic rearrangements have also been demonstrated in propargyl systems, for example,[380] and the product in this case is an allene.[381] 1,4 elimination of BrC—C=C—CBr has been used to prepare conjugated dienes C=C—C=C.[382] Allenes are formed by heating propargylic alcohols with arylboronic acids (**12-27**) and a Pd catalyst.[383] Allenes are also formed from propargylic amines using CuI and a Pd catalyst.[384] In addition, allenes are formed from lithium bromocyclopropylidenoids.[385] Propargylic halides can be alkylated with essentially complete allylic rearrangement, to give allenes, by treatment with Grignard reagents and metallic salts,[386] or with dialkylcuprates R_2Cu.[387] An enantioselective coupling of diazoalkanes with terminal alkynes to give allenes, using a Cu catalyst.[388] Allenes are formed by the coupling of alkylzinc halides and propargyl bromides using a Ni catalyst.[389] Allenes are obtained when propargyl acetates are treated with methylmagnesium iodide.[390] Propargylic ethers give allenes.[391] Propargylic tosylates couple with vinylic

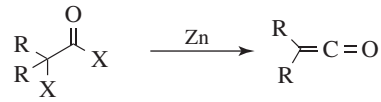
[371] Ranu, B.C.; Guchhait, S.K.; Sarkar, A. *Chem. Commun.* ***1998***, 2113.
[372] Yanada, R.; Negoro, N.; Yanada, K.; Fujita, T. *Tetrahedron Lett.* ***1996***, *37*, 9313.
[373] Ranu, B.C.; Das, A.; Hajra, A. *Synthesis* ***2003***, 1012.
[374] Gaenzler, F.C.; Smith, M.B. *Synlett* ***2007***, 1299.
[375] Ranu, B.C.; Jana, R. *J. Org. Chem.* ***2005***, *70*, 8621.
[376] Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron Lett.* ***2001***, *42*, 3893.
[377] Aruna, S.; Kalyanakumar, R.; Ramakrishnan, V.T. *Synth. Commun.* ***2001***, *31*, 3125.
[378] See Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 9–56; Landor, P.D. in Landor, S.R. *The Chemistry of the Allenes*, Vol. 1, Academic Press, NY, ***1982***; pp. 19–233; Taylor, D.R. *Chem. Rev.* ***1967***, *67*, 317.
[379] Wang, X.; Ramos, B.; Rodriguez, A. *Tetrahedron Lett.* ***1994***, *35*, 6977.
[380] Vermeer, P.; Meijer, J.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* ***1975***, *94*, 112.
[381] See Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 12–19, 26–30; Taylor, D.R. *Chem. Rev.* ***1967***, *67*, 317 (pp. 324–328). See Larock, R.C.; Reddy, Ch.K. *Org. Lett.* ***2000***, *2*, 3325.
[382] Engman, L.; Byström, S.E. *J. Org. Chem.* ***1985***, *50*, 3170.
[383] Yoshida, M.; Gotou, T.; Ihara, M. *Tetrahedron Lett.* ***2004***, *45*, 5573.
[384] Nakmura, H.; Kamakura, T.; Ishikura, M.; Biellmann, J.-F. *J. Am. Chem. Soc.* ***2004***, *126*, 5958.
[385] Azizoglu, A.; Balci, M.; Mieusset, J.-L.; Brinker, U.H. *J. Org. Chem.* ***2008***, *73*, 8182.
[386] See Jeffery-Luong, T.; Linstrumelle, G. *Tetrahedron Lett.* ***1980***, *21*, 5019.
[387] Pasto, D.J.; Chou, S.; Fritzen, E.; Shults, R.H.; Waterhouse, A.; Hennion, G.F. *J. Org. Chem.* ***1978***, *43*, 1389. See also, Tanigawa, Y.; Murahashi, S. *J. Org. Chem.* ***1980***, *45*, 4536.
[388] Chu, W.-D.; Zhang, L.; Zhang, Z.; Zhou, Q.; Mo, F.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* ***2016***, *138*, 14558.
[389] Soler-Yanes, R.; Arribas-Álvarez, I.; Guisán-Ceinos, M.; Buñuel, E.; Cárdenas, D.J. *Chem. Eur. J.* ***2017***, *23*, 1584.
[390] Roumestant, M.; Gore, J. *Bull. Soc. Chim. Fr.* ***1972***, 591, 598; Crabbé, P.; Barreiro, E.; Dollat, J.; Luche, J. *J. Chem. Soc., Chem. Commun.* ***1976***, 183, and references cited therein.
[391] Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J.F. *J. Am. Chem. Soc.* ***1990***, *112*, 8042.

cuprates to give vinylic allenes.[392] Racemic propargyl carbonates gave chiral allenes in the presence of LiF, CO, and a Pd catalyst.[393]

The reaction can be carried out for any combination of halogens, except where one is fluorine. Mechanisms are often complex and depend on the reagent and reaction conditions.[394] For different reagents, mechanisms involving carbocations, carbanions, and free-radical intermediates, as well as concerted mechanisms, have been proposed.

OS **III**, 526, 531; **IV**, 195, 268; **V**, 22, 255, 393, 901; **VI**, 310, **VII**, 241. Also see, OS **IV**, 877, 914, 964.

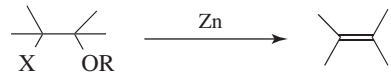
17-21 Dehalogenation of α-Halo Acyl Halides



Ketenes can be prepared by dehalogenation of α-halo acyl halides with zinc or with triphenylphosphine.[395] The reaction generally gives good results when the two R groups are aryl or alkyl, but not when either one is hydrogen.[396]

OS **IV**, 348; **VIII**, 377.

17-22 Elimination of a Halogen and a Hetero Group



The elimination of OR and halogen from β-halo ethers is called the *Boord reaction*. It can be carried out with Zn, Mg, Na, or certain other reagents.[397] The yields are high and the reaction is of broad scope. β-Halo acetals readily yield vinylic ethers, X—C—C(OR)$_2$ → C=C—OR and 2 molar equivalents of SmI_2 in HMPA is effective.[398] Besides β-halo ethers, the reaction can also be carried out on compounds of the formula Z—C—C—Z where X is halogen and Z is OCOR, OTs,[399] NR_2,[400] or SR.[401] When X = Cl and Z = OAc, heating in THF with an excess of SmI_2 followed by treatment with dilute aqueous HCl gives an

[392] Baudouy, R.; Goré, J. *J. Chem. Res. (S)* ***1981***, 278. See also, Elsevier, C.J.; Vermeer, P. *J. Org. Chem.* ***1989***, *54*, 3726.

[393] Wang, Y.; Zhang, W.; Ma, S. *J. Am. Chem. Soc.* ***2013***, *135*, 11517.

[394] See Saunders Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 332–368; Baciocchi, W. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, Supplement D, pt. 2, Wiley, NY, ***1983***, p. 161.

[395] Darling, S.D.; Kidwell, R.L. *J. Org. Chem.* ***1968***, *33*, 3974.

[396] See McCarney, C.C.; Ward, R.S. *J. Chem. Soc., Perkin Trans. 1* ***1975***, 1600. See also, Masters, A.P.; Sorensen, T.S.; Ziegler, T. *J. Org. Chem.* ***1986***, *51*, 3558.

[397] For reagents that produce olefins from β-halo ethers and esters, and from halohydrins, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 263–267.

[398] Park, H.S.; Kim, S.H.; Park, M.Y.; Kim, Y.H. *Tetrahedron Lett.* ***2001***, *42*, 3729.

[399] Reeve, W.; Brown, R.; Steckel, T.F. *J. Am. Chem. Soc.* ***1971***, *93*, 4607.

[400] Gurien, H. *J. Org. Chem.* ***1963***, *28*, 878.

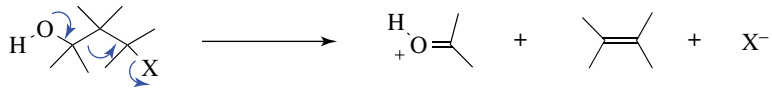
[401] Amstutz, E.D. *J. Org. Chem.* ***1944***, *9*, 310.

alkene.[402] When Z = I and the other Z is an oxygen of an oxazolone (a carbamate unit), heating with In metal in methanol leads to an allylic amine.[403] The Z group may also be OH, but then X is limited to Br and I.[404] Like **17-20**, this method ensures that the new double bond will be in a specific position. The fact that Mg causes elimination in these cases limits the preparation of *Grignard reagents* from these compounds. It has been shown that treatment of β-halo ethers and esters with Zn gives nonstereospecific elimination,[405] so the mechanism cannot be E2. An E1cB mechanism was postulated because of the poor leaving group ability of OR and OCOR. Bromohydrins can be converted to alkenes (elimination of Br, OH) in high yields by treatment with $LiAlH_4/TiCl_3$.[406]

OS **III**, 698, **IV**, 748; **VI**, 675.

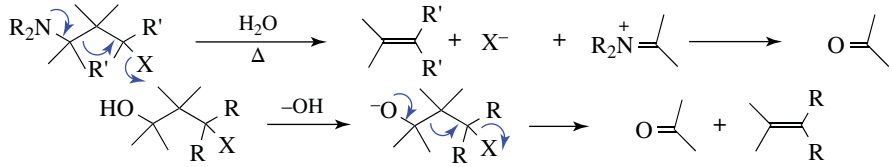
17.F.ii. Fragmentations

When carbon is the positive leaving group (the electrofuge) in an elimination, the reaction is called *fragmentation*.[407] These processes occur on substrates of the form W—C—C—X, where X is a normal nucleofuge (e.g., halogen, $^+OH_2$, OTs, $^+NR_3$) and W is a positive-carbon electrofuge. In most of the cases, W is HO—C— or R_2N—C—, so that the positive charge on the carbon atom is stabilized by the unshared pair of the oxygen or nitrogen. The following is an example:



The mechanisms are mostly E1 or E2. We will discuss only a few fragmentations, since many are possible and not much work has been done on most of them. Reactions **17-23** to **17-26** and **17-28** may be considered fragmentations (see also **19-12** and **19-13**).

17-23 1,3-Fragmentation of γ-Amino Halides, γ-Hydroxy Halides, and 1,3-Diols

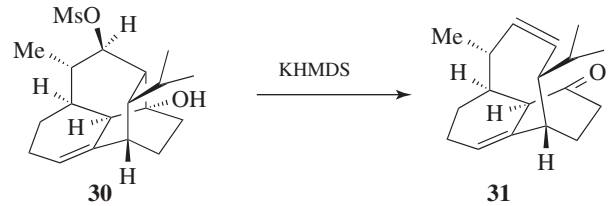


γ-Dialkylamino halides undergo fragmentation when heated with water to give an alkene and an iminium salt, which under the reaction conditions is hydrolyzed to an aldehyde or ketone (**16-2**).[408] γ-Hydroxy halides and tosylates are fragmented with base. In this

[402] Concellón, J.M.; Bernad, P.L.; Bardales, E. *Org. Lett.* ***2001***, *3*, 937.
[403] Yadav, J.S.; Bandyopadhyay, A.; Reddy, B.V.S. *Tetrahedron Lett.* ***2001***, *42*, 6385.
[404] Concellón, J.M.; Pérez-Andrés, J.A.; Rodríguez-Solla, H. *Chem. Eur. J.* ***2001***, *7*, 3062.
[405] House, H.O.; Ro, R.S. *J. Am. Chem. Soc.* ***1965***, *87*, 838.
[406] McMurry, J.E.; Hoz, T. *J. Org. Chem.* ***1975***, *40*, 3797.
[407] Becker, K.B.; Grob, C.A. in Patai, S. *The Chemistry of Functional Groups*, Supplement A, pt. 2, Wiley, NY, ***1977***, pp. 653–723; Grob, C.A. *Angew. Chem. Int. Ed.* ***1969***, *8*, 535.
[408] Grob, C.A.; Ostermayer, F.; Raudenbusch, W. *Helv. Chim. Acta* ***1962***, *45*, 1672.

instance, the base does not play its usual role in elimination reactions, but instead serves to remove a proton from the OH group, and electron transfer generates the carbonyl and an alkene with loss of the leaving group.

Prelog first observed this type of fragmentation in work that solved the structure of quinine and other *Cinchona* alkaloids in a 1,3-elimination ring-opening reaction.[409] Subsequent work by Grob elucidated the mechanism of the reaction,[410] and this 1,3 elimination is often referred to as *Grob fragmentation*.[411] The mechanism of these reactions is often E1, but an E2 mechanism also operates.[412] It has been shown that stereoisomers of cyclic γ-amino halides and tosylates in which the two leaving groups can assume an anti-periplanar conformation react by the E2 mechanism, while those isomers in which the groups cannot assume such a conformation either fragment by the E1 mechanism or do not undergo fragmentation at all, but in either case give rise to side products characteristic of carbocations.[413] An example of a Grob fragmentation is the conversion of **30** to **31** in a synthesis of vinigrol.[414]



30 **31**

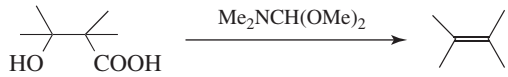
Arynes have been prepared by application of the Grob fragmentation.[415] The conversion of 2-methyldimedone into the corresponding vinylogous acyl triflate and subsequent reduction of the ketone moiety to the alcohol allowed reaction with an ylid-forming reagent ($Et_2O_3PCH_2CO_2Et$/LDA). Subsequent fragmentation/alkene-forming reaction gave the 1,6-enyne. γ-Dialkylamino alcohols do not give fragmentation, since ionization of the OH group requires protonation to give $^+OH_2$, which would convert NR_2 to $^+NR_2H$. The ammonium salt does not have the unshared pair necessary to form the double bond with the carbon.[416]

The C_β–C_γ bond of bicyclic γ-silyloxy-β-hydroxy-α-diazo ketones fragmented when treated with tin(IV) chloride to give 10-, 11-, and 12-membered alkynone cyclic 2-alkynones.[417]

1,3-Diols in which at least one OH group is tertiary or is located on a carbon with aryl substituents can be cleaved to a carbonyl and an alkene by acid treatment.[418] The reaction is most useful synthetically when at least one of the OH groups is on a ring.[419]

[409] Prelog, V.; Zalán, E. *Helv. Chim. Acta* ***1944***, *27*, 535; Prelog, V.; Häfliger, O. *Helv. Chim. Acta* ***1950***, *33*, 2021.
[410] Grob, C.A. *Angew. Chem. Int. Ed.* ***1969***, *8*, 535 and references cited therein; Grob, C.A.; Kiefer, H.R.; Lutz, H.J.; Wilkens, H.J. *Helv. Chim. Acta* ***1967***, *50*, 416.
[411] See Prantz, K.; Mulzer, J. *Chem. Rev.* ***2010***, *110*, 3741.
[412] Fischer, W.; Grob, C.A. *Helv. Chim. Acta* ***1978***, *61*, 2336 and references cited therein.
[413] Geisel, M.; Grob, C.A.; Wohl, R.A. *Helv. Chim. Acta* ***1969***, *52*, 2206 and references cited therein.
[414] Maimone, T.J.; Shi, J.; Ashida, S.; Baran, P.S. *J. Am. Chem. Soc.* ***2009***, *131*, 17066.
[415] Shi, J.; Xu, H.; Qiu, D.; He, J.; Li, Y. *J. Am. Chem. Soc.* ***2017***, *139*, 623.
[416] Grob, C.A.; Hoegerle, R.M.; Ohta, M. *Helv. Chim. Acta* ***1962***, *45*, 1823.
[417] Tsvetkov, N.P.; Bayir, A.; Schneider, S.; Brewer, M. *Org. Lett.* ***2012***, *14*, 264.
[418] Zimmerman, H.E.; English Jr., J. *J. Am. Chem. Soc.* ***1954***, *76*, 2285, 2291, 2294.
[419] For a review, see Caine, D. *Org. Prep. Proced. Int.* ***1988***, *20*, 1.

17-24 Decarboxylation of β-Hydroxy Carboxylic Acids and β-Lactones

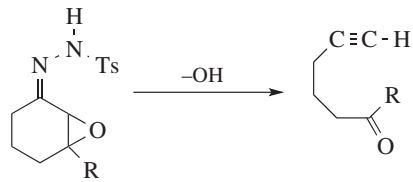


An OH and a CO_2H group can be eliminated from β-hydroxy carboxylic acids by heating with excess dimethylformamide dimethylacetal at reflux.[420] Mono-, di-, tri-, and tetrasubstituted alkenes have been prepared by this method in good yields.[421] There is evidence that the mechanism involves E1 or E2 elimination from the zwitterionic intermediate $^{-}O_2C{-}C{-}C{-}O{-}C{=}N^{+}Me_2$.[422] The reaction has also been accomplished[423] under extremely mild conditions (a few seconds at 0 °C) with PPh_3 and $EtO_2C{-}N{=}N{-}CO_2Et$ (diethyl azodicarboxylate).[424] In a related procedure, β-lactones undergo thermal decarboxylation to give alkenes in high yields. The reaction has been shown to be a stereospecific *syn* elimination.[425] There is evidence that this reaction also involves a zwitterionic intermediate.[426]

The microwave-assisted direct aerobic decarboxylative elimination of arylacetic acids gave the alkene using PIFA [bis(trifluoroacetoxy)iodobenzene] as an oxidant.[427] Heating carboxylic acids or dicarboxylic acids in the presence of a Pd catalyst 190 °C, neat, gave α-olefins and α,ω-dienes.[428]

See OS **VII**, 172, for a related reaction.

17-25 Fragmentation of α,β-Epoxy Hydrazones

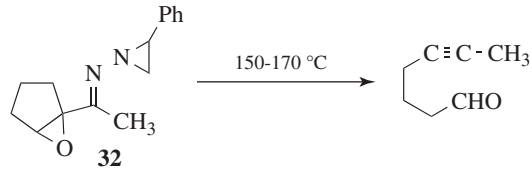


Cyclic α,β-unsaturated ketones[429] can be cleaved by treatment with base of their epoxy tosylhydrazone derivatives to give acetylenic ketones,[430] in what is known as the *Eschenmoser-Tanabe ring cleavage*. The reaction can be applied to the formation of

[420] Hara, S.; Taguchi, H.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* ***1975***, 1545.
[421] See Rüttimann, A.; Wick, A.; Eschenmoser, A. *Helv. Chim. Acta* ***1975***, *58*, 1450.
[422] Mulzer, J.; Brüntrup, G. *Tetrahedron Lett.* ***1979***, 1909.
[423] For another method, see Tanzawa, T.; Schwartz, J. *Organometallics* ***1990***, *9*, 3026.
[424] Mulzer, J.; Lammer, O. *Angew. Chem. Int. Ed.* ***1983***, *22*, 628.
[425] See Adam, W.; Martinez, G.; Thompson, J.; Yany, F. *J. Org. Chem.* ***1981***, *46*, 3359.
[426] Mulzer, J.; Zippel, M.; Brüntrup, G. *Angew. Chem. Int. Ed.* ***1980***, *19*, 465. See also, Moyano, A.; Pericàs, M.A.; Valentí, E. *J. Org. Chem.* ***1989***, 573.
[427] Wu, S.-W.; Liu, J.-L.; Liu, F. *Org. Lett.* ***2016***, *18*, 1.
[428] Kraus, G.A.; Riley, S. *Synthesis* ***2012***, *44*, 3003.
[429] See MacAlpine, G.A.; Warkentin, J. *Can. J. Chem.* ***1978***, *56*, 308, and references cited therein.
[430] Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* ***1967***, *50*, 708; see Tanabe, M.; Crowe, D.F.; Dehn, R.L. *Tetrahedron Lett.* ***1967***, 3943.

acetylenic aldehydes (R = H) by using the corresponding 2,4-dinitro tosylhydrazone derivatives.[431]

Hydrazones (e.g., **32**) prepared from epoxy ketones and ring-substituted *N*-aminoaziridines undergo similar fragmentation when heated.[432]

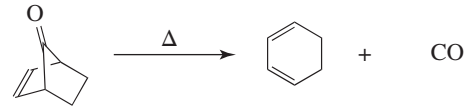


32

The Eschenmoser sulfide-containing method has been reviewed.[433]

OS **VI**, 679.

17-26 Elimination of CO and CO_2 from Bridged Bicyclic Compounds



On heating, bicyclo[2.2.1]hept-2,3-en-7-ones usually lose CO to give cyclohexadienes,[434] in a type of *reverse Diels-Alder reaction* (**15-56**).

Bicyclo[2.2.1]heptadienones undergo the reaction so readily that they cannot generally be isolated, because of the stability of the benzene ring produced. The parent bicyclo[2.2.1]heptadienone has been obtained at 10–15 K in an Ar matrix, where its spectrum could be studied.[435] Such bicyclic systems can be prepared by a *Diels-Alder reaction* between a cyclopentadienone and an alkyne or alkene, so that this reaction is a useful method for the preparation of specifically substituted benzene rings and cyclohexadienes.[436] Unsaturated bicyclic lactones such as 2-oxabicyclo[2.2.2]oct-5-en-3-one can also undergo the reaction, losing CO_2 (see also, **17-33**).

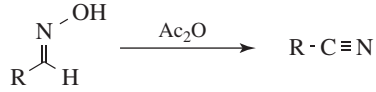
OS **III**, 807; **V**, 604, 1037.

Reversal of the *Diels-Alder reaction* may be considered a fragmentation reaction (see **15-56**).

[431] Corey, E.J.; Sachdev, H.S. *J. Org. Chem.* ***1975***, *40*, 579.
[432] Felix, D.; Müller, R.K.; Horn, U.; Joos, R.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* ***1972***, *55*, 1276.
[433] Hussaini, S.R.; Chamala, R.R.; Wang, Z. *Tetrahedron* ***2015***, *71*, 6017.
[434] See Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***, pp. 16–46.
[435] Birney, D.M.; Wiberg, K.B.; Berson, J.A. *J. Am. Chem. Soc.* ***1988***, *110*, 6631.
[436] See Ogliaruso, M.A.; Romanelli, M.G.; Becker, E.I. *Chem. Rev.* ***1965***, *65*, 261 (pp. 300–348). For references to this and related reactions, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 207–213.

17.F.iii. Reactions in Which C≡N or C═N Bonds Are Formed

17-27 Dehydration of Oximes and Similar Compounds



Aldoximes can be dehydrated to nitriles[437] by many dehydrating agents, of which acetic anhydride is the most common. Among the reagents that are effective under mild conditions[438] are Ph_3P/CCl_4,[439] PPh_3/I_2,[440] $Pd(OAc)_2/PPh_3$ in CH_3CN at reflux,[441] Cu(II) with ultrasound,[442] and ZnO/CH_3COCl under solvent-free conditions.[443] DMF catalyzes the thermal dehydration of aldoximes.[444] Heating an oxime with a Ru catalyst gives the nitrile.[445] Heating with the *Burgess reagent* [$Et_3N^+ {}^-SO_2N{-}CO_2Me$] in polyethylene glycol is effective for this transformation.[446] Sulfuric acid-impregnated silica gel[447] gives the nitrile. Aldehydes can be converted to oximes *in situ* and microwave irradiation on alumina[448] or with ammonium acetate[449] gives the nitrile. Solvent-free reactions are known.[450] The reaction is most successful when the H and OH are *anti*. Hydroxylamines that have an α proton are converted to nitrones when treated with a Mn/salen complex.[451] The Sn- or Ga-catalyzed conversion of oximes to nitriles has been reported,[452] and Ni catalysts have been used.[453] The dehydration of aldoximes used areneselenenic acids (ArSeOH), which are readily generated from diaryl diselenides and H_2O_2 by *in situ* oxidation, and gave the organonitrile.[454]

Quaternary hydrazonium salts (from hydrazines derived from aldehydes) give nitriles when treated with ^-OEt[455] or DBU (see **17-11**),[456] as do dimethylhydrazones

[437] Friedrich, K. in Patai, S.; Rappoport, Z. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 2, Wiley, NY, ***1978***, pp. 1345–1390; Friedrich, K.; Wallenfels, K. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 92–96; Fatiadi, K. in Friedrich, K. in Patai, S.; Rappoport, Z. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 2, Wiley, NY, ***1978***, pp. 1057–1303.

[438] See Jursic, B. *Synth. Commun.* ***1989***, *19*, 689.

[439] Kim, J.N.; Chung, K.H.; Ryu, E.K. *Synth. Commun.* ***1990***, *20*, 2785.

[440] Narsaiah, A.V.; Sreenu, D.; Nagaiah, K. *Synth. Commun.* ***2006***, *36*, 137.

[441] Kim, H.S.; Kim, S.H.; Kim, J.N. *Tetrahedron Lett.* ***2009***, *50*, 1717.

[442] Jiang, N.; Ragauskas, A.J. *Tetrahedron Lett.* ***2010***, *51*, 4479.

[443] Sarvari, M.H. *Synthesis* ***2005***, 787.

[444] Supsana, P.; Liaskopoulos, T.; Tsoungas, P.G.; Varvounis, G. *Synlett* ***2007***, 267.

[445] Yang, S.H.; Chang, S. *Org. Lett.* ***2001***, *3*, 4209.

[446] Miller, C.P.; Kaufman, D.H. *Synlett* ***2000***, 1169.

[447] Sarvari, M.H. *Synthesis* ***2005***, 787.

[448] Bose, D.S.; Narsaiah, A.V. *Tetrahedron Lett.* ***1998***, *39*, 6533.

[449] Das, B.; Ramesh, C.; Madhusudhan, P. *Synlett* ***2000***, 1599.

[450] See Sharghi, H.; Sarvari, M.H. *Synthesis* ***2003***, 243.

[451] Cicchi, S.; Cardona, F.; Brandi, A.; Corsi, M.; Goti, A. *Tetrahedron Lett.* ***1999***, *40*, 1989.

[452] Zhuang, Y.-J.; Liu, J.; Kang, Y.-B. *Tetrahedron Lett.* ***2016***, *57*, 5700.

[453] Li, Y.-T.; Liao, B.-S.; Chen, H.-P.; Liu, S.-T. *Synthesis* ***2011***, *43*, 2649.

[454] Yu, L.; Li, H.; Zhang, X.; Ye, J.; Liu, J.; Xu, Q.; Lautens, M. *Org. Lett.* ***2014***, *16*, 1346. For the use of PhSe(O)OH, see Zhang, X.; Sun, J.; Ding, Y.; Yu, L. *Org. Lett.* ***2015***, *17*, 5840.

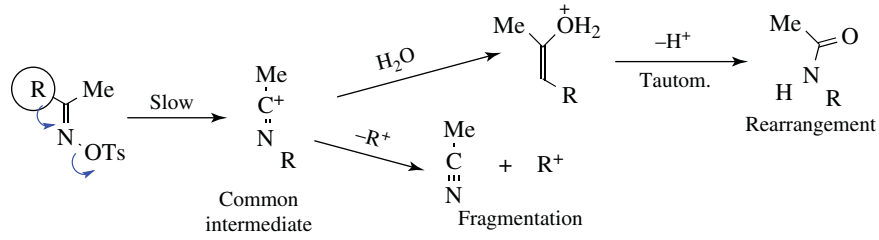
[455] See Ioffe, B.V.; Zelenina, N.L. *J. Org. Chem. USSR* ***1968***, *4*, 1496.

[456] Moore, J.S.; Stupp, S.I. *J. Org. Chem.* ***1990***, *55*, 3374.

($RCH{=}NNMe_2$) when treated with Et_2NLi and HMPA.[457] All these are methods of converting aldehyde derivatives to nitriles. For the conversion of aldehydes directly to nitriles, without isolation of intermediates, see **16-14**.

Certain ketoximes can be converted to nitriles by the action of proton acids or Lewis acids.[458] Among these are the monooxime of α-diketones, and the oximes of α-keto acids, α-dialkylamino ketones, α-hydroxy ketones, β-keto ethers, and similar compounds.[459] These are fragmentation reactions, analogous to **17-23**. For example, α-dialkylamino ketoximes also give amines and aldehydes or ketones besides nitriles.[460] The reaction that normally occurs on treatment of a ketoxime with a Lewis acid or proton acid is the *Beckmann rearrangement* (**18-17**); fragmentations are considered side reactions, often called "abnormal" or "second-order" *Beckmann rearrangements*.[461] Obviously, the substrates mentioned are much more susceptible to fragmentation than are ordinary ketoximes, since in each case an unshared pair of electrons is available to assist in removal of the group cleaving from the carbon. However, fragmentation is a side reaction even with ordinary ketoximes[462] and, in cases where a particularly stable carbocation can be cleaved, may be the main reaction.[463]

There are indications that the mechanism at least in some cases first involves a rearrangement and then cleavage. The ratio of fragmentation to Beckmann rearrangement of a series of oxime tosylates, RC(=NOTs)Me, was not related to the solvolysis rate but *was* related to the stability of R^+ (as determined by the solvolysis rate of the corresponding RCl), which showed that fragmentation did not take place in the rate-determining step.[464] It may be postulated then that the first step in the fragmentation and in the rearrangement is the same and that this is the rate-determining step. The product is determined in the second step. However, in other cases, the simple E1 or E2 mechanisms operate.[465]



OS **V**, 266; **IX**, 281; OS **II**, 622; **III**, 690.

[457] Cuvigny, T.; Le Borgne, J.F.; Larchevêque, M.; Normant, H. *Synthesis* ***1976***, 237.

[458] Gawley, R.E. *Org. React.* ***1988***, *35*, 1; McCarty, C.G. in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 416–439; Casanova, J. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 915–932.

[459] See Olah, G.A.; Vankar, Y.D.; Berrier, A.L. *Synthesis* ***1980***, 45.

[460] Fischer, H.P.; Grob, C.A. *Helv. Chim. Acta* ***1963***, *46*, 936.

[461] See Ferris, A.F. *J. Org. Chem.* ***1960***, *25*, 12.

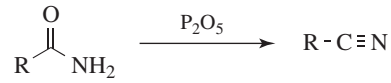
[462] See Hill, R.K.; Conley, R.T. *J. Am. Chem. Soc.* ***1960***, *82*, 645.

[463] Hassner, A.; Nash, E.G. *Tetrahedron Lett.* ***1965***, 525.

[464] Grob, C.A.; Fischer, H.P.; Raudenbusch, W.; Zergenyi, J. *Helv. Chim. Acta* ***1964***, *47*, 1003.

[465] Grob, C.A.; Sieber, A. *Helv. Chim. Acta* ***1967***, *50*, 2520; Green, M.; Pearson, S.C. *J. Chem. Soc. B* ***1969***, 593.

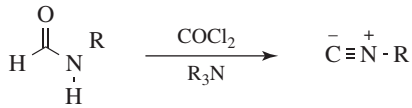
17-28 Dehydration of Unsubstituted Amides



Unsubstituted amides can be dehydrated to nitriles.[466] Phosphorus pentoxide is the most common dehydrating agent for this reaction, but many others, including $POCl_3$, PCl_5, CCl_4/Ph_3P,[467] HMPA,[468] $MeOOCNSO_2NEt_3$ (the *Burgess reagent*),[469] $Me_2N{=}CHCl^+\ Cl^-$,[470] PPh_3/NCS,[471] oxalyl chloride/DMSO/ − 78 °C (*Swern* conditions, see **19-3**),[472] *o*-iodoxybenzoic acid/Et_4NBr,[473] TBAF and hydrosilanes,[474] and $SOCl_2$, have also been used.[475] Heating an amide with paraformaldehyde and formic acid gives the nitrile.[476] It is possible to convert an acid to the nitrile, without isolation of the amide, by heating its ammonium salt with the dehydrating agent,[477] or by other methods.[478] Treatment of an amide with aqueous NaOH and ultrasound leads to the nitrile.[479] *N*-Alkyl-substituted amides can be converted to nitriles and alkyl chlorides by treatment with PCl_5. This is called the *von Braun reaction* (not to be confused with the other von Braun reaction, **10-54**).

OS **I**, 428; **II**, 379; **III**, 493, 535, 584, 646, 768; **IV**, 62, 144, 166, 172, 436, 486, 706; **VI**, 304, 465.

17-29 Conversion of *N*-Alkylformamides to Isonitriles (Isocyanides)



Isocyanides (isonitriles) can be prepared by elimination of water from *N*-alkylformamides[480] with phosgene and a tertiary amine.[481] Other reagents, among

[466] Bieron, J.F.; Dinan, F.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 274–283; Friedrich, K.; Wallenfels, K. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 96–103; Friedrich, K. in Patai, S.; Rapoport, Z. *The Chemistry of Functional Groups*, Supplement C, pt. 2, Wiley, NY, ***1978***, p. 1345.
[467] Harrison, C.R.; Hodge, P.; Rogers, W.J. *Synthesis* ***1977***, 41.
[468] Monson, R.S.; Priest, D.N. *Can. J. Chem.* ***1971***, *49*, 2897.
[469] Claremon, D.A.; Phillips, B.T. *Tetrahedron Lett.* ***1988***, *29*, 2155.
[470] Barger, T.M.; Riley, C.M. *Synth. Commun.* ***1980***, *10*, 479.
[471] Iranpoor, N.; Firouzabadi, H.; Aghapoor, G. *Synth. Commun.* ***2002***, *32*, 2535.
[472] Nakajima, N.; Ubukata, M. *Tetrahedron Lett.* ***1997***, *38*, 2099.
[473] Bhalerao, D.S.; Mahajan, U.S.; Chaudhari, K.H.; Akamanchi, K.G. *J. Org. Chem.* ***2007***, *72*, 662.
[474] Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. *Org. Lett.* ***2009***, *11*, 2461.
[475] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1983–1985.
[476] Heck, M.-P.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* ***1996***, *61*, 6486.
[477] See Imamoto, T.; Takaoka, T.; Yokoyama, M. *Synthesis* ***1983***, 142.
[478] For a list of methods, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1949–1950.
[479] Sivakumar, M.; Senthilkumar, P.; Pandit, A.B. *Synth. Commun.* ***2001***, *31*, 2583.
[480] See Creedon, S.M.; Crowley, H.K.; McCarthy, D.G. *J. Chem. Soc., Perkin Trans. 1* ***1998***, 1015.
[481] Hoffmann, P.; Gokel, G.W.; Marquarding, D.; Ugi, I. in Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, ***1971***, pp. 10–17; Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. *Newer Methods Prep. Org. Chem.* ***1968***, *4*, 37.

them TsCl in quinoline, $POCl_3$ and a tertiary amine,[482] and 2,4,6-trichloro[1,3,5]triazine (cyanuric chloride, TCT) (with microwave irradiation)[483] have also been employed. Formamides react with thionyl chloride (two sequential treatments) to give an intermediate that gives an isonitrile upon electrolysis in DMF with $LiClO_4$.[484]

A variation of this process uses carbodiimides,[485] which can be prepared by the dehydration of *N*,*N*′-disubstituted ureas with various dehydrating agents,[486] among which are TsCl in pyridine, $POCl_3$, PCl_5, P_2O_5/pyridine, and TsCl (with phase-transfer catalysis).[487] Hydrogen sulfide can be removed from the corresponding thioureas by treatment with HgO, NaOCl, or diethyl azodicarboxylate triphenylphosphine.[488] Amines reacted with phenyl chlorothionoformate to give the isothiocyanate.[489]

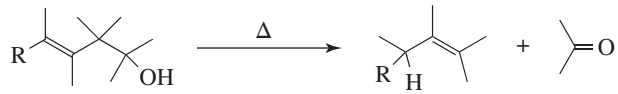
OS **V**, 300, 772; **VI**, 620, 751, 987. See also, OS **VII**, 27.

For the carbodiimide/thiourea dehydration, see OS **V**, 555; **VI**, 951.

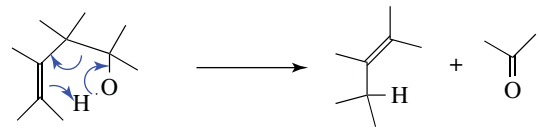
17.F.iv. Reactions in Which C═O Bonds Are Formed

Many elimination-type reactions in which C═O bonds are formed were considered in Chapter 16, along with their more important reverse reactions (also see **12-39** and **12-40**).

17-30 Pyrolysis of β-Hydroxy Alkenes



When pyrolyzed, β-hydroxy alkenes cleave to give alkenes and aldehydes or ketones.[490] Alkenes produced this way are quite pure, since there are no side reactions. The mechanism has been shown to be pericyclic, primarily by observations that the kinetics are first order[491] and that, for ROD, the deuterium appeared in the allylic position of the new alkene.[492] This mechanism is the reverse of that for the oxygen analog of the ene synthesis (**16-53**), as shown.



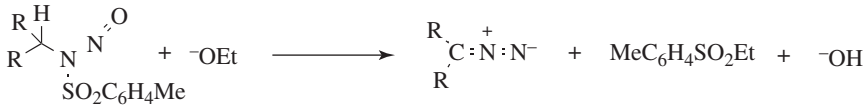
[482] See Obrecht, R.; Herrmann, R.; Ugi, I. *Synthesis* ***1985***, 400.
[483] Porcheddu, A.; Giacomelli, G.; Salaris, M. *J. Org. Chem.* ***2005***, *70*, 2361.
[484] Guirado, A.; Zapata, A.; Gómez, J.L.; Trebalón, L.; Gálvez, J. *Tetrahedron* ***1999***, *55*, 9631.
[485] See Williams, A.; Ibrahim, I.T. *Chem. Rev.* ***1981***, *81*, 589.
[486] Also see Kim, S.; Yi, K.Y. *J. Org. Chem.* ***1986***, *51*, 2613; *Tetrahedron Lett.* ***1986***, *27*, 1925.
[487] Jászay, Z.M.; Petneházy, I.; Töke, L.; Szajáni, B. *Synthesis* ***1987***, 520.
[488] Mitsunobu, O.; Kato, K.; Tomari, M. *Tetrahedron* ***1970***, *26*, 5731.
[489] Li, Z.-Y.; Ma, H.-Z.; Han, C.; Xi, H.-T.; Meng, Q.; Chen, X.; Sun, X.-Q. *Synthesis* ***2013***, *45*, 1667.
[490] Arnold, R.T.; Smolinsky, G. *J. Am. Chem. Soc.* ***1959***, *81*, 6643. For a review, see Marvell, E.N.; Whalley, W. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 2, Wiley, NY, ***1971***, pp. 729–734.
[491] Voorhees, K.J.; Smith, G.G. *J. Org. Chem.* ***1971***, *36*, 1755.
[492] Arnold, R.T.; Smolinsky, G. *J. Org. Chem.* ***1960***, *25*, 128; Smith, G.G.; Taylor, R. *Chem. Ind. (London)* ***1961***, 949.

β-Hydroxyacetylenes react similarly to give the corresponding allenes and carbonyl compounds.[493] The mechanism is the same despite the linear geometry of the triple bonds.

In a related reaction, pyrolysis of allylic ethers that contain at least one α hydrogen gives alkenes and aldehydes or ketones. The mechanism is also pericyclic, analogous to homoallylic alcohols.[494]

17.F.v. Reactions in Which N=N Bonds Are Formed

17-31 Eliminations To Give Diazoalkanes



Various *N*-nitroso-*N*-alkyl compounds undergo elimination to give diazoalkanes.[495] One of the most convenient methods for the preparation of diazomethane involves base treatment of *N*-nitroso-*N*-methyl-*p*-toluenesulfonamide (illustrated above, with R = H).[496] Several other compounds are commonly used to prepare diazomethane and all require base treatment, although the sulfonamide shown, which is commercially available, is most satisfactory. *N*-Nitroso-*N*-methylcarbamate and *N*-nitroso-*N*-methylurea give good yields, but are highly irritating and carcinogenic.[497] For higher diazoalkanes the preferred substrates are nitrosoalkylcarbamates. Most of these reactions probably begin with a 1,3 nitrogen-to-oxygen rearrangement, followed by the actual elimination.

OS **II**, 165; **III**, 119, 244; **IV**, 225, 250; **V**, 351; **VI**, 981.

17.F.vi. Extrusion Reactions

An *extrusion reaction*[498] is one in which a molecule X—Y—Z has an atom or group Y that is initially connected to two other atoms X and Z and which is lost from the molecule, leading to a product in which X is bonded directly to Z. Reactions **14-26** and **17-18** also fit this definition. Reaction **17-26** does not fit the definition, but is often also classified as an extrusion reaction. A scale of extrusion facility has been developed, showing that the ease of extrusion of the common Y groups is in the order: —N=N— > —COO— > —SO_2— > —CO—.[499]

[493] Viola, A.; Proverb, R.J.; Yates, B.L.; Larrahondo, J. *J. Am. Chem. Soc.* ***1973***, *95*, 3609.

[494] Kwart, H.; Slutsky, J.; Sarner, S.F. *J. Am. Chem. Soc.* ***1973***, *95*, 5242; Egger, K.W.; Vitins, P. *Int. J. Chem. Kinet.* ***1974***, *6*, 429.

[495] Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 296–325; Black, T.H. *Aldrichimica Acta* ***1983***, *16*, 3. See Cowell, G.W.; Ledwith, A. *Q. Rev. Chem. Soc.* ***1970***, *24*, 119 (pp. 126–131); Smith, P.A.S. *Open-chain Nitrogen Compounds*, Vol. 2, W.A. Benjamin, NY, ***1966***, pp. 257–258, 474–475.

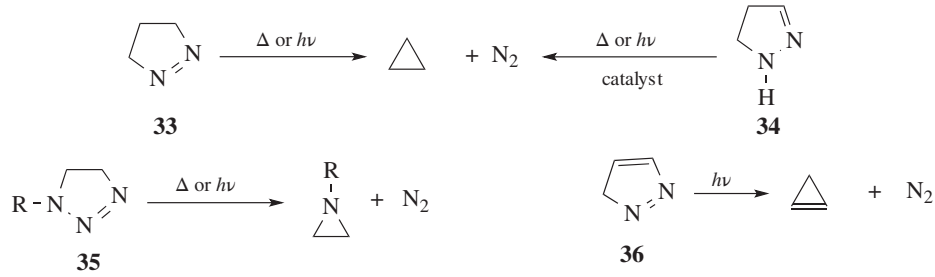
[496] See Hudlicky, M. *J. Org. Chem.* ***1980***, *45*, 5377.

[497] Searle, C.E. *Chem. Br.* ***1970***, *6*, 5.

[498] Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***. For a review of extrusions that are photochemically induced, see Givens, R.S. *Org. Photochem.* ***1981***, *5*, 227.

[499] Paine, A.J.; Warkentin, J. *Can. J. Chem.* ***1981***, *59*, 491.

17-32 Extrusion of N_2 from Pyrazolines, Pyrazoles, and Triazolines



1-Pyrazolines (**33**) can be converted to cyclopropane and N_2 on photolysis[500] or pyrolysis.[501] The tautomeric 2-pyrazolines (**34**), which are more stable than **33**, also give the reaction, but in this case an acidic or basic catalyst is required, the function of which is to convert **34** to **33**.[502] In the absence of such catalysts, **34** does not react.[503] In a similar manner, triazolines (**35**) are converted to aziridines.[504] Side reactions are frequent with both **33** and **35**, and some substrates do not give the reaction at all. However, the reaction has proved synthetically useful in many cases. In general, photolysis gives better yields and fewer side reactions than pyrolysis with both **33** and **35**. 3*H*-Pyrazoles[505] (**36**) are stable to heat, but in some cases can be converted to cyclopropenes on photolysis,[506] although in other cases other types of products are obtained.

The mechanism[507] of the 1-pyrazoline reactions generally involves extrusion of N_2 and formation of diradicals, although the mode of formation and detailed structure (e.g., singlet versus triplet) of these radicals may vary with the substrate and reaction conditions. The reactions of the 3*H*-pyrazoles (**36**) have been postulated to proceed through a diazo compound that loses N_2 to give a vinylic carbene.[508] It is noted that expulsion of N_2 from organic azides used a Au catalyst.[509]

OS **V**, 96, 929. See also, OS **VIII**, 597.

[500] Van Auken, T.V.; Rinehart Jr., K.L. *J. Am. Chem. Soc.* ***1962***, *84*, 3736.

[501] For a review, see Wentrup, C. *Chem. Rev.* ***2017***, *117*, 4562. Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***, pp. 116–151. See Mackenzie, K. in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 1, Wiley, NY, ***1975***, pp. 329–442.

[502] See Jones, W.M.; Sanderfer, P.O.; Baarda, D.G. *J. Org. Chem.* ***1967***, *32*, 1367.

[503] McGreer, D.E.; Wai, W.; Carmichael, G. *Can. J. Chem.* ***1960***, *38*, 2410; Kocsis K.; Ferrini, P.G.; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* ***1960***, *43*, 2178.

[504] For a review, see Scheiner, P. *Sel. Org. Transform.* ***1970***, *1*, 327.

[505] See Sammes, M.P.; Katritzky, A.R. *Adv. Heterocycl. Chem.* ***1983***, *34*, 2.

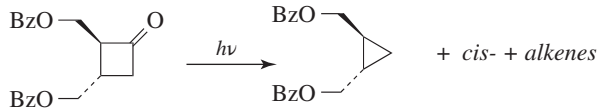
[506] See Pincock, J.A.; Morchat, R.; Arnold, D.R. *J. Am. Chem. Soc.* ***1973***, *95*, 7536.

[507] Engel, P.S. *Chem. Rev.* ***1980***, *80*, 99; Engel, P.S.; Nalepa, C.J. *Pure Appl. Chem.* ***1980***, *52*, 2621; Reedich, D.E.; Sheridan, R.S. *J. Am. Chem. Soc.* ***1988***, *110*, 3697.

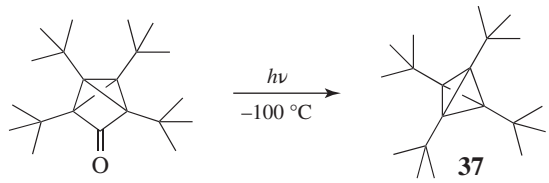
[508] Pincock, J.A.; Morchat, R.; Arnold, D.R. *J. Am. Chem. Soc.* ***1973***, *95*, 7536.

[509] Dash, C.; Yousufuddin, M.; Cundari, T.R.; Dias, H.V.R. *J. Am. Chem. Soc.* ***2013***, *135*, 15479.

17-33 Extrusion of CO or CO_2



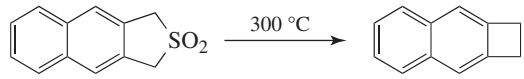
Although the reaction is not general, certain cyclic ketones can be photolyzed to give ring-contracted products.[510] An example is a *trans*-disubstituted cyclobutanone was photolyzed to give the cyclopropane derivative.[511] This reaction was used to synthesize tetra-*tert*-butyltetrahedrane, **37**.[512] The mechanism probably involves a Norrish type I cleavage (Sec. 7.A.vii), loss of CO from the resulting radical, and recombination of the radical fragments.



Certain lactones extrude CO_2 on heating or on irradiation.[513] Decarboxylation of β-lactones (see **17-24**) may be regarded as a degenerate example of this reaction. Unsymmetrical diacyl peroxides RCO—OO—COR′ lose two molecules of CO_2 when photolyzed in the solid state to give the product RR′.[514] Electrolysis was also used, but yields were lower.

There are no OS references, but see OS **VI**, 418, for a related reaction.

17-34 Extrusion of SO_2



In a reaction similar to **17-33**, certain sulfones, both cyclic and acyclic,[515] extrude SO_2 on heating or photolysis to give ring-contracted products.[516] An example is the preparation

[510] See Redmore, D.; Gutsche, C.D. *Adv. Alicyclic Chem.* ***1971***, *3*, 1 (see pp. 91–107); Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***, pp. 47–71.

[511] See Ramnauth, J.; Lee-Ruff, E. *Can. J. Chem.* ***2001***, *79*, 114.

[512] Maier, G.; Pfriem, S.; Schäfer, U.; Matusch, R. *Angew. Chem. Int. Ed.* ***1978***, *17*, 520.

[513] Ried, W.; Wagner, K. *Liebigs Ann. Chem.* ***1965***, *681*, 45.

[514] Lomölder, R.; Schäfer, H.J. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1253.

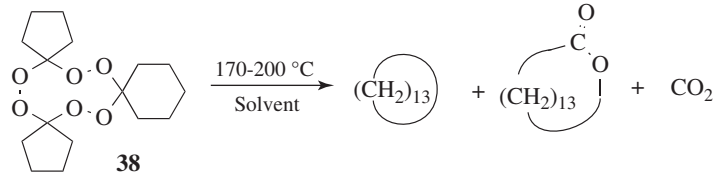
[515] Gould, I.R.; Tung, C.; Turro, N.J.; Givens, R.S.; Matuszewski, B. *J. Am. Chem. Soc.* ***1984***, *106*, 1789.

[516] Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***, pp. 72–90; Kice, J.L. in Kharasch, N.; Meyers, C.Y. *The Chemisry of Organic Sulfur Compounds*, Vol. 2, Pergamon, Elmsford, NY, ***1966***, pp. 115–136; Martial, L.; Bischoff, L. *Synlett* ***2015***, *26*, 1225. For a review using S, Se, and Te compounds, see Guziec Jr., F.S.; SanFilippo, L.J. *Tetrahedron* ***1988***, *44*, 6241.

of naphtho(*b*)cyclobutene shown above.[517] In a different kind of reaction, five-membered cyclic sulfones can be converted to cyclobutenes by treatment with butyllithium followed by $LiAlH_4$.[518] This method is most successful when both the α and α′ position of the sulfone bear alkyl substituents (see also **17-18**). Treating four-membered ring sultams with $SnCl_2$ led to aziridine products via loss of SO_2.[519]

OS **VI**, 482.

17-35 The Story Synthesis

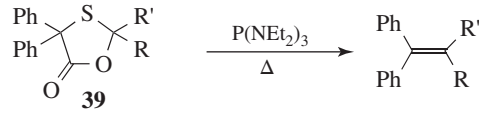


38

When cycloalkylidine peroxides (e.g., **38**) are heated in an inert solvent (e.g., decane), extrusion of CO_2 takes place; the products are the cycloalkane containing three carbon atoms less than the starting peroxide and the lactone containing two carbon atoms less[520] (the *Story synthesis*).[521] The two products are formed in comparable yields, usually ~15–25% each. Although the yields are low, the reaction is useful because there are not many other ways to prepare large rings. The reaction is versatile, having been used to prepare rings of every size from 8 to 33 members.

Both dimeric and trimeric cycloalkylidine peroxides can be synthesized[522] by treatment of the corresponding cyclic ketones with H_2O_2 in acid solution.[523] The trimeric peroxide is formed first and is subsequently converted to the dimeric compound.[524]

17-36 Alkene Synthesis by Two-fold Extrusion

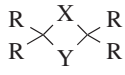


39

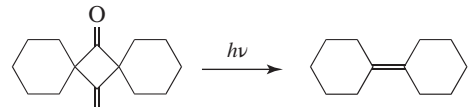
4,4-Diphenyloxathiolan-5-ones (**39**) give good yields of the corresponding alkenes when heated with tris(diethylamino)phosphine.[525] This reaction is an example of a general

[517] Cava, M.P.; Shirley, R.L. *J. Am. Chem. Soc.* ***1960***, *82*, 654.
[518] Photis, J.M.; Paquette, L.A. *J. Am. Chem. Soc.* ***1974***, *96*, 4715.
[519] Kataoka, T.; Iwama, T. *Tetrahedron Lett.* ***1995***, *36*, 5559.
[520] See Sanderson, J.R.; Story, P.R.; Paul, K. *J. Org. Chem.* ***1975***, *40*, 691.
[521] See Story, P.R.; Busch, P. *Adv. Org. Chem.* ***1972***, *8*, 67 (see pp. 79–94).
[522] See Paul, K.; Story, P.R.; Busch, P.; Sanderson, J.R. *J. Org. Chem.* ***1976***, *41*, 1283.
[523] See Ledaal, T. *Acta Chem. Scand.* ***1967***, *21*, 1656. For another method, see Sanderson, J.R.; Zeiler, A.G. *Synthesis* ***1975***, 125.
[524] Story, P.R.; Lee, B.; Bishop, C.E.; Denson, D.D.; Busch, P. *J. Org. Chem.* ***1970***, *35*, 3059. See also, Sanderson, J.R.; Wilterdink, R.J.; Zeiler, A.G. *Synthesis* ***1976***, 479.
[525] Barton, D.H.R.; Willis, B.J. *J. Chem. Soc., Perkin Trans. 1* ***1972***, 305.

type: alkene synthesis by twofold extrusion of X and Y from a molecule of the type **40**.[526] Other examples are photolysis of 1,4-diones[527] (e.g., **41**) and treatment of acetoxy sulfones [$RCH(OAc)CH_2SO_2Ph$] with Mg/EtOH and a catalytic amount of $HgCl_2$.[528]



40



41 1,1'-Bi(cyclohexylidene)

OS **V**, 297.

[526] See Guziec Jr., F.S.; SanFilippo, L.J. *Tetrahedron* ***1988***, *44*, 6241.
[527] Turro, N.J.; Leermakers, P.A.; Wilson, H.R.; Neckers, D.C.; Byers, G.W.; Vesley, G.F. *J. Am. Chem. Soc.* ***1965***, *87*, 2613.
[528] Lee, G.H.; Lee, H.K.; Choi, E.B.; Kim, B.T.; Pak, C.S. *Tetrahedron Lett.* ***1995***, *36*, 5607.

CHAPTER 18

Rearrangements

In a rearrangement reaction, a group moves from one atom to another in the same molecule.[1] Most are migrations from one atom to an adjacent one (called 1,2-shifts), but some are over longer distances (e.g., 1,3- or 1,4-shifts).

The group that migrates:

- may move with its electron pair; these can be called *nucleophilic* or *anionotropic* rearrangements and the migrating group can be regarded as a nucleophile
- may move without its electron pair; these are *electrophilic* or *cationotropic* rearrangements and, in the case of migrating hydrogen, *prototropic* rearrangements
- may move with just one electron; these are radical rearrangements.

The atom or atoms that move begin at the *migration origin* and the new attachment point is the *migration terminus*. However, there are some rearrangements that do not lend themselves to neat categorization in this manner. Among these are those with cyclic transition states (**18-27** to **18-36**). Molecular rearrangements are important components of organic synthesis.[2]

As will be seen, nucleophilic (X**:**) 1,2-shifts are much more common than electrophilic (X^+) or free-radical (X•) 1,2-shifts. The reason for this can be seen by a consideration of the transition states (or in some cases intermediates) involved. In the transition state or intermediate for all three cases, the orbital that connects X overlaps with the orbital on the migration terminus, and the overlap of these orbitals leads to a cyclic transition state that allows the migration.

In any rearrangement, two possible modes of reaction can, in principle, be distinguished. In one of these, the group X becomes completely detached and may end up on the atom of a different molecule (*intermolecular* rearrangement). In the other X migrates in the

[1] de Mayo, P. *Rearrangements in Ground and Excited States*, 3 Vols., Academic Press, NY, ***1980***; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, ***1973***; Collins, C.J.; Eastham, J.F. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 761–821. See also, the series *Mechanisms of Molecular Migrations*.

[2] *Molecular Rearrangements in Organic Synthesis*, Rojas, C.M. (Ed.), Wiley, Hoboken, ***2015***.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

same molecule, which is an *intramolecular* rearrangement. It is usually not difficult to tell whether a given rearrangement is intermolecular or intramolecular. The most common method involves the use of *crossover* experiments. In this type of experiment, rearrangement is carried out on a mixture of W—A—B and V—A—C, where V is closely related to W (say, methyl versus ethyl) and B is closely related to C. In an intramolecular process only A—B—W and A—C—V are recovered, but if the reaction is intermolecular, then not only will these two be found, but also A—B—V and A—C—W.

18.A. MECHANISMS

18.A.i. Nucleophilic Rearrangements[3]

This process of migration of one atom or group to the adjacent atom has been called the *Whitmore 1,2-shift*.[4] Since the migrating group carries the electron pair with it, the migration terminus must be an atom with only six electrons in its outer shell (an open sextet). Such a system can arise in various ways, but two of these are the most important:

1. *Formation of a carbocation*. Carbocations can be formed in a number of ways (Sec. 5.A.iii), but one of the most common methods is the acid treatment of an alcohol to give a carbocation from an intermediate oxonium ion. Once formed, such carbocations are subject to rearrangement to a more stable carbocation. These two steps are of course the same as the first two steps of the S_N1cA or the E1 reactions of alcohols.
2. *Formation of a nitrene*. The decomposition of acyl azides is one of several ways in which acyl nitrenes are formed (Sec. 5.E). Once the nitrene is formed, the R migrates and an electron pair from the nitrogen moves into the C—N bond to give a stable isocyanate.

In both of these cases, after the migration has taken place, the atom at the migration origin must necessarily have an open sextet and in the final step this atom acquires an octet. In the case of carbocations, combinations with a nucleophile (rearrangement with substitution) or loss of H^+ (rearrangement with elimination) constitutes the final step.

In many reactions, the initial steps are simultaneous so there is no formal intermediate. Many investigations have been carried out in attempts to determine, in various reactions, whether intermediates actually form, or whether the steps are simultaneous (see, e.g., the discussions in **16-45** and Sec. 18.A.ii), but the difference between the two possibilities is often subtle, and the question is not always easily answered.[5]

Evidence for the formation of intermediates is that rearrangements occur under conditions where carbocations have previously been encountered: S_N1 conditions, *Friedel-Crafts*

[3] Vogel, P. *Carbocation Chemistry*, Elsevier, NY, ***1985***, pp. 323–372; Shubin, V.G. *Top. Curr. Chem.* ***1984***, *116/117*, 267; Saunders, M.; Chandrasekhar, J.; Schleyer, P.v.R. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 1–53; Kirmse, W. *Top. Curr. Chem.* ***1979***, *80*, 89. For reviews of rearrangements in vinylic cations, see Shchegolev, A.A.; Kanishchev, M.I. *Russ. Chem. Rev.* ***1981***, *50*, 553; Lee, C.C. *Isot. Org. Chem.* ***1980***, *5*, 1.

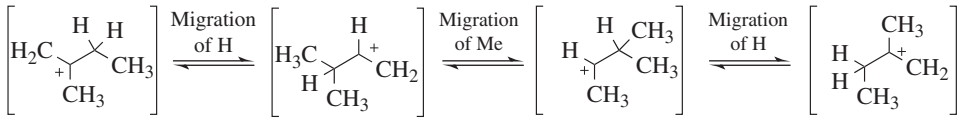
[4] It was first postulated by Whitmore, F.C. *J. Am. Chem. Soc.* ***1932***, *54*, 3274.

[5] The IUPAC designations depend on the nature of the steps. For the rules, see Guthrie, R.D. *Pure Appl. Chem.* ***1989***, *61*, 23 (pp. 44–45).

alkylation, and so on. Solvolysis of neopentyl bromide leads to rearrangement products, and the rate increases with increasing ionizing power of the solvent but is unaffected by concentration of base,[6] so that the first step is carbocation formation. The same compound under S_N2 conditions gave no rearrangement, but slowly gave only ordinary substitution. Thus with neopentyl bromide, formation of a carbocation leads only to rearrangement.

Carbocations usually rearrange to more stable carbocations. Thus the direction of rearrangement is usually primary → secondary → tertiary, based on the relative stability of each carbocation.[7] Each migration is a formally a chemical reaction, and is exothermic by 12–15 kcal mol^{-1} (50–63 kJ mol^{-1}) when the migration generates a tertiary carbocation from a secondary carbocation or a secondary from a primary.[8] Neopentyl- (Me_3CCH_2), neophyl- ($PhCMe_2CH_2$), and norbornyl-type systems are especially prone to carbocation rearrangement reactions. It has been shown that the rate of migration increases with the degree of electron deficiency at the migration terminus.[9]

It was previously mentioned (Sec. 5.A.ii) that stable tertiary carbocations could be obtained, in solution, at very low temperatures. The NMR studies have shown that when these solutions are warmed, rapid migrations of hydride and of alkyl groups take place, resulting in an equilibrium mixture of structures.[10] For example, the *tert*-pentyl (2-methylbutyl) cation[11] equilibrates as shown.



Carbocations that rearrange to give products of identical structure are called *degenerate carbocations* and such rearrangements are *degenerate rearrangements*. Many examples are known.[12]

18.A.ii. The Actual Nature of the Migration

Most nucleophilic 1,2-shifts are intramolecular. The migrating group does not become free, but always remains connected in some way to the substrate. Apart from the evidence from crossover experiments, the strongest evidence is that when the migrating group is chiral, the configuration is *retained* in the product. For example, (+)-$PhCHMeCO_2H$ was converted to

[6] Dostrovsky, I.; Hughes, E.D. *J. Chem. Soc.* ***1946***, 166.

[7] Olah, G.A.; Olah, J.A. *Carbonium Ions*, Vol. 2, Olah, G.A.; Schleyer, P.v.R. (Eds.), Wiley, NY, ***1969***, pp. 715–782; Richey, J.M. *The Chemistry of Alkenes*, Vol. 2, Zabicky, J. (Ed.), Interscience, NY, ***1970***, p. 44.

[8] Arnett, E.M.; Petro, C. *J. Am. Chem. Soc.* ***1978***, *100*, 2563; Saunders, M.; Vogel, P.; Hagen, E.L.; Rosenfeld, J. *Acc. Chem. Res.* ***1973***, *6*, 53; Radom, L.; Pople, J.A.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1972***, *94*, 5935; Brouwer, D.M.; Hogeveen, H. *Prog. Phys. Org. Chem.* ***1972***, *9*, 204.

[9] Borodkin, G.I.; Shakirov, M.M.; Shubin, V.G.; Koptyug, V.A. *J. Org. Chem. USSR* ***1978***, *14*, 290, 924.

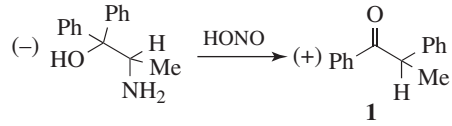
[10] Brouwer, D.M.; Hogeveen, H. *Prog. Phys. Org. Chem.* ***1972***, *9*, 179 (see pp. 203–237); Olah, G.A.; Olah, J.A. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 751–760, 766–778. For a discussion of the rates, see Sorensen, T.S. *Acc. Chem. Res.* ***1976***, *9*, 257.

[11] Brouwer, D.M. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 210; Saunders, M.; Hagen, E.L. *J. Am. Chem. Soc.* ***1968***, *90*, 2436.

[12] Ahlberg, P.; Jonsäll, G.; Engdahl, C. *Adv. Phys. Org. Chem.* ***1983***, *19*, 223; Leone, R.E.; Barborak, J.C.; Schleyer, P.v.R. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1970***, pp. 1837–1939; Leone, R.E.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.* ***1970***, *9*, 860.

(−)-PhCHMeNH$_2$ by the *Curtius* (**18-14**), *Hofmann* (**18-13**), *Lossen* (**18-15**), and *Schmidt* (**18-16**) reactions.[13] In these reactions, the extent of retention varied from 95.8% to 99.6%. Retention of configuration in the migrating group has been shown many times since.[14]

In cases where the steric nature of the migration origin atom or the migration terminus atom can be investigated, the results are mixed, and it has been shown that either inversion or racemization can occur.[15] One example is **1**, where the conversion proceeded with inversion (equivalent to inversion at B).[16]



1 (**18-2**)

Such inversion has been shown in other cases.[17] It is not always necessary for the product to have two steric possibilities in order to investigate the stereochemistry. Thus, in most *Beckmann rearrangements* (**18-17**), only the group *trans* (usually called *anti*) to the hydroxyl group migrates, as illustrated by formation of **2**, which shows inversion.

2

In certain cases of the S_N1-type process, it is possible for migration to take place with net retention of configuration at the migrating terminus because of conformational effects in the carbocation.[18]

A few conclusions may be summarized:

1. The S_N1-type process occurs mostly when the migrating group is a tertiary atom or has one aryl group and at least one other alkyl or aryl group. In other cases, the S_N2-type process is more likely. Inversion of configuration (indicating an S_N2-type process) has been shown for a neopentyl substrate by the use of the chiral neopentyl-1-*d* alcohol.[19] There is other evidence that neopentyl systems undergo rearrangement by a carbocation (S_N1-type) mechanism.[20]
2. The question as to whether a cyclic, bridged cationic species is an intermediate or a transition state has been much debated. When R is aryl or vinyl, then a

[13] Campbell, A.; Kenyon, J. *J. Chem. Soc.* ***1946***, 25, and references cited therein.

[14] See Kirmse, W.; Gruber, W.; Knist, J. *Chem. Ber.* ***1973***, *106*, 1376; Borodkin, G.I.; Panova, Y.B.; Shakirov, M.M.; Shubin, V.G. *J. Org. Chem. USSR* ***1983***, *19*, 103. See Cram, D.J. in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, pp. 251–254; Wheland, G.W. *Advanced Organic Chemistry*, 3rd ed., Wiley, NY, ***1960***, pp. 597–604.

[15] See Winstein, S.; Morse, B.K. *J. Am. Chem. Soc.* ***1952***, *74*, 1133.

[16] Bernstein, H.I.; Whitmore, F.C. *J. Am. Chem. Soc.* ***1939***, *61*, 1324. For other examples, see Tsuchihashi, G.; Tomooka, K.; Suzuki, K. *Tetrahedron Lett.* ***1984***, *25*, 4253.

[17] See Meerwein, H.; Gérard, L. *Liebigs Ann. Chem.* ***1923***, *435*, 174.

[18] Collins, C.J.; Benjamin, B.M. *J. Org. Chem.* ***1972***, *37*, 4358, and references cited therein.

[19] Mosher, H.S. *Tetrahedron* ***1974***, *30*, 1733. See also, Guthrie, R.D. *J. Am. Chem. Soc.* ***1967***, *89*, 6718.

[20] Shiner Jr., V.J.; Imhoff, M.A. *J. Am. Chem. Soc.* ***1985***, *107*, 2121.

bridged cationic species is probably an intermediate and the migrating group lends anchimeric assistance[21] (Sec. 10.C.i, category 3, preceding category 4 for resonance stabilization of this intermediate, when R is aryl). When R is alkyl, a bridged cationic species is a protonated cyclopropane (edge- or corner-protonated; Sec. 15.B.iv). There is much evidence that in simple migrations of a methyl group, the bulk of the products formed do not arise from protonated cyclopropane *intermediates*. Evidence for this statement has already been given (Sec. 10.C.i, category 4c). Further evidence was obtained from experiments involving labeling.

Rearrangement of the neopentyl cation labeled with deuterium in the 1 position gave only *tert*-pentyl products with the label in the 3 position, although if a cyclic, bridged intermediate were an intermediate, the cyclopropane ring could just as well cleave the other way to give *tert*-pentyl derivatives labeled in the 4 position.[22] Another experiment that led to the same conclusion was the generation, in several ways, of $Me_3C^{13}CH_2^+$. The only *tert*-pentyl products isolated were labeled in C-3, that is, $Me_2C^+—^{13}CH_2CH_3$ derivatives; no derivatives of $Me_2C^+—CH_2{}^{13}CH_3$ were found.[23]

Although the bulk of the products are not formed from protonated cyclopropane intermediates, there is considerable evidence that in 1-propyl systems at least, a small part of the product can in fact arise from such intermediates.[24] Among this evidence is the isolation of 10–15% cyclopropanes (mentioned in Sec. 10.C.i, category 4c). Additional evidence comes from propyl cations generated by diazotization of labeled amines ($CH_3CH_2CD_2^+$, $CH_3CD_2CH_2^+$, $CH_3CH_2{}^{14}CH_2^+$), where isotopic distribution in the products indicated that a small amount (∼5%) of the product had to be formed from protonated cyclopropane intermediates.[25] Even more scrambling was found in trifluoroacetolysis of 1-propyl-1-^{14}C-mercuric perchlorate.[26] However, protonated cyclopropane intermediates accounted for < 1% of the products from diazotization of labeled isobutylamine[27] and from formolysis of labeled 1-propyl tosylate.[28]

It is likely that protonated cyclopropane transition states or intermediates are also responsible for certain non-1,2-rearrangements.[29] For example, in superacid solution, the tertiary carbocation of 2,3-dimethylbutyl and the tertiary carbocation of 2-methylpentyl are in equilibrium. It is not possible for these to interconvert solely by 1,2-alkyl or 1,2-hydride shifts unless primary carbocations (which are highly

[21] Rachoń, J.; Goedken, V.; Walborsky, H.M. *J. Org. Chem.* ***1989***, *54*, 1006. For an opposing view, see Kirmse, W.; Plath, P.; Schaffrodt, H. *Chem. Ber.* ***1975***, *108*, 79.

[22] Skell, P.S.; Starer, I.; Krapcho, A.P. *J. Am. Chem. Soc.* ***1960***, *82*, 5257.

[23] Karabatsos, G.J.; Orzech Jr., C.E.; Meyerson, S. *J. Am. Chem. Soc.* ***1964***, *86*, 1994.

[24] Saunders, M.; Vogel, P.; Hagen, E.L.; Rosenfeld, J. *Acc. Chem. Res.* ***1973***, *6*, 53; Lee, C.C. *Prog. Phys. Org. Chem.* ***1970***, *7*, 129; Collins, C.J. *Chem. Rev.* ***1969***, *69*, 543. See also, Cooper, C.N.; Jenner, P.J.; Perry, N.B.; Russell-King, J.; Storesund, H.J.; Whiting, M.C. *J. Chem. Soc., Perkin Trans. 2* ***1982***, 605.

[25] Karabatsos, G.J.; Orzech Jr., C.E.; Fry, J.L.; Meyerson, S. *J. Am. Chem. Soc.* ***1970***, *92*, 606.

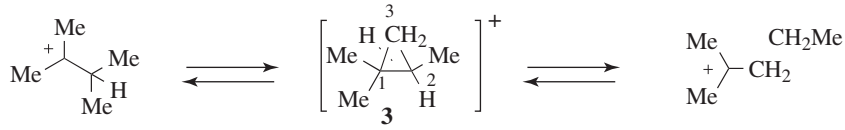
[26] Lee, C.C.; Cessna, A.J.; Ko, E.C.F.; Vassie, S. *J. Am. Chem. Soc.* ***1973***, *95*, 5688. See also, Lee, C.C.; Reichle, R. *J. Org. Chem.* ***1977***, *42*, 2058 and references cited therein.

[27] Karabatsos, G.J.; Hsi, N.; Meyerson, S. *J. Am. Chem. Soc.* ***1970***, *92*, 621. See also, Karabatsos, G.J.; Anand, M.; Rickter, D.O.; Meyerson, S. *J. Am. Chem. Soc.* ***1970***, *92*, 1254.

[28] Karabatsos, G.J.; Fry, J.L.; Meyerson, S. *J. Am. Chem. Soc.* ***1970***, *92*, 614. See also, Lee, C.C.; Zohdi, H.F. *Can. J. Chem.* ***1983***, *61*, 2092.

[29] Sandbeck, D.J.; Markewich, D.J.; East, A.L.L. *J. Org. Chem.* ***2016***, *81*, 1410.

unlikely) are intermediates. However, the reaction can be explained[30] by postulating that (in the forward reaction) it is the 1,2-bond of the intermediate or transition state **3** that opens up rather than the 2,3-bond, which is the one that would open if the reaction were a normal 1,2-shift of a methyl group. In this case, opening of the 1,2-bond produces a tertiary cation, while opening of the 2,3-bond would give a secondary cation.

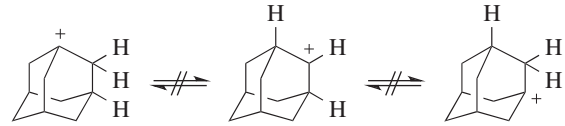


3

3. There has been much discussion of H as migrating group. There is no conclusive evidence that a bridged, cyclic intermediate is or is not a true intermediate, although arguments in favor of each position has been made (Sec. 10.C.i, category 4c).

   The stereochemistry at the migration origin is less often involved, since in most cases migration origin does not end up as a tetrahedral atom; but when there is inversion here, there is an S_N2-type process at the beginning of the migration. This may or may not be accompanied by an S_N2 process at the migration terminus. In some cases, it has been found that, when H is the migrating species, the configuration at A may be *retained*.[31]

   There is evidence that the configuration of the molecule may be important even where the leaving group is gone long before migration takes place. For example, the 1-adamantyl cation (**4**) does not equilibrate intramolecularly, even at temperatures up to 130 °C,[32] though open-chain and cyclic tertiary carbocations undergo such equilibration at 0 °C or below. On the basis of this and other evidence it has been concluded that for a 1,2-shift of hydrogen or methyl to proceed as smoothly as possible, the vacant *p* orbital of the carbon bearing the positive charge and the sp^3 orbital carrying the migrating group must be coplanar,[32] which is not possible for **4**.



4 **4'**

18.A.iii. Migratory Aptitudes[33]

In many reactions, there is no question about which group migrates. For example, in the *Hofmann*, *Curtius*, and similar reactions there is only one possible migrating group in each molecule, and one can measure migratory aptitudes only by comparing the relative

[30] See Saunders, M.; Vogel, P. *J. Am. Chem. Soc.* ***1971***, *93*, 2559, 2561; Kirmse, W.; Loosen, K.; Prolingheuer, E. *Chem. Ber.* ***1980***, *113*, 129.

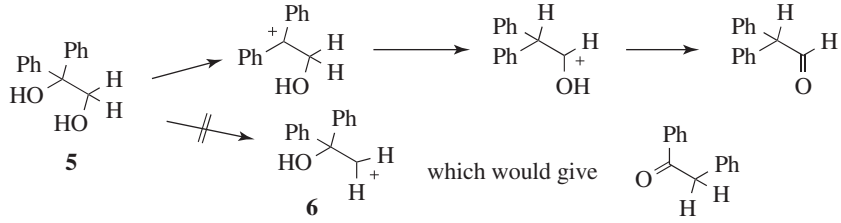
[31] Kirmse, W.; Ratajczak, H.; Rauleder, G. *Chem. Ber.* ***1977***, *110*, 2290.

[32] See Majerski, Z.; Schleyer, P.v.R.; Wolf, A.P. *J. Am. Chem. Soc.* ***1970***, *92*, 5731.

[33] See Koptyug, V.A.; Shubin, V.G. *J. Org. Chem. USSR* ***1980***, *16*, 1685; Wheland, G.W. *Advanced Organic Chemistry*, 3rd ed., Wiley, NY, ***1960***, pp. 573–597.

rearrangement rates of different compounds. In other instances, there are two or more potential migrating groups, but which migrates is settled by the geometry of the molecule. The *Beckmann rearrangement* (**18-17**) provides an example. As seen in the formation of **2**, only the group *trans* to the OH migrates. In compounds whose geometry is not restricted in this manner, there still may be eclipsing effects (Sec. 17.C), so that the choice of migrating group is largely determined by which group is in the right place in the most stable conformation of the molecule.[34] However, in some reactions, especially the W*agner-Meerwein* (**18-1**) and the *pinacol* (**18-2**) rearrangements, the molecule may contain several groups that, geometrically at least, have approximately equal chances of migrating, and these reactions have often been used for the direct study of relative migratory aptitudes. In the *pinacol rearrangement*, there is the additional question of which OH group leaves and which does not, since a group can migrate only if the OH group on *the other* carbon is lost.

The migration of several possible groups will be dealt with first. To study this question, the best type of substrate to use is one of the form $R_2C(OH)—C(OH)R'_2$, since the only thing that determines migratory aptitude is which OH group comes off. Once the OH group is gone, the migrating group is determined. As might be expected, the OH that leaves is the one whose loss gives rise to the more stable carbocation. Thus 1,1-diphenylethanediol (**5**) gives diphenylacetaldehyde, not phenylacetophenone. Obviously, it does not matter in this case whether phenyl has a greater inherent migratory aptitude than hydrogen or not. Only the hydrogen can migrate because **6** is *not* formed.



Remember that carbocation stability is enhanced by groups in the order aryl > alkyl > hydrogen, and this normally determines which side loses the OH group. However, exceptions are known, and which group is lost may depend on the reaction conditions.

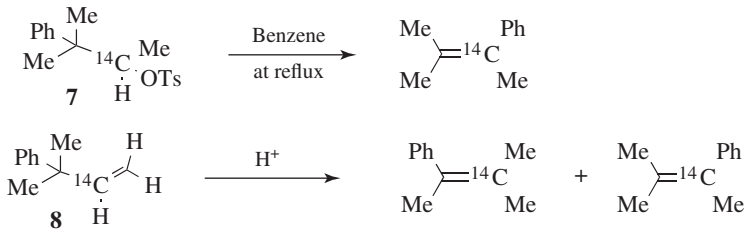
In order to answer the question about inherent migratory aptitudes, the obvious type of substrate to use (in the pinacol rearrangement) is R′RC(OH)—C(OH)RR′, since the same carbocation is formed no matter which OH leaves, and it would seem that a direct comparison of the migratory tendencies of R and R′ is possible. On closer inspection, however, it is clear that several factors are operating. Apart from the question of possible conformational effects, already mentioned, there is also the fact that whether the group R or R′ migrates is determined not only by the relative inherent migrating abilities of R and R′ but also by whether the group that does *not* migrate is better at stabilizing the positive charge that will now be found at the migration origin.[35] Thus, migration of R gives rise to the cation $R'C^+(OH)CR_2R_2'$, while migration of R′ gives the cation $R^+C(OH)CRR_2'$ and these cations have different stabilities. It is possible that in a given case R might be found to

[34] See Cram, D.J. in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, pp. 270–276. For an interesting example, see Nickon, A.; Weglein, R.C. *J. Am. Chem. Soc.* ***1975***, *97*, 1271.

[35] See McCall, M.J.; Townsend, J.M.; Bonner, W.A. *J. Am. Chem. Soc.* ***1975***, *97*, 2743; Brownbridge, P.; Hodgson, P.K.G.; Shepherd, R.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* ***1976***, 2024.

migrate less than R′ not because it actually has a lower inherent migrating tendency, but because it is much better at stabilizing the positive charge. In addition to this factor, the migrating ability of a group is also related to its capacity to render anchimeric assistance to the departure of the nucleofuge.

An example of this effect is the decomposition of tosylate **7**, where only the phenyl group migrates. However, in acid treatment of the corresponding alkene **8**, there is competitive migration of both methyl and phenyl (in these reactions ^{14}C labeling is necessary to determine which group has migrated).[36] Both **7** and **8** give the same carbocation; the differing results must be caused by the fact that in **7** the phenyl group can assist the leaving group, while no such process is possible for **8**.



This example clearly illustrates the difference between migration to a relatively free terminus and one that proceeds with the migrating group lending anchimeric assistance.[37]

Therefore, it is not surprising that clear-cut answers as to relative migrating tendencies are not available. More often than not migratory aptitudes are in the order aryl > alkyl, but exceptions are known, and the position of hydrogen in this series is often unpredictable. In some cases, migration of hydrogen is preferred to aryl migration; in other cases, migration of alkyl is preferred to that of hydrogen. Mixtures are often found, and the isomer that predominates often depends on conditions. For example, the comparison between methyl and ethyl has been made many times in various systems, and in some cases methyl migration has been found to predominate and in others it is ethyl migration that does.[38] However, it can be said that among aryl migrating groups, electron-donating substituents in the *para* and *meta* positions increase the migratory aptitudes, while the same substituents in the *ortho* positions decrease them. Electron-withdrawing groups decrease migrating ability in all positions. The following are a few of the relative migratory aptitudes determined for aryl groups:[39] *p*-anisyl, 500; *p*-tolyl, 15.7; *m*-tolyl, 1.95; phenyl, 1.00; *p*-chlorophenyl, 0.7; *o*-anisyl, 0.3. For the *o*-anisyl group, the poor migrating ability probably has a steric cause, while for the others there is a fair correlation with activation or deactivation of electrophilic aromatic substitution, which is what the process is with respect to the benzene ring. It has been reported that at least in certain systems acyl groups have a greater migratory aptitude than alkyl groups.[40]

[36] Grimaud, J.; Laurent, A. *Bull. Soc. Chim. Fr.* ***1967***, 3599.

[37] See Fischer, A.; Henderson, G.N. *J. Chem. Soc., Chem. Commun.* ***1979***, 279, and references cited therein. See also, Marx, J.N.; Hahn, Y.P. *J. Org. Chem.* ***1988***, *53*, 2866.

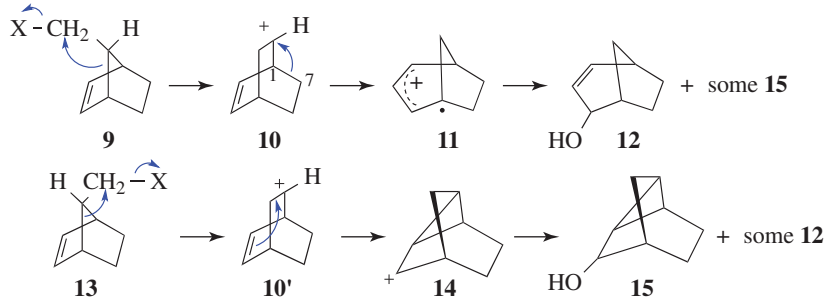
[38] See Wistuba, E.; Rüchardt, C. *Tetrahedron Lett.* ***1981***, *22*, 4069; Jost, R.; Laali, K.; Sommer, J. *Nouv. J. Chim.* ***1983***, *7*, 79.

[39] Bachmann, W.E.; Ferguson, J.W. *J. Am. Chem. Soc.* ***1934***, *56*, 2081.

[40] Le Drian, C.; Vogel, P. *Helv. Chim. Acta* ***1987***, *70*, 1703; *Tetrahedron Lett.* ***1987***, *28*, 1523.

18.A.iv. Memory Effects[41]

Solvolysis of the *endo* bicyclic compound **9** (X = ONs, Sec. 10.G.iii, or Br) gave mostly the bicyclic allylic alcohol **12**, along with a smaller amount of the tricyclic alcohol **15**, while solvolysis of the *exo* isomers, **13**, gave mostly **15**, with smaller amounts of **12**.[42] Note that *endo* and *exo* here refers to the position of the XCH_2 group over the C=C unit or opposite the C=C unit, respectively.



The two isomers gave entirely different ratios of products, although the carbocation initially formed seems to be the same for each (marked **10** and **10′** for convenience). With **10**, a second rearrangement (a shift of the 1,7-bond) follows to give **11**, while with **10′** an intramolecular addition of the positive carbon to the double bond gives **14**. It seems as if **10** and **10′** "remember" how they were formed before they go on to give the second step. Such effects are called *memory effects* and other such cases are known.[43] The causes of these effects are not well understood, although there has been much discussion. One possible cause is differential solvation of the apparently identical ions **10** and **10′**. Other possibilities are: (i) that the ions have geometrical structures that are twisted in opposite senses (e.g., a twisted **10′** might have its positive carbon closer to the double bond than a twisted **10**); (ii) that ion pairing is responsible;[44] and (iii) that nonclassical carbocations are involved.[45]

Twisted **10** Twisted **10'**

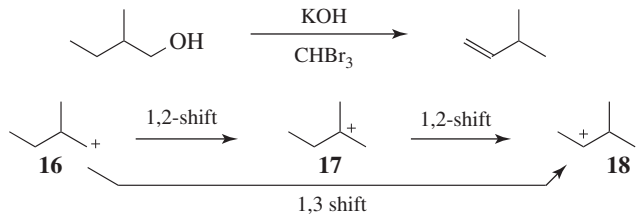
One possibility that has been ruled out is that the steps **9** → **10** → **11** and **13** → **10′** → **14** are concerted, so that **10**/**10′** never exist at all. This possibility has been excluded by several kinds of evidence, including the fact that **9** gives not only **12**, but also some **15**; and **13** gives some **12** along with **15**. This means that some of the **10** and **10′** ions interconvert, a phenomenon known as *leakage*.

[41] For a review, see Berson, J.A. *Angew. Chem. Int. Ed.* ***1968***, *7*, 779.
[42] See Berson, J.A.; Wege, D.; Clarke, G.M.; Bergman, R.G. *J. Am. Chem. Soc.* ***1969***, *91*, 5594, 5601 and other papers in this series.
[43] See Collins, C.J. *Acc. Chem. Res.* ***1971***, *4*, 315; Collins, J.A.; Glover, I.T.; Eckart, M.D.; Raaen, V.F.; Benjamin, B.M.; Benjaminov, B.S. *J. Am. Chem. Soc.* ***1972***, *94*, 899; Svensson, T. *Chem. Scr.* ***1974***, *6*, 22.
[44] See Collins, C.J. *Chem. Soc. Rev.* ***1975***, *4*, 251.
[45] See Kirmse, W.; Günther, B. *J. Am. Chem. Soc.* ***1978***, *100*, 3619.

18.B. LONGER NUCLEOPHILIC REARRANGEMENTS

The question as to whether a group can migrate with its electron pair to an adjacent atom or over longer distances has been much debated. Although claims have been made that alkyl groups can migrate over distance, the evidence is that such migration is extremely rare, if it occurs at all. One experiment that demonstrated that such migrations are rare was the generation of the 3,3-dimethyl-1-butyl cation $Me_3CCH_2CH_2^+$. If 1,3-methyl migrations are possible, this cation would appear to be a favorable substrate, since such a migration would convert a primary cation into the tertiary 2-methyl-2-pentyl cation $Me_2C^+CH_2CH_2CH_3$, while the only possible 1,2-migration (of hydride) would give only a secondary cation. However, no products arising from the 2-methyl-2-pentyl cation were found, with the only rearranged products being those formed by the 1,2-hydride migration.[46] 1,3-Migration of bromine has been reported.[47]

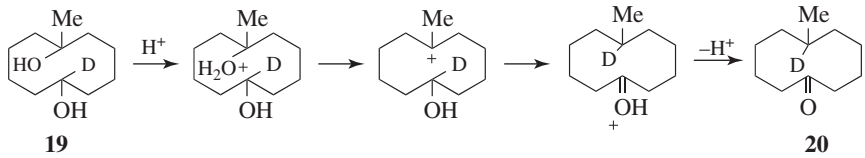
Most of the debate over the possibility of 1,3-migrations has concerned not methyl or bromine but 1,3-hydride shifts.[48] Many instances have been found of *apparent* 1,3-hydride shifts, but the question is whether they are truly direct hydride shifts or whether they occur by another mechanism. There are at least two ways in which indirect 1,3-hydride shifts can take place: (i) by successive 1,2-shifts or (ii) through the intervention of protonated cyclopropanes (Sec. 18.A.ii, category 2). A direct 1,3-shift would have a four-centered transition state, while the transition state for a 1,3-shift involving a protonated cyclopropane intermediate would resemble a three-centered transition state. The evidence is that most reported 1,3-hydride shifts are actually the result of successive 1,2-migrations,[49] but in some cases small amounts of products cannot be accounted for in this way. The reaction of 2-methylbutan-1-ol with KOH and bromoform gave a mixture of alkenes, nearly all of which could have arisen from simple elimination or 1,2-shifts of hydride or alkyl. However, 1.2% of the product was 3-methylbut-1-ene.[50] Hypothetically, 3-methylbut-1-ene could have arisen from a 1,3-shift (direct or through a protonated cyclopropane) or from two successive 1,2-shifts:



However, the same reaction applied to 2-methylbutan-2-ol gave no 3-methylbut-1-ene., which demonstrated that **18** was not formed from **17**. The conclusion made was that **18** was formed directly from **16**. This experiment does not answer the question as to whether **18** was formed by a direct shift or through a protonated cyclopropane, but from other evidence[51]

[46] Skell, P.S.; Reichenbacher, P.H. *J. Am. Chem. Soc.* ***1968***, *90*, 2309.
[47] Reineke, C.E.; McCarthy Jr., J.R. *J. Am. Chem. Soc.* ***1970***, *92*, 6376; Smolina, T.A.; Gopius, E.D.; Gruzdneva, V.N.; Reutov, O.A. *Doklad. Chem.* ***1973***, *209*, 280.
[48] See Fry, J.L.; Karabatsos, G.J. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, p. 527.
[49] See Kirmse, W.; Knist, J.; Ratajczak, H. *Chem. Ber.* ***1976***, *109*, 2296.
[50] Skell, P.S.; Maxwell, R.J. *J. Am. Chem. Soc.* ***1962***, *84*, 3963. See also, Skell, P.S.; Starer, I. *J. Am. Chem. Soc.* ***1962***, *84*, 3962.
[51] Hudson, H.R.; Koplick, A.J.; Poulton, D.J. *Tetrahedron Lett.* ***1975***, 1449; Fry, J.L.; Karabatsos, G.J. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 527.

it appears that 1,3-hydride shifts that do not result from successive 1,2-migrations usually take place through protonated cyclopropane intermediates, which (Sec. 18.A.ii, category 2) account for only a small percentage of the product in any case. However, there is evidence that direct 1,3-hydride shifts occur by way of a bridging hydrogen atom between C1 and C3, and may take place in superacid solutions.[52] Although direct nucleophilic rearrangements over distances greater than 1,2 are rare (or perhaps nonexistent) when the migrating atom or group must move *along* a chain, this is not so for a shift *across* a ring of 8–11 members. Many such transannular rearrangements are known[53] (Sec. 4.Q.ii): the mechanism for the conversion of **19** to **20** is shown.[54]



19 **20**

It is noteworthy that the *methyl* group does not migrate in this system. *It is generally true that alkyl groups do not undergo transannular migration*.[55] In most cases, it is hydride that undergoes this type of migration, though a small amount of phenyl migration has also been shown.[56]

18.C. FREE-RADICAL REARRANGEMENTS[57]

1,2-Free-radical rearrangements are much less common than the nucleophilic type previously considered, for the reasons mentioned in the introductory section to this chapter (preceding Sec. 18.A). Where 1,2-free-radical rearrangements do occur, the general pattern is similar.

1. There must first be generation of a free radical.
2. Then the actual migration occurs, in which the migrating group moves with one electron:

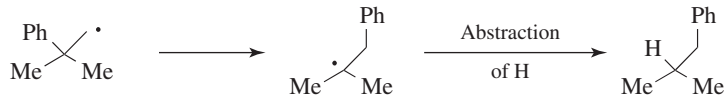
$$R{-}A{-}B\bullet \rightarrow \bullet A{-}B{-}R$$

3. Finally, the new free radical will undergo a further reaction to generate a neutral molecule.

[52] Saunders, M.; Stofko Jr., J.J. *J. Am. Chem. Soc.* ***1973***, *95*, 252.
[53] See Cope, A.C.; Martin, M.M.; McKervey, M.A. *Q. Rev. Chem. Soc.* ***1966***, *20*, 119.
[54] Prelog, V.; Küng, W. *Helv. Chim. Acta* ***1956***, *39*, 1394.
[55] For an apparent exception, see Farcasiu, D.; Seppo, E.; Kizirian, M.; Ledlie, D.B.; Sevin, A. *J. Am. Chem. Soc.* ***1989***, *111*, 8466.
[56] Cope, A.C.; Burton, P.E.; Caspar, M.L. *J. Am. Chem. Soc.* ***1962***, *84*, 4855.
[57] Beckwith, A.L.J.; Ingold, K.U. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 161–310; Wilt, J.W. in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 333–501; Stepukhovich, A.D.; Babayan, V.I. *Russ. Chem. Rev.* ***1972***, *41*, 750; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, London, ***1974***, pp. 498–552; Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***, pp. 235–255; Freidlina, R.Kh. *Adv. Free-Radical Chem.* ***1965***, *1*, 211–278; Pryor, W.A. *Free Radicals*, McGraw-Hill, NY, ***1966***, pp. 266–284. See Kippo, T.; Hamaoka, K.; Ryu, I. *J. Am. Chem. Soc.* ***2013***, *135*, 632.

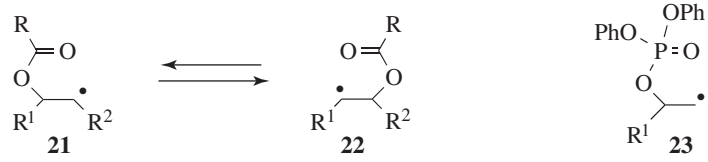
The order of radical stability leads to a prediction that here too, as with carbocation rearrangements, that migrations should be in the order primary → secondary → tertiary. The logical place to look for free-radical rearrangements should be in neopentyl and neophyl systems.

The most common way of generating free radicals for the purpose of detection of rearrangements is by decarbonylation of aldehydes (**14-26**). In this manner, it was found that neophyl radicals *do* undergo rearrangement.[58] Thus, $PhCMe_2CH_2CHO$ treated with di-*tert*-butyl peroxide gave about equal amounts of the normal product $PhCMe_2CH_3$ and of the product arising from migration of phenyl, as shown.[59]



Many other cases of free-radical migration of aryl groups have been found.[60] Intramolecular radical rearrangements are known.[61] The C4 radicals of α- and β-thujone undergo two distinct rearrangement reactions, and it has been proposed that these could serve as simultaneous but independent radical clocks.[62]

A 1,2-shift has been observed in radicals bearing an OCOR group at the β carbon where the oxygen group migrates, as shown in the interconversion of **21** and **22**. This has been proven by ^{18}O isotopic labeling experiments[63] and other mechanistic explorations.[64] A similar rearrangement was observed with phosphatoxy alkyl radicals such as **23**.[65]



A 1,2-shift of hydrogen atoms has been observed in aryl radicals.[66]

It is noteworthy that the extent of migration is much less than with corresponding carbocations: thus in the rearrangement of **21** there was only ~50% migration, whereas the carbocation would have given much more. Also noteworthy is that there was no migration of the methyl group. In general, it may be said that free-radical migration of alkyl groups does not occur at ordinary temperatures. Many attempts have been made to detect such migration on the traditional neopentyl and bornyl types of substrates. However, alkyl migration is not observed, even in substrates where the corresponding carbocations undergo

[58] Antunes, C.S.A.; Bietti, M.; Ercolani, G.; Lanzalunga, O.; Salamone, M. *J. Org. Chem.* ***2005***, *70*, 3884.

[59] Seubold Jr., F.H. *J. Am. Chem. Soc.* ***1953***, *75*, 2532. For the observation of this rearrangement by ESR, see Hamilton Jr., E.J.; Fischer, H. *Helv. Chim. Acta* ***1973***, *56*, 795.

[60] See Walter, D.W.; McBride, J.M. *J. Am. Chem. Soc.* ***1981***, *103*, 7069, 7074. For a review, see Studer, A.; Bossart, M. *Tetrahedron* ***2001***, *57*, 9649.

[61] Prévost, N.; Shipman, M. *Org. Lett.* ***2001***, *3*, 2383.

[62] He, X.; Ortiz de Montellano, P.R. *J. Org. Chem.* ***2004***, *69*, 5684.

[63] Crich, D.; Filzen, G.F. *J. Org. Chem.* ***1995***, *60*, 4834.

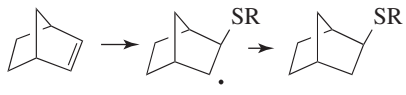
[64] Beckwith, A.L.J.; Duggan, P.J. *J. Chem. Soc., Perkin Trans. 2* ***1992***, 1777; ***1993***, 1673.

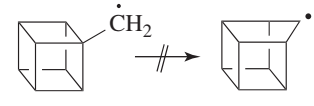
[65] Crich, D.; Yao, Q. *Tetrahedron Lett.* ***1993***, *34*, 5677. See Ganapathy, S.; Cambron R.T.; Dockery, K.P.; Wu, Y.-W.; Harris, J.M.; Bentrude, W.G. *Tetrahedron Lett.* ***1993***, *34*, 5987.

[66] Brooks, M.A.; Scott, L.T. *J. Am. Chem. Soc.* ***1999***, *121*, 5444.

facile rearrangement.[67] Another type of migration that is very common for carbocations, but not observed for free radicals, is 1,2-migration of hydrogen. Examples of the lack of migration of alkyl groups and hydrogen include the following:

1. 3,3-Dimethylpentanal ($EtCMe_2CH_2CHO$) gave no rearranged products on decarbonylation.[68]
2. Addition of RSH to norbornene gave only *exo*-norbornyl sulfides, and the secondary radical is an intermediate, but the corresponding carbocation cannot be formed without rearrangement.[69]





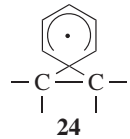
Cubylcarbinyl radical — 1-Homocubyl radical

3. The cubylcarbinyl radical did not rearrange to the 1-homocubyl radical, although doing so would result in a considerable decrease in strain.[70]
4. It was shown[71] that no rearrangement of isobutyl radical to *tert*-butyl radical (which would involve the formation of a more stable radical by a hydrogen shift) took place during the chlorination of isobutane.

The 1,2-migration of alkyl groups has been shown to occur in certain *diradicals*.[72] For example, the following rearrangement has been established by tritium labeling.[73]

In this case, the fact that migration of the methyl group leads directly to a compound in which all electrons are paired undoubtedly contributes to the driving force of the reaction.

The fact that aryl groups migrate, but alkyl groups and hydrogen generally do not, leads to the proposition that **24**, in which the odd electron is not found in the three-membered ring, may be an intermediate.

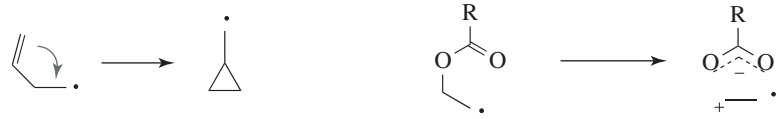


24

[67] Several unsuccessful attempts: Slaugh, L.H.; Magoon, E.F.; Guinn, V.P. *J. Org. Chem.* ***1963***, *28*, 2643.
[68] Seubold Jr., F.H. *J. Am. Chem. Soc.* ***1954***, *76*, 3732.
[69] Cristol, S.J.; Brindell, G.D. *J. Am. Chem. Soc.* ***1954***, *76*, 5699.
[70] Eaton, P.E.; Yip, Y. *J. Am. Chem. Soc.* ***1991***, *113*, 7692.
[71] Brown, H.C.; Russel, G.A. *J. Am. Chem. Soc.* ***1952***, *74*, 3995. See also, Desai, V.R.; Nechvatal, A.; Tedder, J.M. *J. Chem. Soc. B* ***1970***, 386.
[72] See Freidlina, R.Kh.; Terent'ev, A.B. *Russ. Chem. Rev.* ***1974***, *43*, 129.
[73] McKnight, C.; Rowland, F.S. *J. Am. Chem. Soc.* ***1966***, *88*, 3179. See Gajewski, J.J.; Burka, L.T. *J. Am. Chem. Soc.* ***1972***, *94*, 8857, 8860, 8865.

There has been much controversy on this point, but the bulk of the evidence indicates that **24** is a transition state, not an intermediate.[74] Among the evidence is the failure to observe **24** either by ESR[75] or CIDNP.[76] Both of these techniques can detect free radicals with extremely short lifetimes (Sec. 5.C.i).[77]

Besides aryl, both vinylic[78] and acetoxy groups[79] also migrate. Vinylic groups migrate via a cyclopropylcarbinyl radical intermediate,[80] while the migration of acetoxy groups may involve the charge-separated structure shown in the figure (to the right).[81]



Thermal isomerization of 1-(3-butenyl)cyclopropane at 415 °C leads to bicyclo[2.2.1]heptane.[82]

Migration has been observed for chloro (and to a much lesser extent bromo) groups. For example, in the reaction of $Cl_3CCH{=}CH_2$ with bromine under the influence of peroxides, the products were 47% $Cl_3CCHBrCH_2Br$ (the normal addition product) and 53% $BrCCl_2CHClCH_2Br$, which arose by rearrangement. In this particular case the driving force for the rearrangement is the particular stability of dichloroalkyl free radicals.[83] It has been shown that the 1,2-migration of Cl readily occurs if the migration origin is tertiary and the migration terminus primary.[84] Migration of Cl and Br could take place by a transition state in which the odd electron is accommodated in a vacant *d* orbital of the halogen.

Migratory aptitudes have been measured for the phenyl and vinyl groups, and for three other groups, using the system $RCMe_2CH_2\bullet \rightarrow Me_2OC^{\bullet}CH_2R$. Migratory aptitudes were found to be in the order $R = H_2C{=}CH_2 > Me_3CC{=}O > Ph > Me_3CC{\equiv}C > CN$.[85]

In summary, 1,2-free-radical migrations are much less prevalent than the analogous carbocation processes, and are important only for aryl, vinylic, acetoxy, and halogen migrating groups. The direction of migration is normally toward the more stable radical, but "wrong-way" rearrangements are also known.[86]

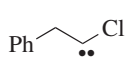
Despite the fact that hydrogen atoms do not migrate 1,2, longer free-radical migrations of hydrogen are known.[87] The most common are 1,5-shifts, but 1,6- and longer shifts have

[74] For molecular orbital calcualtions indicating that **24** is an intermediate, see Yamabe, S. *Chem. Lett.* ***1989***, 1523.
[75] Edge, D.J.; Kochi, J.K. *J. Am. Chem. Soc.* ***1972***, *94*, 7695.
[76] Olah, G.A.; Krishnamurthy, V.V.; Singh, B.P.; Iyer, P.S. *J. Org. Chem.* ***1983***, *48*, 955. **24** has been detected as an intemediate in a different reaction: Effio, A.; Griller, D.; Ingold, K.U.; Scaiano, J.C.; Sheng, S.J. *J. Am. Chem. Soc.* ***1980***, *102*, 6063; Leardini, R.; Nanni, D.; Pedulli, G.F.; Tundo, A.; Zanardi, G.; Foresti, E.; Palmieri, P. *J. Am. Chem. Soc.* ***1989***, *111*, 7723.
[77] See Rüchardt, C.; Trautwein, H. *Chem. Ber.* ***1965***, *98*, 2478.
[78] See Newcomb, M.; Glenn, A.G.; Williams, W.G. *J. Org. Chem.* ***1989***, *54*, 2675.
[79] See Lewis, S.N.; Miller, J.J.; Winstein, S. *J. Org. Chem.* ***1972***, *37*, 1478.
[80] See Giese, B.; Heinrich, N.; Horler, H.; Koch, W.; Schwarz, H. *Chem. Ber.* ***1986***, *119*, 3528.
[81] Barclay, L.R.C.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1984***, *106*, 1793.
[82] Baldwin, J.E.; Burrell, R.C.; Shukla, R. *Org. Lett.* ***2002***, *4*, 3305.
[83] See Freidlina, R.Kh.; Terent'ev, A.B. *Russ. Chem. Rev.* ***1979***, *48*, 828; Freidlina, R.Kh. *Adv. Free-Radical Chem.* ***1965***, *1*, 211 (pp. 231–249).
[84] See Chen, K.S.; Tang, D.Y.H.; Montgomery, L.K.; Kochi, J.K. *J. Am. Chem. Soc.* ***1974***, *96*, 2201.
[85] Lindsay, D.A.; Lusztyk, J.L.; Ingold, K.U. *J. Am. Chem. Soc.* ***1984***, *106*, 7087.
[86] See Dannenberg, J.J.; Dill, K. *Tetrahedron Lett.* ***1972***, 1571.
[87] See Freidlina, R.Kh.; Terent'ev, A.B. *Acc. Chem. Res.* ***1977***, *10*, 9.

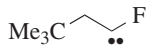
also been found (see **18-29**). The possibility of 1,3-hydrogen shifts has been much investigated, but it is not certain if any actually occur. If they do they are rare, presumably because the most favorable geometry for C•••H•••C in the transition state is linear and this geometry cannot be achieved in a 1,3-shift. 1,4-Shifts are definitely known, but are still not very common. These long shifts are best regarded as internal abstractions of hydrogen. For reactions, see **14-5** and **18-40**. Transannular shifts of hydrogen atoms have also been observed.[88]

18.D. CARBENE REARRANGEMENTS[89]

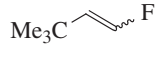
Carbenes can rearrange to alkenes in many cases.[90] A 1,2-hydrogen shift leads to an alkene, and this is often competitive with insertion reactions.[91] Benzylchlorocarbene (**25**) rearranges via a 1,2-hydrogen shift to give the alkene.[92] Similarly, carbene **26** rearranges to alkene **27**, and replacement of H on the α carbon with D showed a deuterium isotope effect of ∼5.[93] Vinylidene carbene ($H_2C{=}C{:}$) rearranges to acetylene.[94] Rearrangement of alkylidene carbene **28** has been calculated to give the highly unstable cyclopentyne (**29**), which cannot be isolated, but can give a [2 + 2] cycloaddition product (**15-59**) when generated in the presence of a simple alkene.[95]



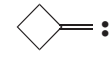
25



26



27



28

29

The spiro carbenes undergo rearrangement reactions.[96]

18.E. ELECTROPHILIC REARRANGEMENTS[97]

Rearrangements in which a group migrates without its electrons are more rare than the two kinds previously considered, but the general principles are the same. A carbanion (or other negative ion) is created first, and the actual rearrangement step involves migration of a group without its electrons. The product of the rearrangement may be stable or may react further, depending on its nature (see also, **18-2**). An *ab initio* study predicts that a [1,2]-alkyl shift in alkyne anions should be facile.[98]

[88] Traynham, J.G.; Couvillon, T.M. *J. Am. Chem. Soc.* ***1967***, *89*, 3205.
[89] See Baird, M.S. *Chem. Rev.* ***2003***, *103*, 1271; Allegretti, P.A.; Ferreira, E.M. *Org. Lett.* ***2011***, *13*, 5924.
[90] de Meijere, A.; Kozhushkov, S.I.; Faber, D.; Bagutskii, V.; Boese, R.; Haumann, T.; Walsh, R. *Eur. J. Org. Chem.* ***2001***, 3607.
[91] Nickon, A.; Stern, A.G.; Ilao, M.C. *Tetrahedron Lett.* ***1993***, *34*, 1391.
[92] Merrer, D.C.; Moss, R.A.; Liu, M.T.H.; Banks, J.-T.; Ingold, K.U. *J. Org. Chem.* ***1998***, *63*, 3010.
[93] Moss, R.A.; Ho, C.-J.; Liu, W.; Sierakowski, C. *Tetrahedron Lett.* ***1992***, *33*, 4287.
[94] Hayes, R.L.; Fattal, E.; Govind, N.; Carter, E.A. *J. Am. Chem. Soc.* ***2001***, *123*, 641.
[95] Gilbert, J.C.; Kirschner, S. *Tetrahedron Lett.* ***1993***, *34*, 599, 603.
[96] Moss, R.A.; Zheng, F.; Krough-Jespersen, K. *Org. Lett.* ***2001***, *3*, 1439.
[97] See Hunter, D.H.; Stothers, J.B.; Warnhoff, E.W. in de Mayo, P. *Rearrangments in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 391–470; Grovenstein Jr., E. *Angew. Chem. Int. Ed.* ***1978***, *17*, 313; Jensen, F.R.; Rickborn, B. *Electrophilic Substitution of Organomercurials*, McGraw-Hill, NY, ***1968***, pp. 21–30; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 223–243.
[98] Borosky, G.L. *J. Org. Chem.* ***1998***, *63*, 3337.

18.F. REACTIONS

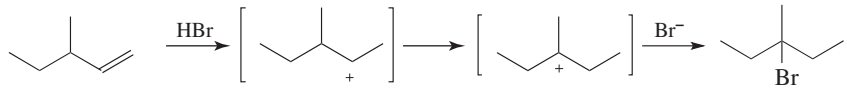
The reactions in this chapter are classified into three main groups. 1,2-Shifts are considered first. Within this group, reactions are classified according to: (i) the identity of the substrate atoms and (ii) the nature of the migrating group. In the second group are the cyclic rearrangements. The third group consists of rearrangements that cannot be fitted into either of the first two categories.

Reactions in which the migration terminus is on an aromatic ring have been treated under aromatic substitution. These are reactions **11-27** to **11-32**, **11-36**, **13-30** to **13-32**, and, partially, **11-33**, **19-74**, and **19-58**. Double-bond shifts have also been treated in other chapters, although they may be considered to be rearrangements (Sec. 8.A, **12-4**, and **12-2**). Other reactions that may be regarded as rearrangements are the *Pummerer* (**19-87**) and *Willgerodt* (**19-8**) reactions.

18.F.i. 1,2-Rearrangements

A. Carbon-to-Carbon Migrations of R, H, and Ar

18-1 Alkyl Shifts, Aryl Shifts: Wagner-Meerwein and Related Reactions



In the reaction shown, the reaction of an alkene with HBr gives the secondary carbocation, which rearranges to the more stable tertiary carboncation via a 1,2-hydride shift prior to reaction with the nucleophilic bromide ion to give the tertiary bromide product. Once formed, a carbocation rearranged via a 1,2-shift, with migration of a hydrogen atom (a 1,2-hydride shift), or of an alkyl group (a 1,2-alkyl shift), or of an aryl group (a 1,2-aryl shift),[99] to generate a more stable carbocation (Sec. 10.C). If the adjacent atoms have more than one proton, formation of the more stable carbocation governs the direction of atom or group migration, as expected. The more stable carbocation will react with a nucleophile (e.g., water, in which case the product is a rearranged alcohol) and this reaction generally occurs after the rearrangement. In other words, the rate of atom or group migration is faster than the rate of trapping the nucleophile by the carbocation. Such a rearrangement is an *exothermic* process by 12–15 kcal mol^{-1} (50–63 kJ mol^{-1}). The energy barrier to transfer a hydrogen atom is lower than that for alkyl or aryl shifts, although the energy barrier for a 1,2-methyl shift is estimated to be < 5 kcal mol^{-1} (20.9 kJ mol^{-1}).[100] For the degenerate rearrangement of 2,3-dimethylbutan-2-ylium, the energy barrier for a 1,2-hydrogen shift was measured to be 3.4 kcal mol^{-1} (14.2 kJ mol^{-1}).[101] Although the difference in energy between a hydrogen shift and a methyl shift is small, hydrogen will migrate preferentially in virtually all cases. The cationic rearrangements mentioned (1,2-hydride shifts, 1,2-alkyl shifts, and 1,2-aryl shifts) all occur with great facility,[102] to form the more stable carbocation.

[99] See Beaulieu, A.; Canesi, S. *J. Org. Chem.* ***2012***, *77*, 2121.
[100] Olah, G.A.; Lukas, J. *J. Am. Chem. Soc.* ***1967***, *89*, 4739.
[101] Saunders, M.; Cline, G.W. *J. Am. Chem. Soc.* ***1990***, *112*, 3955; Saunders, M.; Kates, M.R. *J. Am. Chem. Soc.* ***1978***, *100*, 7082.
[102] Olah, G.A.; Olah, J.A. *Carbonium Ions*, Vol. 2, Olah, G.A.; Schleyer, P.v.R. (Ed.), Wiley, NY, ***1969***, pp. 715–782; Richey, J.M. *The Chemistry of Alkenes*, Vol. 2, Zabicky, J. (Ed.), Interscience, NY, ***1970***, p. 44.

As pointed out in Chapters 5 and 1, the carbocation intermediate that is a direct product of the rearrangement must lead to the more stable product, and loss of a hydrogen β to the positive center to give the more stable alkene, following *Zaitsev's ru*le (Sec. 17.A.i, category 3).[103]

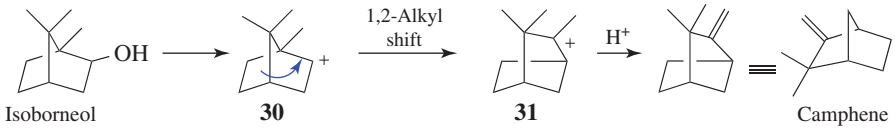
As just mentioned with rearrangements of alkyl carbocations, the direction of rearrangement is usually toward the most stable carbocation (the stability order is tertiary > secondary > primary), but rearrangements in the other direction have also been observed.[104] The product is sometimes a mixture corresponding to an equilibrium mixture of the possible carbocations. Aryl groups can migrate, generally via 1,2-aryl shifts, if the newly formed carbocation is more stable. The migration of aryl groups can involve a phenonium ion (Sec. 10.C.i, item 3).

Rearrangement is usually predominant in neopentyl and neophyl types of substrates, and with these types normal nucleophilic substitution is difficult and normal elimination is, of course, impossible. Under S_N2 conditions, substitution is extremely slow;[105] and under S_N1 conditions, carbocations are formed that rapidly rearrange. However, free-radical substitution, unaccompanied by rearrangement, can be carried out on neopentyl systems, although, as seen previously (Sec. 18.C), neophyl systems undergo rearrangement as well as substitution.

Examples of carbocation rearrangements are found in simpler systems, such as the reaction of 1-bromopropane with $AlBr_3$ that gives 2-bromopropane.

1. Hydride ion can migrate. In the reaction with 1-bromopropane it was hydride that shifted, not bromine, in the conversion of the primary carbocation to a secondary carbocation.
2. The leaving group does not have to be H_2O, but can be any departing species whose loss creates a carbocation, including N_2 from aliphatic diazonium ions[106] (see the section on leaving groups in nucleophilic substitution in Sec. 10.A.ii, category 1). Rearrangement may follow when the carbocation is created by addition of a proton or other positive species to a double bond.

Wagner-Meerwein rearrangements were first discovered in reactions of bicyclic terpenes, and most of the early development of this reaction was with these compounds.[107] An example is the conversion of isoborneol to camphene. It fundamentally involves a 1,2-alkyl shift of an intermediate carbocation, such as **30** → **31**.



[103] See Kaupp, G. *Top. Curr. Chem.* ***1988***, *146*, 57.

[104] See Cooper, C.N.; Jenner, P.J.; Perry, N.B.; Russell-King, J.; Storesund, H.J.; Whiting, M.C. *J. Chem. Soc., Perkin Trans. 2* ***1982***, 605.

[105] See, however, Lewis, R.G.; Gustafson, D.H.; Erman, W.F. *Tetrahedron Lett.* ***1967***, 401; Paquette, L.A.; Philips, J.C. *Tetrahedron Lett.* ***1967***, 4645; Anderson, P.H.; Stephenson, B.; Mosher, H.S. *J. Am. Chem. Soc.* ***1974***, *96*, 3171.

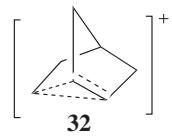
[106] In Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, see the articles by White, E.H.; Woodcock, D.J., pp. 407–497 (pp. 473–483) and by Banthorpe, D.V., pp. 585–667 (pp. 586–612).

[107] See Hogeveen, H.; van Kruchten, E.M.G.A. *Top. Curr. Chem.* ***1979***, *80*, 89; Arbuzov, B.A.; Isaeva, Z.G. *Russ. Chem. Rev.* ***1976***, *45*, 673; Banthorpe, D.V.; Whittaker, D. *Q. Rev. Chem. Soc.* ***1966***, *20*, 373.

When alcohols are treated with acids, simple substitution (e.g., **10-47**) or elimination (**17-1**) usually accounts for most or all of the products. In many cases, however, especially where two or three alkyl or aryl groups are on the β carbon, some or all of the product is rearranged. These rearrangements have been called *Wagner-Meerwein rearrangements*, although this term is nowadays reserved for relatively specific transformations such as isoborneol to camphene and related reactions.

2-Norbornyl cations (see **30**), besides displaying the 1,2-shifts of a CH_2 group illustrated for the isoborneol → camphene conversion, are also prone to rapid hydride shifts from the 3 to the 2 position (known as 3,2-shifts). These 3,2-shifts usually take place from the *exo* side;[108] that is, the 3-*exo* hydrogen migrates to the 2-*exo* position.[109] This stereoselectivity is analogous to the behavior previously seen for norbornyl systems, namely, that nucleophiles attack norbornyl cations from the *exo* side (Sec. 10.C.i, category 4) and that addition to norbornenes is also usually from the *exo* direction (Sec. 15.B.iii).

The Wagner-Meerwein rearrangement has been observed for a secondary to a secondary carbocation rearrangement, leading to some controversy. Winstein[110] described norbornyl cations in terms of the resonance structures represented by the nonclassical ion **32**.[111] This view was questioned, primarily by Brown,[112] who suggested that the facile rearrangements could be explained by a series of fast 1,3-Wagner-Meerwein shifts.[113] There is considerable evidence, however, that *the norbornyl cation rearranges with σ participation*,[114] and there is strong NMR evidence for the nonclassical ion in superacids at low temperatures.[115]



32

As alluded to above, the term "Wagner-Meerwein rearrangement" is not precise. Some use it to refer to all the rearrangements in this section and in **18-2**. Others use it only when an alcohol is converted to a rearranged alkene. Many use the term only for rearrangements that involve a nonclassical carbocation intermediate. Terpene chemists call the migration of a methyl group the *Nametkin rearrangement*. The term *retropinacol rearrangement* is often applied to some or all of these. Fortunately, this disparity in nomenclature does not seem to cause much confusion.

[108] See Berson, J.A.; Hammons, J.H.; McRowe, A.W.; Bergman, R.G.; Remanick, A.; Houston, D. *J. Am. Chem. Soc.* ***1967***, *89*, 2590.

[109] For an example of a 3,2-endo shift, see Wilder Jr., P.; Hsieh, W. *J. Org. Chem.* ***1971***, *36*, 2552.

[110] See Winstein, S. *Q. Rev. Chem. Soc.* ***1969***, *23*, 141.

[111] Berson, J.A. in de Mayo, P. *Molecular Rearrangements*, Vol. 1, Academic Press, NY, ***1980***, p. 111; Sargent, G.D. *Q. Rev. Chem. Soc.* ***1966***, *20*, 301; Olah, G.A. *Acc. Chem. Res.* ***1976***, *9*, 41; Scheppele, S.E. *Chem. Rev.* ***1972***, *72*, 511.

[112] Brown, H.C. *The Non-Classical Ion Problem*, Plenum, New York, ***1977***; Brown, H.C. *Tetrahedron* ***1976***, *32*, 179; Brown, H.C.; Kawakami, J.H. *J. Am. Chem. Soc.* ***1970***, *92*, 1990. See also, Story, R.R.; Clark, B.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, New York, ***1972***, p. 1007.

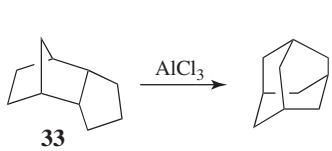
[113] Brown, H.C.; Ravindranathan, M. *J. Am. Chem. Soc.* ***1978***, *100*, 1865.

[114] Coates, R.M.; Fretz, E.R. *J. Am. Chem. Soc.* ***1977***, *99*, 297; Brown, H.C.; Ravindranathan, M. *J. Am. Chem. Soc.* ***1977***, *99*, 299.

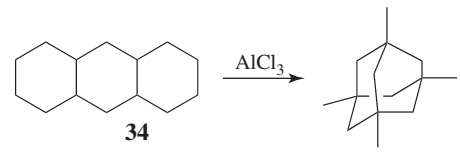
[115] Olah, G.A. *Carbocations and Electrophilic Reactions*, Verlag Chemie/Wiley, New York, ***1974***, pp. 80–89; Olah, G.A.; White, A.M.; DeMember, J.R.; Commeyras, A.; Lui, C.Y. *J. Am. Chem. Soc.* ***1970***, *92*, 4627.

Catalytic asymmetric Wagner-Meerwein shifts have been observed.[116] An asymmetric, Pd-catalyzed Wagner-Meerwein shift has been reported with allenic alcohols.[117]

Some alkanes undergo Wagner-Meerwein rearrangements if treated with Lewis acids and a small amount of initiator. An interesting application of this reaction is the conversion of tricyclic molecules to adamantane and its derivatives.[118] It has been found that *all* tricyclic alkanes containing 10 carbons are converted to adamantane by treatment with a Lewis acid, such as $AlCl_3$. If the substrate contains more than 10 carbons, alkyl-substituted adamantanes are produced. Such reactions are referred to as *Schleyer adamantization*. Two examples are the $AlCl_3$-mediated reactions of **33** and **34**.



33



34

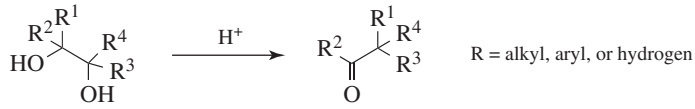
If 14 or more carbons are present, the product may be diamantane or a substituted diamantane.[119] These reactions are successful because of the high thermodynamic stability of adamantane, diamantane, and similar diamond-like molecules. The most stable of a set of C_nH_m isomers (called the *stabilomer*) will be the end product if the reaction reaches equilibrium.[120] Best yields are obtained by the use of "sludge" catalysts[121] (i.e., a mixture of AlX_3 and *tert*-butyl bromide or *sec*-butyl bromide).[122] Though it is certain that these adamantane-forming reactions take place by nucleophilic 1,2-shifts, the exact pathways are not easy to unravel because of their complexity.[123] Treatment of adamantane-2-^{14}C with $AlCl_3$ results in total carbon scrambling on a statistical basis.[124]

As already indicated, the mechanism of the Wagner-Meerwein rearrangement is usually nucleophilic. Carbanion mechanisms (electrophilic) have also been found.[94] Thus Ph_3CCH_2Cl treated with sodium gave Ph_2CHCH_2Ph along with unrearranged products.[125] This is called the *Grovenstein-Zimmerman rearrangement*. The intermediate is $Ph_3CCH_2^-$, and the phenyl moves without its electron pair. Only aryl and vinylic groups,[126] and not alkyl groups, migrate by the electrophilic mechanism (see the introduction preceding Sec. 18.A) and transition states or intermediates analogous to **21** and **22** are likely.[127]

OS **V**, 16, 194; **VI**, 378, 845.

[116] Trost, B.M.; Yasukata, T. *J. Am. Chem. Soc.* ***2001***, *123*, 7162.
[117] Trost, B.M.; Xie, J. *J. Am. Chem. Soc.* ***2006***, *128*, 6044.
[118] See McKervey, M.A.; Rooney, J.J. in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, ***1990***, pp. 39–64; McKervey, M.A. *Tetrahedron* ***1980***, *36*, 971; *Chem. Soc. Rev.* ***1974***, *3*, 479; Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, ***1978***, pp. 178–202; Bingham, R.C.; Schleyer, P.v.R. *Fortschr. Chem. Forsch.* ***1971***, *18*, 1 (pp. 3–23).
[119] See Gund, T.M.; Osawa, E.; Williams Jr., V.Z.; Schleyer, P.v.R. *J. Org. Chem.* ***1974***, *39*, 2979.
[120] Godleski, S.A.; Schleyer, P.v.R.; Osawa, E.; Wipke, W.T. *Prog. Phys. Org. Chem.* ***1981***, *13*, 63.
[121] See Williams Jr., V.Z.; Schleyer, P.v.R.; Gleicher, G.J.; Rodewald, L.B. *J. Am. Chem. Soc.* ***1966***, *88*, 3862; Robinson, M.J.T.; Tarratt, H.J.F. *Tetrahedron Lett.* ***1968***, 5.
[122] See Olah, G.A.; Wu, A.; Farooq, O.; Prakash, G.K.S. *J. Org. Chem.* ***1989***, *54*, 1450.
[123] See Klester, A.M.; Ganter, C. *Helv. Chim. Acta* ***1985***, *68*, 734.
[124] Majerski, Z.; Liggero, S.H.; Schleyer, P.v.R.; Wolf, A.P. *Chem. Commun.* ***1970***, 1596.
[125] Grovenstein Jr., E.; Williams Jr., L.P. *J. Am. Chem. Soc.* ***1961***, *83*, 412; Zimmerman, H.E.; Zweig, A. *J. Am. Chem. Soc.* ***1961***, *83*, 1196. See also, Grovenstein Jr., E.; Cheng, Y. *J. Am. Chem. Soc.* ***1972***, *94*, 4971.
[126] See Grovenstein Jr., E.; Black, K.W.; Goel, S.C.; Hughes, R.L.; Northrop, J.H.; Streeter, D.L.; VanDerveer, D. *J. Org. Chem.* ***1989***, *54*, 1671, and references cited therein.
[127] Bertrand, J.A.; Grovenstein Jr., E.; Lu, P.; VanDerveer, D. *J. Am. Chem. Soc.* ***1976***, *98*, 7835.

18-2 The Pinacol Rearrangement



When 1.2-diols (*vic*-diols; glycols) are treated with acids,[128] they rearrange to give aldehydes or ketones, although elimination without rearrangement can also be accomplished. This reaction is called the *pinacol rearrangement*; the reaction gets its name from a prototype compound pinacol ($Me_2COHCOHMe_2$), which is rearranged to pinacolone (Me_3CCOCH_3).[129]

In this type of reaction, reduction can compete with rearrangement.[130] The reaction has been accomplished many times, with alkyl, aryl, hydrogen, and even ethoxycarbonyl (CO_2Et)[131] as migrating groups. In most cases, each carbon has at least one alkyl or aryl group, and the reaction is most often carried out with tri- and tetrasubstituted glycols. As mentioned earlier, glycols in which the four R groups are not identical can give rise to more than one product, depending on which group migrates (see Sec. 18.A.iii for a discussion of migratory aptitudes). A noncatalytic reaction is possible in supercritical water.[132]

Stereodifferentiation is possible in this reaction.[133] When TMSOTf was used to initiate the reaction, it was shown to be highly regioselective.[134] Mixtures are often produced, and which group preferentially migrates may depend on the reaction conditions as well as on the nature of the substrate. Thus the action of cold, concentrated sulfuric acid on 2-methyl-1,1-diphenylpropane-1,2-diol produces mainly 3,3-diphenylbutan-2-one (methyl migration), while treatment of 2-methyl-1,1-diphenylpropane-1,2-diol with acetic acid containing a trace of sulfuric acid gives mostly 2-methyl-1,2-diphenylpropan-1-one (phenyl migration).[135] If at least one R is hydrogen, aldehydes can be produced as well as ketones. Generally, aldehyde formation is favored by the use of mild conditions (lower temperatures, weaker acids), because under more drastic conditions the aldehydes may be converted to ketones (**18-4**). The reaction has been carried out in the solid state, by treating solid substrates with HCl gas or with a solid organic acid.[136] Organocatalysts have been used for an enantioselective vinylogous pinacol rearrangement.[137]

The mechanism involves a simple 1,2-shift. A carbocation where all four R groups are Me has been trapped by the addition of tetrahydrothiophene.[138] A migration takes place from the tertiary position because carbocations stabilized by an oxygen atom are even more

[128] See Lopez, L.; Mele, G.; Mazzeo, C. *J. Chem. Soc., Perkin Trans. 1* ***1994***, 779.

[129] Bartók, M.; Molnár, A. in Patai, S. *The Chemistry of Functional Groups*, Supplement E, Wiley, NY, ***1980***, pp. 722–732; Collins, C.J.; Eastham, J.F. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 762–771.

[130] Grant, A.A.; Allukian, M.; Fry, A.J. *Tetrahedron Lett.* ***2002***, *43*, 4391.

[131] Kagan, J.; Agdeppa Jr., D.A.; Mayers, D.A.; Singh, S.P.; Walters, M.J.; Wintermute, R.D. *J. Org. Chem.* ***1976***, *41*, 2355. See Berner, D.; Cox, D.P.; Dahn, H. *J. Am. Chem. Soc.* ***1982***, *104*, 2631.

[132] Ikushima, Y.; Hatakeda, K.; Sato, O.; Yokoyama, T.; Arai, M. *J. Am. Chem. Soc.* ***2000***, *122*, 1908.

[133] Paquette, L.A.; Lanter, J.C.; Johnston, J.N. *J. Org. Chem.* ***1997***, *62*, 1702.

[134] Kudo, K.; Saigo, K.; Hashimoto, Y.; Saito, K.; Hasegawa, M. *Chem. Lett.* ***1992***, 1449.

[135] Ramart-Lucas, P.; Salmon-Legagneur, F. *C. R. Acad. Sci.* ***1928***, *188*, 1301.

[136] Toda, F.; Shigemasa, T. *J. Chem. Soc., Perkin Trans. 1* ***1989***, 209.

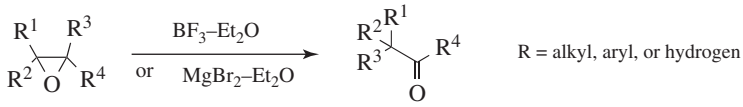
[137] Wu, H.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* ***2016***, *55*, 15411.

[138] Bosshard, H.; Baumann, M.E.; Schetty, G. *Helv. Chim. Acta* ***1970***, *53*, 1271.

stable than tertiary alkyl cations (Sec. 5.A.ii). In addition, the new carbocation can immediately stabilize itself by losing a proton.

It is obvious that other compounds in which a positive charge can be placed on a carbon α to one bearing an OH group can also give this rearrangement. β-Amino alcohols rearrange on treatment with nitrous acid in a reaction called the *semipinacol rearrangement*.[139] Allylic alcohols[140] can rearrange on treatment with a strong acid that protonates the double bond.[141] Catalytic asymmetric semipinacol rearrangements have been reported.[142] Electrophilic iodine compounds have been used to induce semipinacol rearrangements.[143] The aqueous media $Zn/AlCl_3$-mediated pinacol coupling reactions been reported.[144]

Epoxides are converted to aldehydes or ketones on treatment with certain metallic catalysts[145] including treatment with iron complexes,[146] $IrCl_3$,[147] or with $BiOClO_4$.[148] Acidic reagents such as BF_3-etherate or $MgBr_2$-etherate, 5 M $LiClO_4$ in ether,[149] In,[150] Sm,[151] Au/Ag,[152] Bi,[153] or sometimes by heat alone[154] can also be used.[155]



R = alkyl, aryl, or hydrogen

The *Meinwald rearrangement* converts epoxides to carbonyl compounds.[156] Several reagents mediate this transformation, including Cu compounds.[157] The mechanism of palladium hydride catalysis for the isomerization of epoxides to ketones has been examined.[158]

A closely related reaction of vinyl epoxides gives alkenyl ketones upon treatment with Ga compounds.[159] It has been shown that epoxides are intermediates in the pinacol rearrangements of certain glycols.[160] Among the evidence for the mechanism given is that

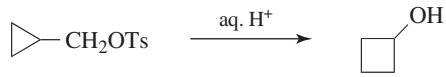
[139] Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* ***2011***, *111*, 7523.
[140] See Wang, B.M.; Song, Z.L.; Fan, C.A.; Tu, Y.Q.; Chen, W.M. *Synlett* ***2003***, 1497; Hurley, P.B.; Dake, G.R. *Synlett* ***2003***, 2131.
[141] See Luzzio, F.A. *Tetrahedron* ***2012***, *68*, 5323.
[142] Wang, S.-H.; Li, B.-S.; Tu, Y.-Q. *Chem. Commun.* ***2014***, *50*, 2398.
[143] Tsuji, N.; Kobayashi, Y.; Takemoto, Y. *Chem. Commun.* ***2014***, *50*, 13691.
[144] Hazarika, B.K.; Dutta, D.K. *Synth. Commun.* ***2010–2011***, *41*, 1088.
[145] See Miyashita, A.; Shimada, T.; Sugawara, A.; Nohira, H. *Chem. Lett.* ***1986***, 1323; Maruoka, K.; Nagahara, S.; Ooi, T.; Yamamoto, H. *Tetrahedron Lett.* ***1989***, *30*, 5607.
[146] Suda, K.; Baba, K.; Nakajima, S.-I.; Takanami, T. *Tetrahedron Lett.* ***1999***, *40*, 7243.
[147] Karamé, I.; Tommasino, M.L.; LeMaire, M. *Tetrahedron Lett.* ***2003***, *44*, 7687.
[148] Anderson, A.M.; Blazek, J.M.; Garg, P.; Payne, B.J.; Mohan, R.S. *Tetrahedron Lett.* ***2000***, *41*, 1527.
[149] Sankararaman, S.; Nesakumar, J.E. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 3173.
[150] Ranu, B.C.; Jana, U. *J. Org. Chem.* ***1998***, *63*, 8212.
[151] Yoshimura, A.; Saeki, T.; Nomoto, A.; Ogawa, A. *Tetrahedron* ***2015***, *71*, 5347.
[152] Gudla, V.; Balamurugan, R. *Tetrahedron Lett.* ***2012***, *53*, 5243.
[153] Bhatia, K.A.; Eash, K.J.; Leonard, N.M.; Oswald, M.C.; Mohan, R.S. *Tetrahedron Lett.* ***2001***, *42*, 8129.
[154] For a list of reagents with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1277–1280.
[155] Zhuang, M.; Du, H. *Org. Biomol. Chem.* ***2013***, *11*, 1460.
[156] See Meinwald, J.; Labana, S.S.; Chadha, M.S. *J. Am. Chem. Soc.* ***1963***, *85*, 582; Wang, S.; Zhao, C.; Liu, T.; Yu, L.; Yang, F.; Tang, J. *Tetrahedron* ***2016***, *72*, 7025.
[157] Robinson, M.W.C.; Pillinger, K.S.; Mabbett, I.; Timms, D.A.; Graham, A.E. *Tetrahedron* ***2010***, *66*, 8377.
[158] Vyas, D.J.; Larionov, E.; Besnard, C.; Guénée, L.; Mazet, C. *J. Am. Chem. Soc.* ***2013***, *135*, 6177.
[159] Deng, X.-M.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* ***2005***, *70*, 6537.
[160] See Tamura, K.; Moriyoshi, T. *Bull. Chem. Soc. Jpn.* ***1974***, *47*, 2942.

$Me_2COHCOHMe_2$, $Me_2COHC(NH_2)Me_2$, and $Me_2COHCClMe_2$ gave the reaction at different rates (as expected) but yielded the *same mixture* of two products, pinacol and pinacolone, indicating a common intermediate.[161] Base-induced rearrangement is also known, but the products are usually different.[162] The regioselective isomerization of 2,3-diubstiuted epoxides gave ketones.[163] A semipinacol rearrangement of *cis*-fused β-lactam diols gave keto-bridged bicyclo lactams.[164] The asymmetric rearrangement of racemic epoxides were catalyzed by chiral Brønsted acids.

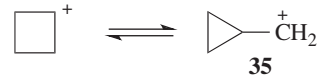
Epoxides are converted to 1,2-diketones with Bi, DMSO, O_2, and a catalytic amount of $Cu(OTf)_2$ at 100 °C.[165] α,β-Epoxy ketones are also converted to 1,2-diketones with a Ru catalyst[166] or an Fe catalyst.[167] Epoxides with an α-hydroxyalkyl substituent give a pinacol rearrangement product in the presence of a $ZnBr_2$[168] or $Tb(OTf)_3$[169] catalyst to give a γ-hydroxy ketone. β-Hydroxy ketones can be prepared by treating the silyl ethers of α,β-epoxy alcohols with $TiCl_4$.[170]

OS **I**, 462; **II**, 73, 408; **III**, 312; **IV**, 375, 957; **V**, 326, 647; **VI**, 39, 320; **VII**, 129. See also, OS **VII**, 456.

18-3 Modification of Ring Size



When a positive charge is placed on a carbon α to an alicyclic ring, ring expansion can take place,[171] as in the interconversion of the cyclobutyl cation and the cyclopropylcarbinyl cation (**35**).



35

The new carbocation, and the old one, can then give products by combination with a nucleophile, or by elimination, so that this reaction is a special case of **18-1**. Often, both rearranged and unrearranged products are formed, so that, for example, cyclobutylamine and cyclopropylmethylamine give similar mixtures of the two alcohols shown at the

[161] Pocker, Y. *Chem. Ind. (London)* ***1959***, 332. See also, Herlihy, K.P. *Aust. J. Chem.* ***1981***, *34*, 107.
[162] See Yandovskii, V.N.; Ershov, B.A. *Russ. Chem. Rev.* ***1972***, *41*, 403, 410. Also see Hodgson, D.M.; Robinson, L.A.; Jones, M.L. *Tetrahedron Lett.* ***1999***, *40*, 8637.
[163] Lamb, J.R.; Mulzer, M.; LaPointe, A.M.; Coates, G.W. *J. Am. Chem. Soc.* ***2015***, *137*, 15049.
[164] Grainger, R.S.; Betou, M.; Male, L.; Pitak, M.B.; Coles, S.J. *Org. Lett.* ***2012***, *14*, 2234.
[165] Antoniotti, S.; Duñach, E. *Chem. Commun.* ***2001***, 2566.
[166] Chang, C.-L.; Kumar, M.P.; Liu, R.-S. *J. Org. Chem.* ***2004***, *69*, 2793.
[167] Suda, K.; Baba, K.; Nakajima, S.; Takanami, T. *Chem. Commun.* ***2002***, 2570.
[168] Tu, Y.Q.; Fan, C.A.; Ren, S.K.; Chan, A.S.C. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 3791.
[169] Bickley, J.F.; Hauer, B.; Pena, P.C.A.; Roberts, S.M.; Skidmore, J. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1253.
[170] Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem. Soc.* ***1986***, *108*, 3827.
[171] See Hesse, M. *Ring Enlargement in Organic Chemistry*, VCH, NY, ***1991***; Gutsche, C.D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***; Baldwin, J.E.; Adlington, R.M.; Robertson, J. *Tetrahedron* ***1989***, *45*, 909; Salaün, J. in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, ***1987***, pp. 809–878; Conia, J.M.; Robson, M.J. *Angew. Chem. Int. Ed.* ***1975***, *14*, 473. For a list of ring expansions and contractions, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1283–1302.

opening of this section on treatment with nitrous acid (a small amount of 3-buten-1-ol is also produced). When the carbocation is formed by diazotization of an amine, the reaction is called the *Demjanov rearrangement*,[172] but of course similar products are formed when the carbocation is generated in other ways.

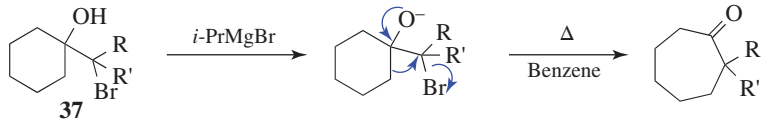
The expansion reaction has been performed on rings of C_3–C_8,[173] but yields are best with the smaller rings, where relief of small-angle strain provides a driving force for the reaction. Strain is apparently much less of a factor in the cyclobutyl–cyclopropylmethyl interconversion (for a discussion of this interconversion, Sec. 10.C.i). The influence of substituents on this rearrangement has been examined.[174] It is noted that a hybrid of a [1,2]-sigmatropic hydrogen shift (also see **18-29**) and a two-electron electrocyclic ring opening has been discovered for cyclopropylcarbinyl cations that was labeled as a "hiscotropic" rearrangement.[175]

A related rearrangement involves cyclopropyl propargylic alcohols, which gives an alkylidene cyclobutanone in the presence of Ag and Au catalysts,[176] or of Ru and In catalysts.[177] Cyclopropylcarbinyl rearrangements are catalyzed by ionic liquids under solvent-free conditions.[178] Methylenecyclopropanes rearrange to cyclobutenes in the presence of 1 atm of CO and Pt catalyst[179] or a Pd catalyst, mediated by a Cu catalyst.[180] Arylvinylidenecyclopropanes rearrange to bicyclic systems in the presence of a Lewis acid.[181]

Ring expansions of certain hydroxyamines such as **36** are analogous to the semipinacol rearrangement (**18-2**). This reaction is called the *Tiffeneau-Demjanov ring expansion*.

36

These expansions have been performed on rings of C_4–C_8 and the yields are better than for the simple Demjanov ring expansion. A similar reaction has been used to expand rings of from five to eight members.[182] In this case, a cyclic alcohol with a pendant bromoalkyl group of the form **37** is treated with a Grignard reagent, which, acting as a base, removes the OH proton to give the alkoxide which, when heated to reflux, displaces the bromide to give ring enlargement.



37

[172] See Smith, P.A.S.; Baer, D.R. *Org. React.* ***1960***, *11*, 157. See also, Chow, L.; McClure, M.; White, J. *Org. Biomol. Chem.* ***2004***, *2*, 648.
[173] See Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165 (see pp. 182–186); Breslow, R. in Mayo, P. *Molecular Rearrangements*, Vol. 1, Wiley, NY, ***1963***, pp. 233–294.
[174] Wiberg, K.B.; Shobe, D.; Nelson, G.C. *J. Am. Chem. Soc.* ***1993***, *115*, 10645.
[175] Nouri, D.H.; Tantillo, D.J. *J. Org. Chem.* ***2006***, *71*, 3686.
[176] Markham, J.P.; Staben, S.T.; Toste, F.D. *J. Am. Chem. Soc.* ***2005***, *127*, 9708.
[177] Trost, B.M.; Xie, J.; Maulide, N. *J. Am. Chem. Soc.* ***2008***, *130*, 17258.
[178] Ranu, B.C.; Banerjee, S.; Das, A. *Tetrahedron Lett.* ***2006***, *47*, 881.
[179] Fürstner, A.; Aïssa, C. *J. Am. Chem. Soc.* ***2006***, *128*, 6306.
[180] Shi, M.; Liu, L.-P.; Tang, J. *J. Am. Chem. Soc.* ***2006***, *128*, 7430.
[181] Xu, G.-C.; Liu, L.-P.; Lu, J.-M.; Shi, M. *J. Am. Chem. Soc.* ***2005***, *127*, 14552.
[182] See Sisti, A.J.; Vitale, A.C. *J. Org. Chem.* ***1972***, *37*, 4090.

The reaction has been done with **37** in which at least one R group is phenyl or methyl,[183] but fails when both R groups are hydrogen.[184] Medium-size ring ketones have been prepared using α-chloro-α-diazoacetate.[185]

A positive charge generated on a three-membered ring gives ring opening to an allylic cation.[186] As seen in Sec. 10.G.i, category 7, this ring opening is the reason nucleophilic substitutions are not feasible at a cyclopropyl substrate. The reaction is often used to convert cyclopropyl halides and tosylates to allylic products, especially for the purpose of ring expansion.[187] The stereochemistry of such cyclopropyl cleavages is governed by the principle of orbital symmetry conservation (for a discussion, see **18-27**, the Möbius-Hückel method).

Three-membered rings can also be cleaved to unsaturated products in at least two other ways.

1. Upon pyrolysis, cyclopropanes open to propenes.[188] In the simplest case, cyclopropane gives propene when heated to 400 to 500 °C. The mechanism is generally regarded[189] as involving a diradical intermediate[190] (recall that free-radical 1,2-migration is possible for diradicals, Sec. 18.C).
2. The generation of a carbene or carbenoid carbon in a three-membered ring can lead to allenes, and allenes are often prepared in this way.[191] Flash vacuum pyrolysis of 1-chlorocyclopropene thermally rearranges to chloroallene.[192] One way to generate such a species is treatment of a 1,1-dihalocyclopropane with an alkyllithium compound (**12-38**).[193]

In contrast, the generation of a carbene or carbenoid at a cyclopropylmethyl carbon gives ring expansion to give cyclobutene.[194] The activation parameters for this ring expansion has been reported.[195]

Some free-radical ring enlargements are also known.[196] This reaction has been used to make rings of 6, 7, 8, and 13 members. This reaction has been extended to the expansion of rings by three or four carbons, by the use of a substrate containing $(CH_2)_nX$ ($n = 3$ or 4)

[183] Sisti, A.J.; Rusch, G.M. *J. Org. Chem.* ***1974***, *39*, 1182.
[184] Sisti, A.J. *J. Org. Chem.* ***1968***, *33*, 3953.
[185] Dousset, M.; Le Jeune, K.; Cohen, S.; Parrain, J.-L.; Chouraqui, G. *Synthesis* ***2016***, *48*, 2439.
[186] Marvell, E.N. *Thermal Electrocylic Reactions*, Academic Press, NY, ***1980***, pp. 23–53; Sorensen, T.S.; Rauk, A. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 1–78.
[187] Skell, P.S.; Sandler, S.R. *J. Am. Chem. Soc.* ***1958***, *80*, 2024.
[188] See Berson, J.A. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 324–352; *Ann. Rev. Phys. Chem.* ***1977***, *28*, 111; Bergman, R.G. in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 191–237; Frey, H.M. *Adv. Phys. Org. Chem.* ***1966***, *4*, 147 (see pp. 148–170). Also see Baldwin, J.E.; Day, L.S.; Singer, S.R. *J. Am. Chem. Soc.* ***2005***, *127*, 9370.
[189] See Baldwin, J.E.; Grayston, M.W. *J. Am. Chem. Soc.* ***1974***, *96*, 1629, 1630.
[190] See Bergman, R.G.; Carter, W.L. *J. Am. Chem. Soc.* ***1969***, *91*, 7411.
[191] See Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 20–23; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 462–467.
[192] Billups, W.E.; Bachman, R.E. *Tetrahedron Lett.* ***1992***, *33*, 1825.
[193] See Baird, M.S.; Baxter, A.G.W. *J. Chem. Soc., Perkin Trans. 1* ***1979***, 2317, and references cited therein.
[194] See Gutsche, C.D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***, pp. 111–117.
[195] Shen, Y.-m.; Moss, R.M.; Krogh-Jespersen, K. *Org. Lett.* ***2012***, *14*, 910.
[196] Dowd, P.; Choi, S. *Tetrahedron* ***1991***, *47*, 4847. For a related ring expansion, see Baldwin, J.E.; Adlington, R.M.; Robertson, J. *J. Chem. Soc., Chem. Commun.* ***1988***, 1404.

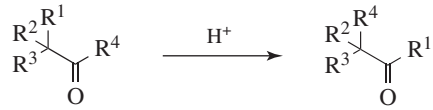
instead of CH_2Br.[197] By this means, 5-, 6-, and 7-membered rings were enlarged to 8–11-membered rings. A β-keto ester such as 2-carboxyethyl cyclohexanone is converted to 3-carboxyethyl cylcoheptanone when treated with $CF_3CO_2ZnCH_2I$.[198]

The Cr-catalyzed reaction of *meso*-epoxides with CO led to β-lactones.[199] The reaction of thiiranes with dimethyloxosulfonium methylid, generated from trimethyloxosulfonium iodide and sodium hydride, gave thietanes *via* ring expansion.[200] A Pd-catalyzed rearrangement led to ring expansion of piperidones and piperidines bearing a spirocyclopropane ring to give functionalized caprolactam and azepine derivatives.[201] A rare aziridine to azetidine rearrangement of *N*-alkylidene-(2,3-dibromo-2-methylpropyl)amines and *N*-(2,3-dibromo-2-methylpropylidene)benzylamines upon heating with sodium borohydride in methanol gave 3-methoxy-3-methylazetidines.[202]

Six-membered ring cyclic hydroxamic acids undergo a thermal ring contraction to give pyrrolidine derivatives via reaction with Tf_2O and DBU or Et_3N.[203] The reaction of cyclohexanonone silylenol ethers with perfluorobutanesulfonyl azide gave a one-carbon ring contraction to give the cyclopentane *N*-acyl sulfonamide product.[204] The Pd-catalyzed reaction of tetrahydroazepine (in the presence of TFA, morpholine, and $POEt)_3$, gave the isomerized product, the 2-allylic pyrrolidine.[205] Photolysis has been used for ring contraction of cyclic α-diazo ketones[206] to cycloakanecarboxylic esters.[207]

OS **III**, 276; **IV**, 221, 957; **V**, 306, 320; **VI**, 142, 187; **VII**, 12, 114, 117, 129, 135; **VIII**, 179, 467, 556, 578.

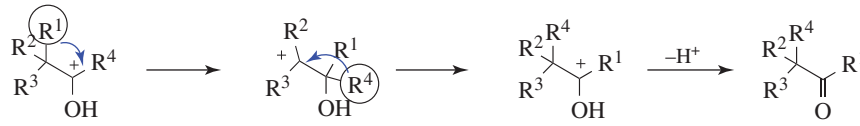
18-4 Acid-Catalyzed Rearrangements of Aldehydes and Ketones



Rearrangements of this type, where a group α to a carbonyl "changes places" with a group attached to the carbonyl carbon, occur when migratory aptitudes are favorable.[208] The R^2, R^3, and R^4 groups may be alkyl or hydrogen. Certain aldehydes have been converted to ketones, and ketones to other ketones (though more drastic conditions are required for the latter), but no rearrangement of a ketone to an aldehyde ($R^1 = H$) has so far been reported.

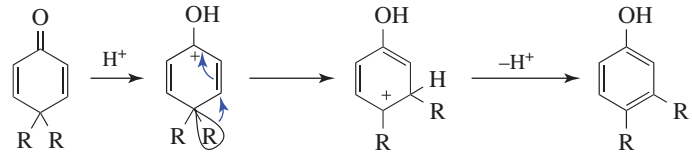
[197] Dowd, P.; Choi, S. *J. Am. Chem. Soc.* ***1987***, *109*, 6548; Dowd, P.; Choi, S. *Tetrahedron Lett.* ***1991***, *32*, 565.
[198] Xue, S.; Liu, Y.-K.; Li, L.-Z.; Guo, Q.-X. *J. Org. Chem.* ***2005***, *70*, 8245.
[199] Ganji, P.; Ibrahim, H. *Chem. Commun.* ***2012***, *48*, 10138.
[200] Dong, J.; Xu, J. *Org. Biomol. Chem.* ***2017***, *15*, 836.
[201] Stepek, O.R.A.; Gobbi, A.; Fauber, B.P.; Gaines, S. *J. Org. Chem.* ***2015***, *80*, 10218.
[202] Stanković, S.; Catak, S.; D'hooghe, M.; Goossens, H.; Tehrani, K.A.; Bogaert, P.; Waroquier, M.; van Speybroeck, V.; De Kimpe, N. *J. Org. Chem.* ***2011***, *76*, 2157.
[203] Pichette, S.; Aubert-Nicol, S.; Lessard, J.; Spino, C. *J. Org. Chem.* ***2012***, *77*, 11216.
[204] Mitcheltree, M.J.; Konst, Z.A.; Herzon, S.B. *Tetrahedron* ***2013***, *69*, 5634.
[205] Dubovyk, I.; Pichugin, D.; Yudin, A.K. *Angew. Chem. Int. Ed.* ***2011***, *50*, 5924.
[206] Redmore, D.; Gutsche, C.D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***, pp. 125–136.
[207] See Jones Jr., M.; Ando, W. *J. Am. Chem. Soc.* ***1968***, *90*, 2200. See Lee, Y.R.; Suk, J.Y.; Kim, B.S. *Tetrahedron Lett.* ***1999***, *40*, 8219.
[208] See Fry, A. *Mech. Mol. Migr.* ***1971***, *4*, 113; Collins, C.J.; Eastham, J.F. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 771–790.

There are two mechanisms,[209] each beginning with protonation of the oxygen and each involving two migrations. In either case, the rearrangement must produce a carbocation that is more stable than the initially formed oxocarbenium ion. In one pathway, the migrations are in opposite directions:[210]



In the other pathway, the migrations are in the same direction. The actual mechanism of this pathway is not certain, but a protonated epoxide intermediate[211] is one possibility.[212] If the reaction is carried out with ketone labeled in the C=O group with ^{14}C, the first pathway predicts that the product will contain all the ^{14}C in the C=O carbon, while in the second pathway the label will be in the α carbon (demonstrating migration of oxygen). The results of such experiments[213] have shown that in some cases only the C=O carbon was labeled, in other cases only the α carbon, while in still others both carbons bore the label, indicating that in these cases both pathways were in operation. With α-hydroxy aldehydes and ketones, the process may stop after only one migration (this is called the α-*ketol rearrangement*). The α-ketol rearrangement can also be brought about by base catalysis, but only if the alcohol is tertiary, since if R^1 or R^2 = hydrogen, enolization of the substrate is more favored than rearrangement.

18-5 The Dienone-Phenol Rearrangement

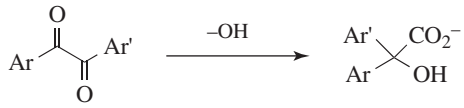


Cyclohexadienone derivatives that have two alkyl groups in the 4 position undergo, on acid treatment,[214] 1,2-migration of one of these groups from the initially formed vinylogous oxocarbenium ion, followed by loss of a proton to give the phenol. Note that a photochemical version of this reaction has been observed.[215] The driving force in the overall reaction (the *dienone-phenol rearrangement*) is of course creation of an aromatic system.[216] Note that both intermediates shown are arenium ions (Sec. 5.A.ii), analogous to those generated by attack of a phenol on an electrophile.[217]

[209] Favorskii, A.; Chilingaren, A. *C. R. Acad. Sci.* ***1926***, *182*, 221.
[210] Collins, C.J.; Bowman, N.S. *J. Am. Chem. Soc.* ***1959***, *81*, 3614.
[211] Zook, H.D.; Smith, W.E.; Greene, J.L. *J. Am. Chem. Soc.* ***1957***, *79*, 4436.
[212] Some such pathway is necessary to account for the migration of oxygen that is found. It may involve a protonated epoxide, a 1,2-diol, or simply a 1,2-shift of an OH group.
[213] See Fry, A.; Oka, M. *J. Am. Chem. Soc.* ***1979***, *101*, 6353.
[214] See Chalais, S.; Laszlo, P.; Mathy, A. *Tetrahedron Lett.* ***1986***, *27*, 2627.
[215] Guo, Z.; Schultz, A.G. *Org. Lett.* ***2001***, *3*, 1177.
[216] Perkins, M.J.; Ward, P. *Mech. Mol. Migr.* ***1971***, *4*, 55 (pp. 90–103); Miller, B. *Mech. Mol. Migr.* ***1968***, *1*, 247; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 55–68; Waring, A.J. *Adv. Alicyclic Chem.* ***1966***, *1*, 129 (pp. 207–223). See Miller, B. *Acc. Chem. Res.* ***1975***, *8*, 245.
[217] See Vitullo, V.P.; Grossman, N. *J. Am. Chem. Soc.* ***1972***, *94*, 3844; Planas, A.; Tomás, J.; Bonet, J. *Tetrahedron Lett.* ***1987***, *28*, 471.

Sometimes, in the reaction of a phenol with an electrophile, a kind of reverse rearrangement (called the *phenol-dienone rearrangement)* takes place, though without an actual migration.[218] An example is the reaction of 2,4,6-tribromopenol with bromine to give 2,4,4,6-tetrabromocyclohexa-2,5-dien-1-one.

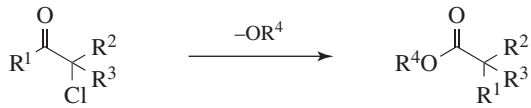
18-6 The Benzil-Benzilic Acid Rearrangement



When treated with base, α-diketones rearrange to give the salts of α-hydroxy acids, a reaction known as the *benzil-benzilic acid rearrangement* (benzil is PhCOCOPh; benzilic acid is Ph_2COHCO_2H).[219] A Rh-catalyzed version of this reaction has also been reported.[220] Though the reaction is usually illustrated with aryl groups, it can also be applied to aliphatic diketones[221] and to α-keto aldehydes. The use of an alkoxide instead of hydroxide gives the corresponding ester directly,[222] although alkoxide ions that are readily oxidized (e.g., ^-OEt or $^-OCHMe_2$) are not useful here, since they reduce the benzil to a benzoin. The mechanism is similar to the rearrangements in **18-1** to **18-4**, but there is a difference: The migrating group does not move to a carbocation. The first step is attack of the base at the carbonyl group, the same as the first step of the tetrahedral mechanism of nucleophilic substitution (Sec. 16.A.i) and of many additions to the C=O bond (Chapter 16). The mechanism has been intensely studied,[210] and there is much evidence for it.[223] The reaction is irreversible.

OS **I**, 89.

18-7 The Favorskii Rearrangement

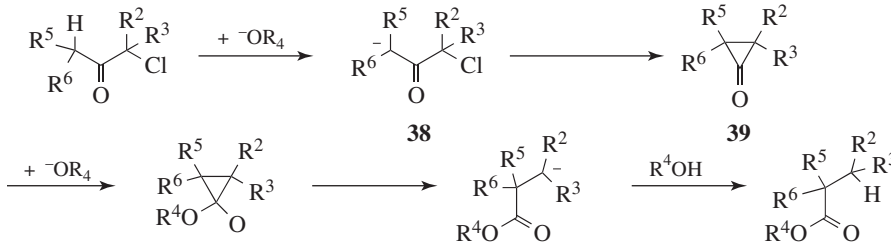


The reaction of α-halo ketones (chloro, bromo, or iodo) with alkoxide ions[224] to give rearranged esters is called the *Favorskii rearrangement*.[225] The use of hydroxide ions or amines as bases leads to the free carboxylic acid (salt) or amide, respectively, instead of the ester. Cyclic α-halo ketones give ring contraction, as in the conversion of 2-chlorocyclohexan-1-one to alkyl cyclopentanecarboxylate. The reaction has also been carried out on α-hydroxy

[218] See Ershov, V.V.; Volod'kin, A.A.; Bogdanov, G.N. *Russ. Chem. Rev.* ***1963***, *32*, 75.
[219] See Selman, S.; Eastham, J.F. *Q. Rev. Chem. Soc.* ***1960***, *14*, 221.
[220] Shimizu, I.; Tekawa, M.; Maruyama, Y.; Yamamoto, A. *Chem. Lett.* ***1992***, 1365.
[221] For an example, see Schaltegger, A.; Bigler, P. *Helv. Chim. Acta* ***1986***, *69*, 1666.
[222] Doering, W. von E.; Urban, R.S. *J. Am. Chem. Soc.* ***1956***, *78*, 5938.
[223] See Screttas, C.G.; Micha-Screttas, M.; Cazianis, C.T. *Tetrahedron Lett.* ***1983***, *24*, 3287.
[224] See Giordano, C.; Castaldi, G.; Casagrande, F.; Abis, L. *Tetrahedron Lett.* ***1982***, *23*, 1385.
[225] Boyer, L.E.; Brazzillo, J.; Forman, M.A.; Zanoni, B. *J. Org. Chem.* ***1996***, *61*, 7611; Hunter, D.H.; Stothers, J.B.; Warnhoff, E.W. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 437–461; Rappe, C. in Patai, S. *The Chemistry of the Carbon-Halogen Bond*, pt. 2, Wiley, NY, ***1973***, pp. 1084–1101; Redmore, D.; Gutsche, C.D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***, pp. 46–69; Shmidt, E.Yu.; Bidusenko, I.A.; Protsuk, N.I.; Mikhaleva, A.I.; Trofimo, B.A. *Russ. J. Org. Chem.* ***2013***, *49*, 8.

ketones[226] and on α,β-epoxy ketones, which give β-hydroxy acids.[227] The fact that an epoxide gives a reaction analogous to a halide indicates that the oxygen and halogen are leaving groups in a nucleophilic substitution step.

Investigation of the mechanism[228] of the Favorskii rearrangement shows that initial deprotonation of an α-hydrogen atom gives an enolate anion, **38**, which is followed by displacement to give a cyclopropanone, **39**. Attack by the alkoxide leads to a tetrahedral intermediate, which opens to a carbanion that is protonated.



The finding[229] that 1-chloro-3-phenylpropan-2-one and 1-chloro-1-phenylpropan-2-one *both* give 3-phenylpropanoic acid (this behavior is typical) shows that both reactions go through a common intermediate. Another important result was determined by radioactive labeling. 2-Chlorocyclohexan-1-one, in which C-1 and C-2 were equally labeled with ^{14}C, was converted to the alkyl cyclopentanecarboxylate. The product was found to contain 50% of the label on the carbonyl carbon, 25% on C-1, and 25% on C-2.[230] Now the carbonyl carbon, which originally carried half of the radioactivity, still had this much, so the rearrangement did not directly affect *it*. However, if the C-6 carbon had migrated to C-2, the other half of the radioactivity would be only on C-1 of the product. The effect of ring size on the photo-Favorskii ring contraction reaction has been discussed.[231]

If the C-2 carbon had migrated to C-6, then this half of the radioactivity would be found solely on C-2 of the product. The fact that C-1 and C-2 were equally labeled showed that *both migrations occurred*, with equal probability. Since C-2 and C-6 of 2-chlorocyclohexan-1-one are not equivalent, this means that there must be a symmetrical intermediate.[232] The type of intermediate that best fits the circumstances is a cyclopropanone, **39**,[233] and the mechanism (for the general case) is formulated (replacing R^1 of our former symbolism with CHR^5R^6, since it is obvious that for this mechanism an α-hydrogen is required on the nonhalogenated side of the carbonyl).

The intermediate corresponding to the cyclopropanone (**39**) for the reaction of 2-chlorocyclohexan-1-one is a symmetrical compound, and the three-membered ring can be

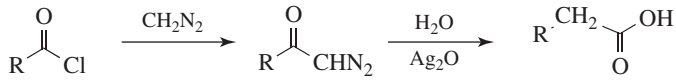
[226] Craig, J.C.; Dinner, A.; Mulligan, P.J. *J. Org. Chem.* ***1972***, *37*, 3539.
[227] See Mouk, R.W.; Patel, K.M.; Reusch, W. *Tetrahedron* ***1975***, *31*, 13.
[228] See Baretta, A.; Waegell, B. *React. Intermed. (Plenum)* ***1982***, *2*, 527. For a theoretical study, see Hamblin, G.D.; Jimenez, R.P.; Sorensen, T.S. *J. Org. Chem.* ***2007***, *72*, 8033.
[229] Bordwell, F.G.; Scamehorn, R.G.; Springer, W.R. *J. Am. Chem. Soc.* ***1969***, *91*, 2087.
[230] Loftfield, R.B. *J. Am. Chem. Soc.* ***1951***, *73*, 4707.
[231] Kammath, V.B.; Šolomek, T.; Ngoy, B.P.; Heger, D.; Klán, P.; Rubina, M.; Givens, R.S. *J. Org. Chem.* ***2013***, *78*, 1718.
[232] A preliminary migration of the chlorine from C-2 to C-6 was ruled out by the fact that recovered 2-chlorocyclohexan-1-one had the same isotopic distribution as the starting 2-chlorocyclohexan-1-one.
[233] See Wasserman, H.H.; Clark, G.M.; Turley, P.C. *Top. Curr. Chem.* ***1974***, *47*, 73; Turro, N.J. *Acc. Chem. Res.* ***1969***, *2*, 25.

opened with equal probability on either side of the carbonyl, accounting for the results with ^{14}C. In the general case, the cyclopropanone is not symmetrical and should open on the side that gives the more stable carbanion.[234] When the cyclopropanone is unsymmetrical, the ring opens to give the more stabilized product. The cyclopropanone intermediate has been isolated for di-*tert*-butylmethyl ketones,[235] and it has also been trapped.[236] Also, cyclopropanones synthesized by other methods have been shown to give Favorskii products on treatment with NaOMe or other bases.[237]

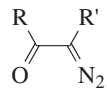
The mechanism discussed is in accord with all the facts when the halo ketone contains an α hydrogen on the other side of the carbonyl group. However, ketones that do not have an α hydrogen also rearrange to give the same type of product in what is usually called the *quasi-Favorskii rearrangement*. The quasi-Favorskii rearrangement cannot take place by the cyclopropanone mechanism. The mechanism that is generally accepted (called the *semibenzilic mechanism*[238]) is a base-catalyzed pinacol rearrangement-type mechanism similar to that of **18-6**. This mechanism requires inversion at the migration terminus and this has been found.[239] It has been shown that even where there *is* an appropriately situated α hydrogen, the semibenzilic mechanism may still operate.[240] An interesting analog of the Favorskii rearrangement treats a ketone, such as 4-*tert*-butylcyclohexanone, without an α halogen with $Tl(NO_3)_3$ to give 3-*tert*-butylcyclopentane-1-carboxylic acid.[241]

OS **IV**, 594; **VI**, 368, 711.

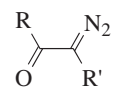
18-8 The Arndt-Eistert Synthesis



In the *Arndt-Eistert synthesis*, an acyl halide is converted to a carboxylic acid with one additional carbon.[242] This rearrangement is called the *Wolff rearrangement*.[243] It is the best method of increasing a carbon chain by one from a *carboxylic acid* (see **10-76** and **16-30**). The diazo ketone can exist in two conformations, called *s*-(*E*) and *s*-(*Z*).



s-Z



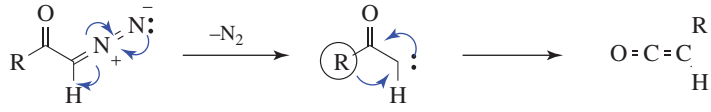
s-E

[234] See Rappe, C.; Knutsson, L.; Turro, N.J.; Gagosian, R.B. *J. Am. Chem. Soc.* ***1970***, *92*, 2032.
[235] Pazos, J.F.; Pacifici, J.G.; Pierson, G.O.; Sclove, D.B.; Greene, F.D. *J. Org. Chem.* ***1974***, *39*, 1990.
[236] See Baldwin, J.E.; Cardellina, J.H.I. *Chem. Commun.* ***1968***, 558.
[237] Wharton, P.S.; Fritzberg, A.R. *J. Org. Chem.* ***1972***, *37*, 1899.
[238] Tchoubar, B.; Sackur, O. *C. R. Acad. Sci.* ***1939***, *208*, 1020.
[239] Baudry, D.; Bégué, J.; Charpentier-Morize, M. *Bull. Soc. Chim. Fr.* ***1971***, 1416.
[240] See Salaun, J.R.; Garnier, B.; Conia, J.M. *Tetrahedron* ***1973***, *29*, 2895.
[241] Ferraz, H.M.; Silva Jr., J.F. *Tetrahedron Lett.* ***1997***, *38*, 1899.
[242] Meier, H.; Zeller, K. *Angew. Chem. Int. Ed.* ***1975***, *14*, 32; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 475–493; Whittaker, D. in Patai, S. *The Chemistry of Diazonium and Diazo Compounds*, pt. 2, Wiley, NY, ***1978***, pp. 593–644.
[243] Kirmse, W. *Eur. J. Org. Chem.* ***2002***, 2193. See Sudrik, S.G.; Sharma, J.; Chavan, V.B.; Chaki, N.K.; Sonawane, H.R.; Vijayamohanan, K.P. *Org. Lett.* ***2006***, *8*, 1089.

Studies have shown that the *Wolff rearrangement* takes place preferentially from the *s*-(*Z*) conformation.[244]

If an alcohol R′OH is used instead of water, the ester RCH_2CO_2R' is isolated.[245] In a similar manner, treatment with ammonia gives the amide. Other catalysts are sometimes used (e.g., colloidal Pt, Cu, etc.), but occasionally the diazo ketone is simply heated or photolyzed in the presence of water, an alcohol, or ammonia, with no catalyst at all but using ultrasound.[246] The photolysis method[247] often gives better results than the Ag catalysis method. Of course, diazo ketones prepared in any other way also give the rearrangement.[248] The reaction is of wide scope. The R group may be alkyl or aryl and may contain many functional groups including unsaturation, but not including groups acidic enough to react with CH_2N_2 or diazo ketones (e.g., **10-5** and **10-19**). Sometimes the reaction is performed with other diazoalkanes (i.e., $R'CHN_2$) to give RCHR′COOH. An asymmetric variation converted ketones to esters using an azaferrocene catalyst.[249]

The mechanism is generally regarded as involving formation of a carbene.[250]



The first step of this process is reaction **12-10**. The actual rearrangement occurs in the second step after treatment of the diazo ketone with water and silver oxide or with silver benzoate and triethylamine. It is the divalent carbon that has the open sextet and to which the migrating group brings its electron pair. The actual product of the reaction is thus the ketene, which then reacts with water (**15-3**), an alcohol (**15-5**), or ammonia or an amine (**15-8**). Particularly stable ketenes[251] (e.g., $Ph_2C{=}C{=}O$) have been isolated and others have been trapped in other ways (e.g., as β-lactams,[252] **16-90**). The purpose of the catalyst is not well understood, though many suggestions have been made. This mechanism is strictly analogous to that of the *Curtius rearrangement* (**18-14**). Although the mechanism as shown above involves a free carbene, and there is much evidence to support this,[253] it is also possible that at least in some cases the two steps are concerted and a free carbene is absent.

When the *Wolff rearrangement* is carried out photochemically, the mechanism is basically the same,[247] but another pathway can intervene. Some of the ketocarbene originally formed can undergo a carbene–carbene rearrangement, through an oxirene intermediate.[254]

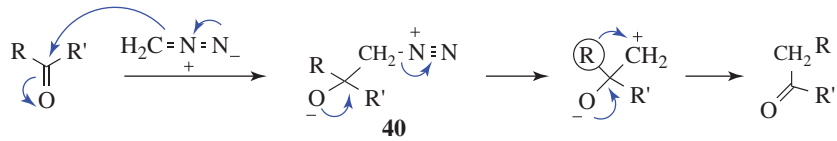
[244] Tomioka, H.; Okuno, H.; Izawa, Y. *J. Org. Chem.* ***1980***, *45*, 5278.
[245] Winum, J.-Y.; Kamal, M.; Leydet, A.; Roque, J.-P.; Montero, J.-L. *Tetrahedron Lett.* ***1996***, *37*, 1781.
[246] For a list of methods, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1850–1851.
[247] See Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 185–195.
[248] See Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* ***1980***, *21*, 4461.
[249] Wiskur, S.L.; Fu, G.C. *J. Am. Chem. Soc.* ***2005***, *127*, 6176.
[250] See Scott, A.P.; Platz, M.S.; Radom, L. *J. Am. Chem. Soc.* ***2001***, *123*, 6069.
[251] See Farlow, R.A.; Thamatloor, D.A.; Sunoj, R.B.; Hadad, C.M. *J. Org. Chem.* ***2002***, *67*, 3257.
[252] Kirmse, W.; Horner, L. *Chem. Ber.* ***1956***, *89*, 2759. Also see, Horner, L.; Spietschka, E. *Chem. Ber.* ***1956***, *89*, 2765.
[253] See Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 476–480. See also, Torres, M.; Ribo, J.; Clement, A.; Strausz, O.P. *Can. J. Chem.* ***1983***, *61*, 996; Tomoika, H.; Hayashi, N.; Asano, T.; Izawa, Y. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 758.
[254] See Lewars, Y. *Chem. Rev.* ***1983***, *83*, 519.

This rearrangement was shown by ^{14}C labeling experiments, where diazo ketones labeled in the carbonyl group gave rise to ketenes that bore the label at both C=C carbons.[255] In general, the smallest degree of scrambling (and thus of the oxirene pathway) was found when R′ = H. An intermediate believed to be an oxirene has been detected by laser spectroscopy.[256] The oxirene pathway is not found in the thermal Wolff rearrangement. It is likely that an excited singlet state of the carbene is necessary for the oxirene pathway to intervene.[257] In the photochemical process, ketocarbene intermediates, in the triplet state, have been isolated in an Ar matrix at 10–15 K, where they have been identified by UV-visible, IR, and ESR spectra.[258] These intermediates went on to give the rearrangement via the normal pathway, with no evidence for oxirene intermediates. A photochemical Wolff rearrangement has been reported using flow conditions (Sec. 7.D).[259]

OS **III**, 356; **VI**, 613, 840.

18-9 Homologation of Aldehydes and Ketones

Aldehydes and ketones[260] can be converted to their homologs with diazomethane.[261] Several other reagents[262] are also effective, including Me_3SiI, and then silica gel.[263] With the diazomethane reaction, formation of an epoxide (**16-46**) is a side reaction. Superficially, this reaction appears to be similar to the insertion of carbenes into C—H bonds (which is **12-21**), and IUPAC names the reaction with diazomethane as an insertion, but the mechanism is quite different. However, this reaction is a true rearrangement and no free carbene is involved. The first step is an addition to the C=O bond to give betaine **40**, which can sometimes be isolated. As shown in **16-46**, intermediate **40** can also go to the epoxide. The evidence for this mechanism has been summarized in the review by Gutsche.[261] Note that this mechanism is essentially the same as in the apparent "insertions" of oxygen (**18-19**) and nitrogen (**18-16**) into ketones.



[255] Fenwick, J.; Frater, G.; Ogi, K.; Strausz, O.P. *J. Am. Chem. Soc.* ***1973***, *95*, 124; Zeller, K. *Chem. Ber.* ***1978***, *112*, 678. See also, Majerski, Z.; Redvanly, C.S. *J. Chem. Soc., Chem. Commun.* ***1972***, 694.

[256] Tanigaki, K.; Ebbesen, T.W. *J. Am. Chem. Soc.* ***1987***, *109*, 5883. See also, Bachmann, C.; N'Guessan, T.Y.; Debû, F.; Monnier, M.; Pourcin, J.; Aycard, J.; Bodot, H. *J. Am. Chem. Soc.* ***1990***, *112*, 7488.

[257] Csizmadia, I.G.; Gunning, H.E.; Gosavi, R.K.; Strausz, O.P. *J. Am. Chem. Soc.* ***1973***, *95*, 133.

[258] McMahon, R.J.; Chapman, O.L.; Hayes, R.A.; Hess, T.C.; Krimmer, H. *J. Am. Chem. Soc.* ***1985***, *107*, 7597.

[259] Fuse, S.; Otake, Y.; Nakamura, H. *Eur. J. Org. Chem.* ***2017***, 6466.

[260] See Yamamoto, M.; Nakazawa, M.; Kishikawa, K.; Kohmoto, S. *Chem. Commun.* ***1996***, 2353.

[261] See Gutsche, C.D. *Org. React.* ***1954***, *8*, 364.

[262] See Aoyama, T.; Shioiri, T. *Synthesis* ***1988***, 228.

[263] Lemini, C.; Ordoñez, M.; Pérez-Flores, J.; Cruz-Almanza, R. *Synth. Commun.* ***1995***, *25*, 2695.

The difluorohomologation of ketones followed by halogenation was reported using first a silylation reaction, and second the addition of difluorocarbene using Me_3SiCF_2Br activated by a bromide ion, with the final reaction of the intermediate cyclopropanes with *N*-bromo- or *N*-iodosuccinimide to give α,α-difluoro-β-halo-substituted ketones.[264]

Aldehydes give fairly good yields of methyl ketones; that is, hydrogen migrates in preference to alkyl. The most abundant side product is not the homologous aldehyde, but the epoxide. However, the yield of aldehyde at the expense of methyl ketone can be increased by the addition of methanol. If the aldehyde contains electron-withdrawing groups, the yield of epoxides is increased and the ketone is formed in smaller amounts, if at all. Ketones give poorer yields of homologous ketones. Epoxides are usually the predominant product here, especially when one or both R groups contain an electron-withdrawing group. The yield of ketones also decreases with increasing length of the chain. The use of a Lewis acid increases the yield of ketone.[265] Cyclic ketones,[266] three membered[267] and larger, behave particularly well and give good yields of ketones with the ring expanded by one.[268] Aliphatic diazo compounds ($RCHN_2$ and R_2CN_2) are sometimes used instead of diazomethane, with the expected results.[269] Ethyl diazoacetate can be used analogously, in the presence of a Lewis acid or of triethyloxonium fluoroborate,[270] to give a β-keto ester.

When unsymmetrical ketones were used in this reaction (with BF_3 as catalyst), the less highly substituted carbon preferentially migrated.[271] The reaction can be made regioselective by applying this method to the α-halo ketone, in which case only the other carbon migrates.[272] The ethyl diazoacetate procedure has also been applied to the acetals or ketals of α,β-unsaturated aldehydes and ketones.[273]

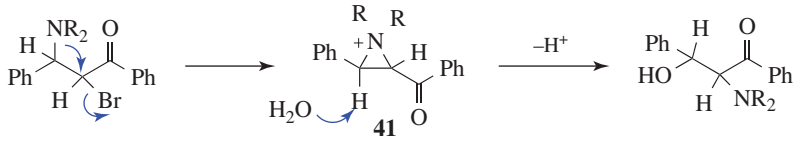
1,3-Diketones are converted to 1,4-diketones upon treatment with $CF_3CO_2ZnCH_2I$.[274] In a related reaction, alkenes insert into aldehydes in the presence of a Rh catalyst to give the corresponding ketone.[275] Bicyclic ketones can be expanded to form monocyclic ketones in the presence of certain reagents. Treatment of a bicyclo[4.1.0]hexan-4-one derivative with SmI_2 led to a cyclohexanone.[276] The SmI_2 also converts α-halomethyl cyclic ketones to the next larger ring ketone[277] and cyclic ketones to the next larger ring ketone in the presence of CH_2I_2.[278]

OS **IV**, 225, 780. For homologation of carboxyl acid derivatives, see OS **IX**, 426.

[264] See Fedorov, O.V.; Kosobokov, M.D.; Levin, V.V.; Struchkova, M.I.; Dilman, A.D. *J. Org. Chem.* ***2015***, *80*, 5870.
[265] See Müller, E.; Kessler, H.; Zeeh, B. *Fortschr. Chem. Forsch.* ***1966***, *7*, 128 (see pp. 137–150).
[266] See Krief, A.; Laboureur, J.L. *Tetrahedron Lett.* ***1987***, *28*, 1545; Krief, A.; Laboureur, J.L.; Dumont, W. *Tetrahedron Lett.* ***1987***, *28*, 1549; Abraham, W.D.; Bhupathy, M.; Cohen, T. *Tetrahedron Lett.* ***1987***, *28*, 2203; Trost, B.M.; Mikhail, G.K. *J. Am. Chem. Soc.* ***1987***, *109*, 4124.
[267] See Turro, N.J.; Gagosian, R.B. *J. Am. Chem. Soc.* ***1970***, *92*, 2036.
[268] See Gutsche, C.D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***, pp. 81–98. For a review pertaining to bridged bicyclic ketones, see Krow, G.R. *Tetrahedron* ***1987***, *43*, 3.
[269] See Loeschorn, C.A.; Nakajima, M.; Anselme, J. *Bull. Soc. Chim. Belg.* ***1981***, *90*, 985.
[270] See Baldwin, S.W.; Landmesser, N.G. *Synth. Commun.* ***1978***, *8*, 413.
[271] Liu, H.J.; Majumdar, S.P. *Synth. Commun.* ***1975***, *5*, 125.
[272] Dave, V.; Warnhoff, E.W. *J. Org. Chem.* ***1983***, *48*, 2590.
[273] Doyle, M.P.; Trudell, M.L.; Terpstra, J.W. *J. Org. Chem.* ***1983***, *48*, 5146.
[274] Xue, S.; Li, L.-Z.; Liu, Y.-K.; Guo, Q.-X. *J. Org. Chem.* ***2006***, *71*, 215.
[275] Aïssa, C.; Fürstner, A. *J. Am. Chem. Soc.* ***2007***, *129*, 14836.
[276] Lee, P.H.; Lee, J. *Tetrahedron Lett.* ***1998***, *39*, 7889.
[277] Hasegawa, E.; Kitazume, T.; Suzuki, K.; Tosaka, E. *Tetrahedron Lett.* ***1998***, *39*, 4059.
[278] Fukuzawa, S.; Tsuchimoto, T. *Tetrahedron Lett.* ***1995***, *36*, 5937.

B. Carbon-to-Carbon Migrations of Other Groups

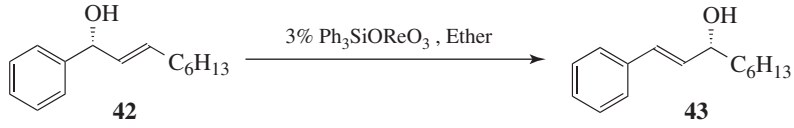
18-10 Migrations of Halogen, Hydroxyl, Amino, and so on



When a nucleophilic substitution is carried out on a substrate that has a neighboring group (Sec. 10.C) on the adjacent carbon, a cyclic intermediate can be generated that is opened on the opposite side, resulting in migration of the neighboring group. In the example shown above (NR_2 = morpholino),[279] the reaction took place via an aziridinium salt **41** to give an α-amino-β-hydroxy ketone. Sulfonate esters and halides can also migrate in this reaction.[280]

α-Halo and α-acyloxy epoxides undergo ready rearrangement to α-halo and α-acyloxy ketones, respectively.[281] These substrates are prone to rearrange upon standing without a catalyst, although an acid catalyst is necessary in some cases. It is also possible for one of the R groups (alkyl, aryl, or hydrogen) to migrate instead. In a related reaction, α-bromoaziridines undergo rearrangement to the isomerized α-bromoaziridine in the presence of $MgBr_2$.[282]

Allylic alcohols migrate to give a new allylic alcohol in the presence of a Re catalyst. An example is the conversion of **42** to **43**.[283]



Variations using Rh[284] or Ir[285] catalysts are known, and methanesulfonic acid catalyzes the isomerization.[286] With a Ru catalyst, allylic alcohols isomerize to an aliphatic ketone.[287] There is a similar Au-catalyzed isomerization of allylic acetates.[288]

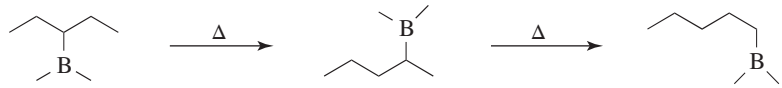
The *Meyer-Schuster rearrangement* is an acid-catalyzed rearrangement of a propargyl alcohol to a conjugated carbonyl compound.[289] A rearrangement was also catalyzed by a

[279] Southwick, P.L.; Walsh, W.L. *J. Am. Chem. Soc.* ***1955***, *77*, 405. See also, Kiss, L.; Mangelinckx, S.; Fülöp, F.; De Kimpe, N. *Org. Lett.* ***2007***, *9*, 4399.
[280] See Peterson, P.E. *Acc. Chem. Res.* ***1971***, *4*, 407. See also, Kobrina, L.S.; Kovtonyuk, V.N. *Russ. Chem. Rev.* ***1988***, *57*, 62; Warren, S. *Acc. Chem. Res.* ***1978***, *11*, 403.
[281] For a review, see McDonald, R.N. *Mech. Mol. Migr.* ***1971***, *3*, 67.
[282] Karikomi, M.; Takayama, T.; Haga, K.; Hiratani, K. *Tetrahedron Lett.* ***2005***, *46*, 6541.
[283] See Morrill, C.; Beutner, G.L.; Grubbs, R.H. *J. Org. Chem.* ***2006***, *71*, 7813.
[284] Boeda, F.; Mosset, P.; Crévisy, C. *Tetrahedron Lett.* ***2006***, *47*, 5021.
[285] Mantilli, L.; Gérard, D.; Torche, S.; Besnard, C.; Mazet, C. *Pure Appl. Chem.* ***2010***, *82*, 1461.
[286] Leleti, R.R.; Hu, B.; Prashad, M.; Repič, O. *Tetrahedron Lett.* ***2007***, *48*, 8505.
[287] Ito, M.; Kitahara, S.; Ikariya, T. *J. Am. Chem. Soc.* ***2005***, *127*, 6172.
[288] Marion, N.; Gealageas, R.; Nolan, S.P. *Org. Lett.* ***2007***, *9*, 2653.
[289] Meyer, K.H.; Schuster, K. *Ber.* ***1922***, *55*, 819; Swaminathan, S.; Narayan, K.V. *Chem. Rev.* ***1971***, *71*, 429.

cationic Rh-bisphosphane complex.[290] An Au-catalyzed rearrangement of ethoxyalkynyl carbinols gave α,β-unsaturated esters,[291] and enones have been prepared from propargylic alcohols.[292] The base-induced isomerization of a propargylic alcohol gave a conjugated ketone,[293] and a combination of Mo/Au led to rapid 1,3-rearrangement of propargyl alcohols.[294] The perrhenate-catalyzed rearrangement of 1-silylalkyn-3-ols formed α,β-unsaturated acylsilanes.[295] The Fe-catalyzed preparation of acyclic β-amino ketones by Meyer-Schuster rearrangement of 3-aryl propargyl alcohols was followed by reaction with amines.[296] A Cu-catalyzed arylative Meyer-Schuster rearrangement of substituted propargylic alcohols and diaryliodonium salts gave primarily (*E*) trisubstituted enones.[297] 2-Acylfurans were prepared by rearrangement of 6-hydroxyhex-2-en-4-ynals.[298] Methyl triflate has been used to catalyze the reaction.[299]

In the presence of a Cu catalyst, alkenyl epoxides (vinyl oxiranes) rearrange to a 2,5-dihydrofuran.[300] Alkenyl thiiranes are similarly converted to 2,5-dihydrothiophenes with a Cu catalyst.[301]

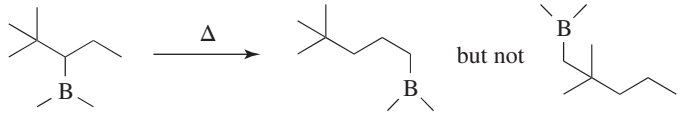
18-11 Migration of Boron



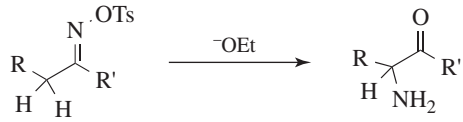
Boranes are prepared by the reaction of BH_3 (B_2H_6) or an alkylborane with an alkene (**15-11**). When a nonterminal borane is heated at temperatures ranging from 100 to 200 °C, the boron moves toward the end of the chain.[302] The reaction is catalyzed by small amounts of borane or other species containing B—H bonds. The boron can move past a branch [dimethyl(2-methylbutyl)borane to dimethyl(3-methylbutyl)borane], but not past a double branch. The reaction is an equilibrium mixture of organoboranes. The migration can go quite a long distance, including a migration of 11 positions.[303] If the boron is on a cycloalkyl ring, it can move around the ring; if any alkyl chain is also on the ring, the boron may move from the ring to the chain, ending up at the end of the chain.[304] The reaction is

[290] Tanaka, K.; Shoji, T.; Hirano, M. *Eur. J. Org. Chem.* ***2007***, 2687.
[291] Lopez, S.S.; Engel, D.A.; Dudley, G.B. *Synlett* ***2007***, 949.
[292] Pennell, M.N.; Unthank, M.G.; Turner, P.; Sheppard, T.D. *J. Org. Chem.* ***2011***, *76*, 1479. Also see Yang, Y.; Shen, Y.; Wang, X.; Zhang, Y.; Wang, D.; Shi, X. *Tetrahedron Lett.* ***2016***, *57*, 2280.
[293] Sonye, J.P.; Koide, K. *J. Org. Chem.* ***2007***, *72*, 1846.
[294] Egi, M.; Yamaguchi, Y.; Fujiwara, N.; Akai, S. *Org. Lett.* ***2008***, *10*, 1867.
[295] Nikolaev, A.; Orellana, A. *Org. Lett.* ***2015***, *17*, 5796.
[296] Tao, R.; Yin, Y.; Duan, Y.; Sun, Y.; Sun, Y.; Cheng, F.; Pan, J.; Lu, C.; Wang, Y. *Tetrahedron* ***2017***, *73*, 1762.
[297] Collins, B.S.L.; Suero, M.G.; Gaunt, M.J. *Angew. Chem. Int. Ed.* ***2013***, *52*, 5799.
[298] Tharra, P.; Baire, B. *J. Org. Chem.* ***2015***, *80*, 8314.
[299] Yang, L.; Zeng, Q. *Synthesis* ***2017***, *49*, 3149.
[300] Batory, L.A.; McInnis, C.E.; Njardarson, J.T. *J. Am. Chem. Soc.* ***2006***, *128*, 16054.
[301] Rogers, E.; Araki, H.; Batory, L.A.; McInnis, C.E.; Njardarson, J.T. *J. Am. Chem. Soc.* ***2007***, *129*, 2768.
[302] Brown, H.C. *Hydroboration*, W.A. Benjamin, NY, ***1962***, pp. 136–149; Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1966***, *88*, 1433; Brown, H.C.; Racherla, U.S. *J. Organomet. Chem.* ***1982***, *241*, C37.
[303] Logan, T.J. *J. Org. Chem.* ***1961***, *26*, 3657.
[304] Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1967***, *89*, 561.

useful for the migration of double bonds in a controlled way (see **12-2**). The mechanism may involve a π complex, at least partially.[305]

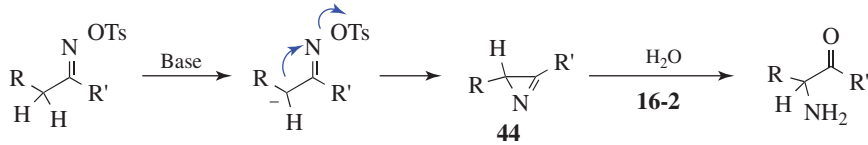


18-12 The Neber Rearrangement



α-Amino ketones can be prepared by treatment of ketoxime tosylates with a base such as ethoxide or pyridine.[306] This reaction is called the *Neber rearrangement*. The R group is usually aryl, although the reaction has been carried out with R = alkyl or hydrogen. The R′ group may be alkyl or aryl, but not hydrogen. The *Beckmann rearrangement* (**18-17**) and the abnormal Beckmann reaction (elimination to the nitrile, **17-28**) may be side reactions, although these generally occur in acid media.

The mechanism of the Neber rearrangement involves an azirine intermediate **44**.[307]



The best evidence for this mechanism is that the azirine intermediate has been isolated.[308] In contrast to the *Beckmann rearrangement*, this reaction is sterically indiscriminate:[309] Both a *syn* and an *anti* ketoxime give the same product. The mechanism is shown as stepwise, but it is possible that the first two steps are concerted, and it is also possible that what is shown as the second step is actually two steps: loss of OTs to give a nitrene, and formation of the azirine.

N-Chloroimines prepared in other ways also give the reaction.[310] Indoles have been prepared via a Neber rearrangement.[311] Organocatalysts have been used for asymmetric Neber reactions.[312]

OS **V**, 909; **VII**, 149.

[305] See Wood, S.E.; Rickborn, B. *J. Org. Chem.* ***1983***, *48*, 555; Field, L.D.; Gallagher, S.P. *Tetrahedron Lett.* ***1985***, *26*, 6125.
[306] For a review, see Conley, R.T.; Ghosh, S. *Mech. Mol. Migr.* ***1971***, *4*, 197 (pp. 289–304).
[307] See Hatch, M.J.; Cram, D.J. *J. Am. Chem. Soc.* ***1953***, *75*, 38.
[308] Neber, P.W.; Burgard, A. *Liebigs Ann. Chem.* ***1932***, *493*, 281; Parcell, R.F. *Chem. Ind. (London)* ***1963***, 1396.
[309] House, H.O.; Berkowitz, W.F. *J. Org. Chem.* ***1963***, *28*, 2271.
[310] Baumgarten, H.E.; Petersen, J.M.; Wolf, D.C. *J. Org. Chem.* ***1963***, *28*, 2369.
[311] Taber, D.F.; Tian, W. *J. Am. Chem. Soc.* ***2006***, *128*, 1058.
[312] Sakamoto, S.; Inokuma, T.; Takemoto, Y. *Org. Lett.* ***2011***, *13*, 6374.

C. Carbon-to-Nitrogen Migrations of R and Ar

The reactions in this group are nucleophilic migrations from a carbon atom to a nitrogen atom. In each case the nitrogen atom either has six electrons in its outer shell (and thus invites the migration of a group carrying an electron pair) or else loses a nucleofuge concurrently with the migration (Sec. 18.A.i).[313]

In many cases, it is not certain whether the nucleofuge X is lost first, creating an intermediate nitrene[314] or nitrenium ion, or whether migration and loss of the nucleofuge are simultaneous.[315] It is likely that both possibilities can exist, depending on the substrate and reaction conditions.

18-13 The Hofmann Rearrangement

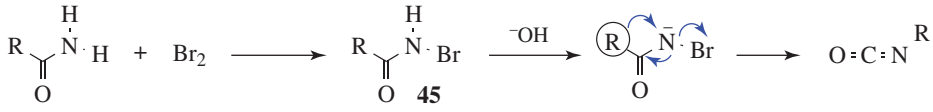
$$RCONH_2 + NaOBr \longrightarrow R{-}N{=}C{=}O \xrightarrow[\textbf{16-2}]{\text{Hydrolysis}} RNH_2$$

In the *Hofmann rearrangement*, an unsubstituted amide is treated with sodium hypobromite (or sodium hydroxide and bromine, which is essentially the same thing) to give an isocyanate, but this compound is seldom isolated[316] since it is usually hydrolyzed under the reaction conditions. The final isolated product is a primary amine that has *one carbon fewer than the starting amide*.[317] The R group may be alkyl or aryl, but if it is an alkyl group of more than about six or seven carbons, low yields are obtained unless Br_2 and NaOMe are used instead of Br_2 and NaOH.[318] Another modification uses NBS/NaOMe.[319] Under these conditions the product of addition to the isocyanate is the carbamate RNHCOOMe (**16-7**), which is easily isolated or can be hydrolyzed to the amine.[320] A mixture of NBS and DBU (see **17-11**) in methanol gives the carbamate,[321] as does electrolysis in methanol.[322] Hypervalent iodine reagents have been used for the preparation of carbamates.[323] Side reactions when NaOH is the base are formation of ureas RNHCONHR and acyl ureas RCONHCONHR by addition, respectively, of RNH_2 and $RCONH_2$ to RNCO (**16-18**). The microwave-assisted Hofmann rearrangement of aromatic benzamides was mediated by tribromoisocyanuric acid/KOH/MeOH.[324]

The mechanism shown follows the pattern outlined in the discussion preceding this reaction. The first step is an example of **12-51** and intermediate *N*-halo amides (**45**) have been isolated. Compound **45** is acidic because of the presence of two electron-withdrawing groups (acyl and halo) on the nitrogen, and in the second step, **45** loses a proton to the base.

[313] Smith, P.A.S. in de Mayo, P. *Molecular Rearrangements*, Vol. 1, Wiley, NY, ***1963***, pp. 258–550.
[314] See Boyer, J.H. *Mech. Mol. Migr.* ***1969***, *2*, 267.
[315] As discussed by Lwowski, W. in Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***, pp. 217–221.
[316] See Sy, A.O.; Raksis, J.W. *Tetrahedron Lett.* ***1980***, *21*, 2223.
[317] See Wallis, E.S.; Lane, J.F. *Org. React.* ***1946***, *3*, 267.
[318] See Radlick, P.; Brown, L.R. *Synthesis* ***1974***, 290.
[319] Huang, X.; Keillor, J.W. *Tetrahedron Lett.* ***1997***, *38*, 313.
[320] See Gogoi, P.; Konwar, D. *Tetrahedron Lett.* ***2007***, *48*, 531.
[321] Huang, X.; Seid, M.; Keillor, J.W. *J. Org. Chem.* ***1997***, *62*, 7495. For reactions using flow conditions (Sec. 7.D), see Sagandira, C.R.; Watts, P. *Eur. J. Org. Chem.* ***2017***, *23*, 6554.
[322] Matsumura, Y.; Maki, T.; Satoh, Y. *Tetrahedron Lett.* ***1997***, *38*, 8879.
[323] See Yoshimura, A.; Middleton, K.R.; Luedtke, M.W.; Zhu, C.; Zhdankin, V.V. *J. Org. Chem.* ***2012***, *77*, 11399; Borah, A.J.; Phukan, P. *Tetrahedron Lett.* ***2012***, *53*, 3035.
[324] Miranda, L.S.M.; da Silva, T.R.; Crespo, L.T.; Esteves, P.M.; de Matos, L.F.; Diederichs, C.C.; de Souza, R.O.M.A. *Tetrahedron Lett.* ***2011***, *52*, 1639.

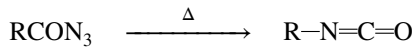
It is possible that the third step is actually two steps: loss of bromide to form a nitrene, followed by the actual migration, but most of the available evidence favors the concerted reaction.[325]



A variation of the Hofmann rearrangement treated a β-hydroxy primary amide with $PhI(O_2CCF_3)_3$ in aqueous acetonitrile, giving an isocyanate via —CON—I, which reacts with the hydroxyl group intramolecularly to give a cyclic carbamate.[326] Note that carbamates are converted to isocyanates by heating with Montmorillonite K-10.[327] Imides react to give amino acids; for example, phthalimide gives *o*-aminobenzoic acid. α-Hydroxy and α-halo amides give aldehydes and ketones by way of the unstable α-hydroxy- or α-haloamines. However, a side product with an α-halo amide is a *gem*-dihalide. Ureas analogously give hydrazines.

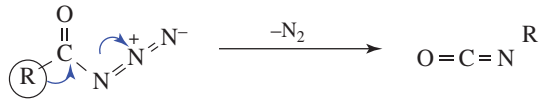
OS **II**, 19, 44, 462; **IV**, 45; **VIII**, 26, 132.

18-14 The Curtius Rearrangement



The *Curtius rearrangement* involves heating acyl azides to yield isocyanates.[328] The reaction gives good yields of isocyanates, since no water is present to hydrolyze them to the amine. Of course, they can be subsequently hydrolyzed, and indeed the reaction *can* be carried out in water or alcohol, in which case the products are amines, carbamates, or acylureas, as in **18-13**.[329] This is a very general reaction and can be applied to almost any carboxylic acid: aliphatic, aromatic, alicyclic, heterocyclic, unsaturated, and containing many functional groups. Acyl azides can be prepared as in **10-42** or by treatment of acylhydrazines (hydrazides) with nitrous acid (analogous to **12-48**). The Curtius rearrangement is catalyzed by Lewis acids or protic acids, but these are usually not necessary.

The mechanism is similar to that in **18-13** to give an isocyanate. Also note the exact analogy between this reaction and **18-8**. However, in this case, there is no evidence for a free nitrene and it is probable that the conversion is concerted.[330]

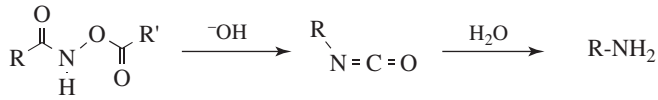


[325] See Imamoto, T.; Kim, S.; Tsuno, Y.; Yukawa, Y. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 2776.
[326] Yu, C.; Jiang, Y.; Liu, B.; Hu, L. *Tetrahedron Lett.* ***2001***, *42*, 1449.
[327] Uriz, P.; Serra, M.; Salagre, P.; Castillon, S.; Claver, C.; Fernandez, E. *Tetrahedron Lett.* ***2002***, *43*, 1673.
[328] See Banthorpe, D.V. in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 397–405. See Yoshimura, K.; Okano, K.; Ishikawa, R.; Yamamoto, H.; Sumimoto, M.; Hori, K. *J. Phys. Org. Chem.* ***2012***, *25*, 394.
[329] See Pfister, J.R.; Wyman, W.E. *Synthesis* ***1983***, 38. See also, Ma, B.; Lee, W.-C. *Tetrahedron Lett.* ***2010***, *51*, 385.
[330] See, Smalley, R.K.; Bingham, T.E. *J. Chem. Soc. C* ***1969***, 2481.

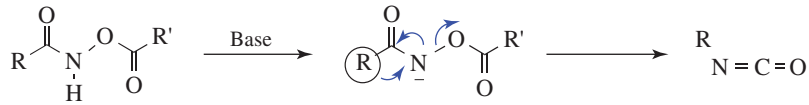
Alkyl azides can be similarly pyrolyzed to give imines, in an analogous reaction:[331] The R groups may be alkyl, aryl, or hydrogen, though if hydrogen migrates, the product is the unstable $R_2C{=}NH$. The mechanism is essentially the same as that of the Curtius rearrangement. However, in pyrolysis of tertiary alkyl azides, there is evidence that free alkyl nitrenes are intermediates.[332] The reaction can also be carried out with acid catalysis, in which case lower temperatures can be used, though the acid may hydrolyze the imine (**16-2**). Cycloalkyl azides give ring expansion, as in the conversion of 1-azido-1-alkylcyclohexane to 7-alkyl-3,4,5,6-tetrahydro-2*H*-azepine.[333] Aryl azides also give ring expansion on heating, as in the conversion of azidobenzene to *N*-phenyl-2*H*-azepin-7-amine by heating with aniline.[334]

OS **III**, 846; **IV**, 819; **V**, 273; **VI**, 95, 910. Also see, OS **VI**, 210.

18-15 The Lossen Rearrangement



The *O*-acyl derivatives of hydroxamic acids[335] give isocyanates when treated with bases or sometimes even just on heating, in a reaction known as the *Lossen rearrangement*.[336] The mechanism is similar to that of **18-13** and **18-14**:



In a similar reaction, aromatic acyl halides are converted to amines in one laboratory step by treatment with hydroxylamine-*O*-sulfonic acid.[337] Metal-assisted Lossen rearrangements are known.[338] Unsymmetrical ureas were prepared using bromodimethylsulfonium bromide as a mediator.[339] A chiral Lossen rearrangement is known.[340]

The *Tiemann rearrangement*[341] is an old reaction in which *N*-phenylurea was formed by tosylation of benzamidoxine. Various *N*-substituted cyanamides were prepared by the

[331] See Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, ***1984***; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrnagements*, Van Nostrand-Reinhold, Princeton, ***1973***, pp. 45–52; in Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***, see the chapters by Lewis, F.D.; Saunders Jr., W.H. pp. 47–97 (pp. 47–78) and by Smith, P.A.S. pp. 99–162.
[332] Montgomery, F.C.; Saunders Jr., W.H. *J. Org. Chem.* ***1976***, *41*, 2368.
[333] Smith, P.A.S.; Lakritz, J. cited in Smith, P.A.S. in de Mayo, P. *Molecular Rearrangments*, Vol. 1, Wiley, NY, ***1963***, p. 474.
[334] Huisgen, R.; Vossius, D.; Appl, M. *Chem. Ber.* ***1958***, *91*, 1,12.
[335] See Bauer, L.; Exner, O. *Angew. Chem. Int. Ed.* ***1974***, *13*, 376.
[336] Lossen, W. *Justus Liebigs Ann. Chem.* ***1872***, *161*, 347; Lossen, W. *Justus Liebigs Ann. Chem.* ***1875***, *175*, 271; Lossen, W. *Justus Liebigs Ann. Chem.* ***1875***, *175*, 313. See Strotman, N.A.; Ortiz, A.; Savage, S.A.; Wilbert, C.R.; Ayers, S.; Kiau, S. *J. Org. Chem.* ***2017***, *82*, 4044.
[337] Wallace, R.G.; Barker, J.M.; Wood, M.L. *Synthesis* ***1990***, 1143.
[338] Jašíková, L.; Hanikýřová, E.; Škríba, A.; Jašík, J.; Roithová, J. *J. Org. Chem.* ***2012***, *77*, 2829.
[339] Yadav, D.K.; Yadav, A.K.; Srivastava, V.P.; Watal, G.; Yadav, L.D.S. *Tetrahedron Lett.* ***2012***, *53*, 2890.
[340] Chandrasekhar, S.; Sridhar, M. *Tetrahedron: Asymmetry* ***2000***, *11*, 3467.
[341] Tiemann, F. *Ber. Dtsch. Chem. Ges.* ***1891***, *24*, 4162. Also see Partridge, M.W.; Turner, H.A. *J. Pharm. Pharmacol.* ***1953***, *5*, 103; Wang, C.-H.; Hsieh, T.-H.; Lin, C.-C.; Yeh, W.-H.; Lin, C.-A.; Chien, T.-C. *Synlett* ***2015***, *26*, 1823.

Tiemann rearrangement of amidoximes with arylsulfonyl chlorides and diisopropylethylamine.[342]

18-16 The Schmidt Reaction

$$RCOOH + HN_3 \xrightarrow{H^+} R{-}N{=}C{=}O \xrightarrow{H_2O} RNH_2$$

There are actually three reactions given the name *Schmidt reaction*, involving the addition of hydrazoic acid to carboxylic acids, aldehydes and ketones, and alcohols and alkenes.[343] The most common is the reaction with carboxylic acids, illustrated above.[344] Sulfuric acid is a common catalyst, but Lewis acids have also been used. Triflic acid has been used for chemoselective Schmidt reactions.[345] Good results are obtained for aliphatic R, especially for long chains. When R is aryl, the yields are variable, being best for sterically hindered compounds like mesitoic acid. This method has the advantage over **18-13** and **18-14** in that there is just one laboratory step from the acid to the amine, but conditions are more drastic.[346] Under the acid conditions employed, the isocyanate is virtually never isolated. The Schmidt reaction has been done in ionic liquids.[347] Interconverting isomeric allylic azides were treated with $SnCl_4$ to give an intramolecular Schmidt reaction that led to substituted lactams stereoselectively.[348] Hexafluoroisopropanol has been used as a solvent.[349]

The reaction between a ketone and hydrazoic acid is a method for "insertion" of NH between the carbonyl group and one R group, converting a ketone into an amide.[350] Either or both of the groups attached to the carbonyl carbon may be aryl. In general, dialkyl ketones and cyclic ketones react more rapidly than alkyl aryl ketones, and these more rapidly than diaryl ketones. Diaryl ketones require sulfuric acid and do not react in concentrated HCl, though HCl is strong enough for dialkyl ketones. Dialkyl and cyclic ketones react sufficiently faster than diaryl or aryl alkyl ketones or carboxylic acids or alcohols, so that these functions may be present in the same molecule without interference. Cyclic ketones give lactams.[351] With alkyl aryl ketones, it is the aryl group that generally migrates to the nitrogen, except when the alkyl group is bulky.[352] The reaction of acylsilanes and alkyl azides with triflic acid gave the amide.[353]

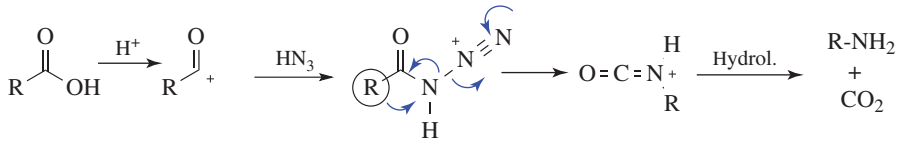
The reaction has been applied to a few aldehydes, but rarely. With aldehydes the product is usually the nitrile (**16-14**). Even with ketones, conversion to the nitrile is often a side reaction, especially with the type of ketone that gives **17-28**. A useful variation of the Schmidt reaction treats a cyclic ketone such as cyclohexanone with an alkyl azide (RN_3)[354]

[342] Lin, C.-C.; Hsieh, T.-H.; Liao, P.-Y.; Liao, Z.-Y.; Chang, C.-W.; Shih, Y.-C.; Yeh, W.-H.; Chien, T.-C. *Org. Lett.* ***2014***, *16*, 892.
[343] Banthorpe, D.V. in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 405–434.
[344] See Koldobskii, G.I.; Ostrovskii, V.A.; Gidaspov, B.V. *Russ. Chem. Rev.* ***1978***, *47*, 1084.
[345] Rokade, B.V.; Prabhu, K.R. *J. Org. Chem.* ***2012***, *77*, 5364.
[346] See Smith, P.A.S. *Org. React.* ***1946***, *3*, 337 (pp. 363–366).
[347] Nandi, G.C.; Laali, K.K. *Tetrahedron Lett.* ***2013***, *54*, 2177.
[348] Liu, R.; Gutierrez, O.; Tantillo, D.J.; Aubé, J. *J. Am. Chem. Soc.* ***2012***, *134*, 6528. See Motiwala, H.F.; Fehl, C.; Li, S.-W.; Hirt, E.; Porubsky, P.; Aubé, J. *J. Am. Chem. Soc.* ***2013***, *135*, 9000.
[349] Motiwala, H.F.; Charaschanya, M.; Day, V.W.; Aubé, J. *J. Org. Chem.* ***2016***, *81*, 1593.
[350] See Koldobskii, G.I.; Tereschenko, G.F.; Gerasimova, E.S.; Bagal, L.I. *Russ. Chem. Rev.* ***1971***, *40*, 835; Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 137–145.
[351] See Krow, G.R. *Tetrahedron* ***1981***, *37*, 1283.
[352] Exceptions to this statement: see Tomita, M.; Minami, S.; Uyeo, S. *J. Chem. Soc. C* ***1969***, 183.
[353] Yu, C.-J.; Li, R.; Gu, P. *Tetrahedron Lett.* ***2016***, *57*, 3568.
[354] See Furness, K.; Aubé, J. *Org. Lett.* ***1999***, *1*, 495.

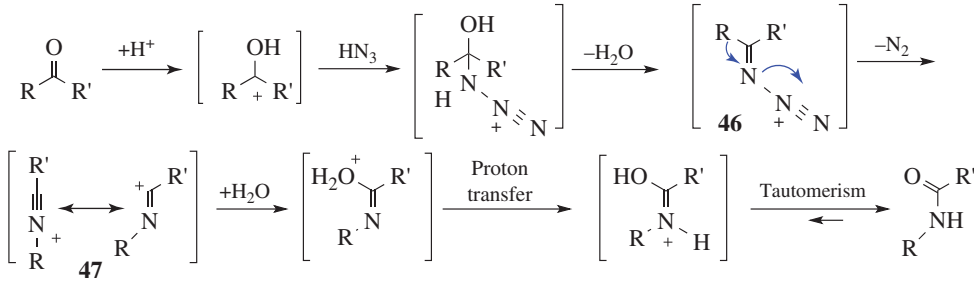
in the presence of $TiCl_4$, generating a lactam such as caprolactam (azepan-2-one).[355] An intramolecular Schmidt reaction gives bicyclic amines.[356] Another variation treats a silyl enol ether of a cyclic ketone with $TMSN_3$ and photolyzes the product with UV light to give a lactam.[357] Nitrogen-containing heterocycles have been prepared via an intramolecular Schmidt reaction of acyl chlorides and alkyl azides.[358]

Alcohols and alkenes react with HN_3 to give alkyl azides,[359] which in the course of reaction rearrange in the same way as discussed in reaction **18-14**.[331] The *Mitsunobu reaction* (**10-17**) can be used to convert alcohols to alkyl azides, and an alternative reagent for azides, $(PhO)_2PON_3$, for use in the Mitsunobu reaction, is now available.[360] In the presence of an Au catalyst, an acetylenic azide was converted to a pyrrole derivative.[361]

There is evidence that the mechanism with carboxylic acids[350] is similar to that of **18-14**, except that it is the protonated azide that undergoes the rearrangement:[362]



The first step is the same as that of the $A_{AC}1$ mechanism (**16-58**), which explains why good results are obtained with hindered substrates. The mechanism with ketones involves formation of **46**, which loses nitrogen to give a nitrilium ion **47**, which reacts with water.



Intermediates such as **46** have been independently generated in aqueous solution.[363] Note the similarity of this mechanism to those of "insertion" of CH_2 (**18-9**) and of O (**18-19**). The three reactions are essentially analogous, both in products and in mechanism.[350,364]

[355] Sahasrabudhe, K.; Gracias, V.; Furness, K.; Smith, B.T.; Katz, C.E.; Reddy, D.S.; Aubé, J. *J. Am. Chem. Soc.* ***2003***, *125*, 7914. See Mossman, C.J.; Aubé, J. *Tetrahedron* ***1996***, *52*, 3403.

[356] See Yao, L.; Aubé, J. *J. Am. Chem. Soc.* ***2007***, *129*, 2766.

[357] Evans, P.A.; Modi, D.P. *J. Org. Chem.* ***1995***, *60*, 6662.

[358] Gu, P.; Kang, X.-Y.; Sun, J.; Wang, B.-J.; Yi, M.; Li, X.-Q.; Xue, P.; Li, R. *Org. Lett.* ***2012***, *14*, 5796.

[359] See Kumar, H.M.S.; Reddy, B.V.S.; Anjaneyulu, S.; Yadav, J.S. *Tetrahedron Lett.* ***1998***, *39*, 7385. Also see, Saito, A.; Saito, K.; Tanaka, A.; Oritani, T. *Tetrahedron Lett.* ***1997***, *38*, 3955.

[360] Thompson, A.S.; Humphrey, G.R.; DeMarco, A.M.; Mathre, D.J.; Grabowski, E.J.J. *J. Org. Chem.* ***1993***, *58*, 5886.

[361] Gorin, D.J.; Davis, N.R.; Toste, F.D. *J. Am. Chem. Soc.* ***2005***, *127*, 11260.

[362] This mechanism is controversial: Vogler, E.A.; Hayes, J.M. *J. Org. Chem.* ***1979***, *44*, 3682.

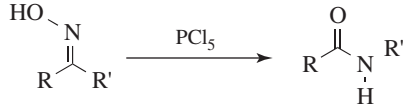
[363] Amyes, T.L.; Richard, J.P. *J. Am. Chem. Soc.* ***1991***, *113*, 1867.

[364] See Ostrovskii, V.A.; Koshtaleva, T.M.; Shirokova, N.P.; Koldobskii, G.I.; Gidaspov, B.V. *J. Org. Chem. USSR* ***1974***, *10*, 2365 and references cited therein.

Also note the similarity of the latter part of this mechanism to that of the *Beckmann rearrangement* (**18-17**).

OS **V**, 408; **VI**, 368; **VII**, 254; **X**, 207. See also, OS **V**, 623.

18-17 The Beckmann Rearrangement



When oximes are treated with PCl_5 or a number of other reagents, they rearrange to substituted amides in a reaction called the *Beckmann rearrangement*.[365] Reagents used include concentrated H_2SO_4 acid, propylphosphonic anhydride,[366] formic acid, liquid SO_2, silica gel,[367] Ti,[368] Cu,[369] W,[370] Fe,[371] Ru,[372] Y,[373] I_2,[374] $HgCl_2$,[375] triphosphazene,[376] neat with $FeCl_3$,[377] cyanuric acid,[378] and polyphosphoric acid.[379] Organocatalysts have been used.[380] Simply heating the oxime of benzophenone neat leads to *N*-phenyl benzamide.[381] The complex of pivaloyl chloride and DMF converted ketoximes to the amide or lactam via the Beckmann rearrangement.[382] The reaction has been done in supercritical water[383] and in ionic liquids.[384] A polymer-bound Beckman rearrangement has been reported.[385] Microwave-assisted Beckmann rearrangements are known.[386]

[365] Beckmann, E. *Ber. Dtsch. Chem. Ges.* ***1886***, *19*, 988; Donaruma, L.G.; Heldt, W.Z. *Org. React.* ***1960***, *11*, 1; Gawley, R.E. *Org. React.* ***1988***, *35*, 1; McCarty, C.G. in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 408–439. Also see, Tian, B.-X.; An, N.; Deng, W.-P.; Eriksson, L.A. *J. Org. Chem.* ***2013***, *78*, 6782. See Cho, H. *Tetrahedron* ***2014***, *70*, 3527.

[366] Augustine, J.K.; Kumar, R.; Bombrun, A.; Mandal, A.B. *Tetrahedron Lett.* ***2011***, *52*, 1074.

[367] Costa, A.; Mestres, R.; Riego, J.M. *Synth. Commun.* ***1982***, *12*, 1003.

[368] Mitsudome, T.; Matsuno, T.; Sueoka, S.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Tetrahedron Lett.* ***2012***, *53*, 5211.

[369] Sharma, S.K.; Bishopp, S.D.; Allen, C.L.; Lawrence, R.; Bamford, M.J.; Lapkin, A.A.; Plucinski, P.; Watson, R.J.; Williams, J.M.J. *Tetrahedron Lett.* ***2011***, *52*, 4252; Martínez-Asencio, A.; Yus, M.; Ramón, D.J. *Tetrahedron* ***2012***, *68*, 3948.

[370] Kaur, G.; Rajput, J.K.; Arora, P.; Devi, N. *Tetrahedron Lett.* ***2014***, *55*, 1136.

[371] Mahajan, S.; Sharma, B.; Kapoor, K.K. *Tetrahedron Lett.* ***2015***, *56*, 1915; Jefferies, L.R.; Weber, S.R.; Cook, S.P. *Synlett* ***2015***, *26*, 331.

[372] De, S.K. *Synth. Commun.* ***2004***, *34*, 3431.

[373] De, S.K. *Org. Prep. Proceed. Int.* ***2004***, *36*, 383.

[374] See Xu, F.; Wang, N.-G.; Tian, Y.-P.; Chen, Y.-M.; Liu, W.-C. *Synth. Commun.* ***2012***, *42*, 3532.

[375] Ramalingan, C.; Park, Y.-T. *J. Org. Chem.* ***2007***, *72*, 4536.

[376] Hashimoto, M.; Obora, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2008***, *73*, 2894.

[377] Khodaei, M.M.; Meybodi, F.A.; Rezai, N.; Salehi, P. *Synth. Commun.* ***2001***, *31*, 2047.

[378] Furuya, Y.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* ***2005***, *127*, 11240. In ionic liquids, see Betti, C.; Landini, D.; Maia, A.; Pasi, M. *Synlett* ***2008***, 908.

[379] See Beckwith, A.L.J. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 131–137.

[380] Patil, D.; Dalal, D. *Synth. Commun.* ***2013***, *43*, 118.

[381] Chandrasekhar, S.; Gopalaiah, K. *Tetrahedron Lett.* ***2001***, *42*, 8123.

[382] Narahari, S.R.; Reguri, B.R.; Mukkanti, K. *Tetrahedron Lett.* ***2011***, *52*, 4888.

[383] Boero, M.; Ikeshoji, T.; Liew, C.C.; Terakura, K.; Parrinello, M. *J. Am. Chem. Soc.* ***2004***, *126*, 6280.

[384] Maia, A.; Albanese, D.C.M.; Landini, D. *Tetrahedron* ***2012***, *68*, 1947; Sugamoto, K.; Matsushita, Y.-i.; Matsui, T. *Synth. Commun.* ***2010–2011***, *41*, 879.

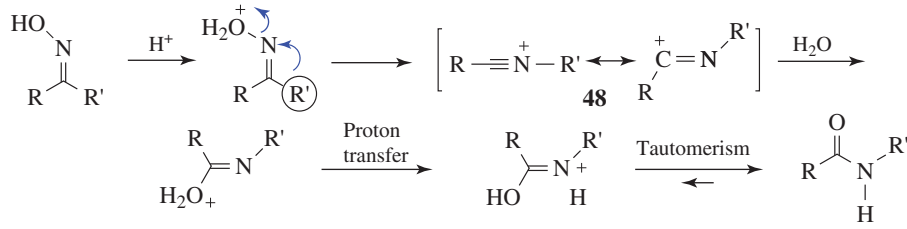
[385] His, S.; Meyer, C.; Cossy, J.; Emeric, G.; Greiner, A. *Tetrahedron Lett.* ***2003***, *44*, 8581.

[386] Thakur, A.J.; Boruah, A.; Prajapati, D.; Sandhu, J.S. *Synth. Commun.* ***2000***, *30*, 2105. On silica with microwave irradiation, see Loupy, A.; Régnier, S. *Tetrahedron Lett.* ***1999***, *40*, 6221.

The oximes of cyclic ketones give ring enlargement to give the lactam,[387] as in the formation of caprolactam (see **18-16**) from the oxime of cyclohexanone. Solvent-free reactions are known.[388] Cyclic ketones can be converted directly to lactams in one laboratory step by treatment with NH_2OSO_2OH and formic acid (**16-13** takes place first, then the Beckmann rearrangement).[389]

Of the groups attached to the carbon of the C=N unit, the one that migrates in the Beckman rearrangement is generally the one *anti* to the hydroxyl, which is often used as a method of determining the configuration of the oxime. However, it is not unequivocal. It is known that with some oximes the *syn* group migrates and that with others, especially where R and R′ are both alkyl, mixtures of the two possible amides are obtained. However, in most cases, the oxime undergoes isomerization under the reaction conditions *before* migration takes place.[390] The scope of the reaction is quite broad and R and R′ may be alkyl, aryl, or hydrogen. However, hydrogen very seldom migrates, so the reaction is not generally a means of converting aldoximes to unsubstituted amides ($RCONH_2$). This latter conversion can be accomplished, however, by treatment of the aldoxime with nickel acetate under neutral conditions[391] or by heating the aldoxime for 60 hours at 100 °C after it has been adsorbed onto silica gel.[392] As in the case of the *Schmidt rearrangement* (**18-16**), when the oxime is derived from an alkyl aryl ketone, it is generally the aryl group that preferentially migrates.[393]

In the first step of the mechanism, the OH group is converted by the reagent to a better leaving group, for example, proton acids convert it to $^+OH_2$. After that, the mechanism[394] follows a course analogous to that for the *Schmidt reaction* of ketones (**18-16**) from the formation of nitrilium ion **48** onwards.[395]



Alternative modes of reaction are possible. For example, when PCl_5 is used to induce the reaction, a N—O—PCl_4 species is formed, which generates **48**. Nitrilium ion intermediates have been detected by NMR and UV spectroscopy.[396] The rearrangement has also

[387] See Krow, G.R. *Tetrahedron* ***1981***, *37*, 1283.

[388] Sharghi, H.; Hosseini, M. *Synthesis* ***2002***, 1057; Eshghi, H.; Gordi, Z. *Synth. Commun.* ***2003***, *33*, 2971; Moghaddam, F.M.; Rad, A.A.R.; Zali-Boinee, H. *Synth. Commun.* ***2004***, *34*, 2071.

[389] Olah, G.A.; Fung, A.P. *Synthesis* ***1979***, 537. See also, Novoselov, E.F.; Isaev, S.D.; Yurchenko, A.G.; Vodichka, L.; Trshiska, Ya. *J. Org. Chem. USSR* ***1981***, *17*, 2284.

[390] See Lansbury, P.T.; Mancuso, N.R. *Tetrahedron Lett.* ***1965***, 2445.

[391] Field, L.; Hughmark, P.B.; Shumaker, S.H.; Marshall, W.S. *J. Am. Chem. Soc.* ***1961***, *83*, 1983. See also, Leusink, A.J.; Meerbeek, T.G.; Noltes, J.G. *Recl. Trav. Chim. Pays-Bas* ***1977***, *96*, 142.

[392] Chattopadhyaya, J.B.; Rama Rao, A.V. *Tetrahedron* ***1974***, *30*, 2899.

[393] See Arisawa, M.; Yamaguchi, M. *Org. Lett.* ***2001***, *3*, 311.

[394] See Nguyen, M.T.; Vanquickenborne, L.G. *J. Chem. Soc., Perkin Trans. 2* ***1993***, 1969.

[395] Donaruma, L.G.; Heldt, W.Z. *Org. React.* ***1960***, *11*, 1 (pp. 5–14); Smith, P.A.S. in de Mayo, P. *Molecular Rearrangments*, Vol. 1, Wiley, NY, ***1963***, 483–507 (pp. 488–493).

[396] Gregory, B.J.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* ***1970***, 338.

been found to take place by a different mechanism, involving formation of a nitrile by fragmentation, and then addition by a *Ritter reaction* (**16-85**).[397] Beckmann rearrangements have also been carried out photochemically.[398] A computational study compared converted versus stepwise mechanisms for the Beckmann rearrangement, and found that proton relay between the substrate and the solvent molecules controls the reaction, and migration and N—O bond scission occur simultaneously.[399]

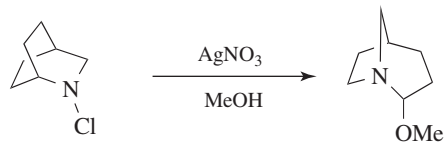
Not only do oximes undergo the Beckmann rearrangement, but so also do esters of oximes with many acids, both organic and inorganic. A side reaction with many substrates is the formation of nitriles (the "abnormal" Beckmann rearrangement, **17-28**). The *O*-carbonates of imines, such as $Ph_2C{=}N{-}OCO_2Et$ react with $BF_3{\bullet}OEt_2$ to give the corresponding amide, in this case *N*-phenyl benzamide.[400]

If the rearrangement of oxime sulfonates is induced by organoaluminum reagents,[401] the nitrilium ion intermediate **48** is captured by the nucleophile originally attached to the Al. By this means an oxime can be converted to an imine, an imino thioether (R—N=C—SR), or an imino nitrile (R—N=C—CN).[402] In the last case, the nucleophile comes from added trimethylsilyl cyanide. In the presence of LiI, 2-benzyloxypyridine is converted to *N*-benzyl-2-pyridone.[403]

Thioamides were prepared from ketoximes via Beckmann rearrangement.[404]

OS **II**, 76, 371; **VIII**, 568.

18-18 The Stieglitz and Related Rearrangements



In addition to the reactions discussed at **18-13** to **18-17**, other rearrangements are known in which an alkyl group migrates from C to N. Certain bicyclic *N*-haloamines, for example *N*-chloro-2-azabicyclo[2.2.2]octane (above), undergo rearrangement when solvolyzed in the presence of silver nitrate.[405] This reaction is similar to the *Wagner-Meerwein rearrangement* (**18-1**) and is initiated by the silver-catalyzed departure of the chloride ion.[406] Similar reactions have been used for ring expansions and contractions, analogous to those discussed for reaction **18-3**.[407] An example is the conversion of 1-(*N*-chloroamino)cyclopropanols to

[397] Palmere, R.M.; Conley, R.T.; Rabinowitz, J.L. *J. Org. Chem.* ***1972***, *37*, 4095.
[398] See, Suginome, H.; Yagihashi, F. *J. Chem. Soc., Perkin Trans. 1* ***1977***, 2488.
[399] Yamabe, S.; Tsuchida, N.; Yamazaki, S. *J. Org. Chem.* ***2005***, *70*, 10638.
[400] Anilkumar, R.; Chandrasekhar, S. *Tetrahedron Lett.* ***2000***, *41*, 5427.
[401] For a review, see Maruoka, K.; Yamamoto, H. *Angew. Chem. Int. Ed.* ***1985***, *24*, 668.
[402] Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* ***1983***, *105*, 2831; Maruoka, K.; Nakai, S.; Yamamoto, H. *Org. Synth.* ***66***, 185.
[403] Lanni, E.L.; Bosscher, M.A.; Ooms, B.; Shandro, C.A.; Ellsworth, B.A.; Anderson, C.E. *J. Org. Chem.* ***2008***, *73*, 6425.
[404] Liu, L.-F.; An, N.; Pi, H.-J.; Ying, J.; Du, W.; Deng, W.-P. *Synlett* ***2011***, *22*, 979.
[405] Gassman, P.G.; Fox, B.L. *J. Am. Chem. Soc.* ***1967***, *89*, 338. See also, Hoffman, R.V.; Kumar, A.; Buntain, G.A. *J. Am. Chem. Soc.* ***1985***, *107*, 4731.
[406] See Kovacic, P.; Lowery, M.K.; Roskos, P.D. *Tetrahedron* ***1970***, *26*, 529.
[407] Hoffman, R.V.; Buntain, G.A. *J. Org. Chem.* ***1988***, *53*, 3316.

β-lactams.[408] Methyl prolinate was converted to the 2-piperidone upon treatment with SmI_2 and pivalic acid/THF.[409]

The name "*Stieglitz rearrangement*" is generally applied to the rearrangements of trityl *N*-haloamines or hydroxylamines to aryl imines via treatment with base or PCl_5, respectively. These reactions are similar to the rearrangements of alkyl azides (**18-14**), and the name Stieglitz rearrangement is also given to the rearrangement of trityl azides. Another similar reaction is the rearrangement undergone by tritylamines when treated with lead tetraacetate ($Ar_3CNH_2 \rightarrow Ar_2C{=}NAr$).[410]

D. Carbon-to-Oxygen Migrations of R and Ar

18-19 The Baeyer-Villiger Rearrangement[411]

The treatment of ketones with peroxy acids, such as peroxybenzoic or peroxyacetic acid, or with other peroxy compounds in the presence of acid catalysts,[412] gives carboxylic esters by migration of an alkyl group oxygen[413] and gives the carboxylic acid parent of the peroxy acid as a by-product. In other words, there is a C → O rearrangement, and the reaction is called the *Baeyer-Villiger rearrangement*.[414] A particularly good reagent is peroxytrifluoroacetic acid. Reactions with this reagent are rapid and clean, giving high yields of product, although it is often necessary to add a buffer, such as Na_2HPO_4, to prevent transesterification of the product with trifluoroacetic acid that is also formed during the reaction. The reaction is often applied to cyclic ketones to give lactones.[415] Hydrogen peroxide has been used with a catalytic amount of $MeReO_3$,[416] a W catalyst,[417] or a diselenide catalyst.[418] Heterogeneous catalysts are used for the Baeyer-Villiger reaction.[419]

[408] Wasserman, H.H.; Glazer, E.A.; Hearn, M.J. *Tetrahedron Lett.* ***1973***, 4855.
[409] Honda, T.; Ishikawa, F. *Chem. Commun.* ***1999***, 1065.
[410] Sisti, A.J.; Milstein, S.R. *J. Org. Chem.* ***1974***, *39*, 3932.
[411] For a review, see Renz, M.; Meunier, B. *Eur. J. Org. Chem.* ***1999***, 737. For a review of green procedures, see ten Brink, G.-J.; Arends, I.W.C.E.; Sheldon, R.A. *Chem. Rev.* ***2004***, *104*, 4105. See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 278–282.
[412] Bach, R.D. *J. Org. Chem.* ***2012***, *77*, 6801. See Poladura, B.; Martínez-Castañeda, Á.; Rodríguez-Solla, H.; Llavona, R.; Concellón, C.; del Amo, V. *Org. Lett.* ***2013***, *15*, 2810.
[413] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1665–1667.
[414] Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, ***1990***, pp. 186–195; Plesnicar, B. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 254–267; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 321–329; Lewis, S.N. in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 237–244. Also see, Carlqvist, P.; Eklund, R.; Brinck, T. *J. Org. Chem.* ***2001***, *66*, 1193.
[415] See Geibel, I.; Dierks, A.; Schmidtmann, M.; Christoffers, J. *J. Org. Chem.* ***2016***, *81*, 7790; Rong, H.-J.; Cheng, Y.-F.; Liu, F.-F.; Ren, S.-J.; Qu, J. *J. Org. Chem.* ***2017***, *82*, 532.
[416] Phillips, A.M.F.; Romão, C. *Eur. J. Org. Chem.* ***1999***, 1767. In an ionic liquid, see Bernini, R.; Coratti, A.; Fabrizi, G.; Goggiamani, A. *Tetrahedron Lett.* ***2003***, *44*, 8991.
[417] Ma, Q.; Xing, W.; Xu, J.; Peng, X. *Chem. Lett.* ***2014***, *43*, 941.
[418] ten Brink, G.-J.; Vis, J.-M.; Arends, I.W.C.E.; Sheldon, R.A. *J. Org. Chem.* ***2001***, *66*, 2429.
[419] For a review, see Jiménez-Sanchidrián, C.; Ruiz, J.R. *Tetrahedron* ***2008***, *64*, 2011.

Transition metal catalysts have been used with peroxy acids to facilitate the oxidation.[420] Polymer-supported peroxy acids have been used,[421] and solvent-free reactions are known.[422] Potassium peroxomonosulfate supported on acidic silica gel has been used.[423]

Enantioselective synthesis[424] of chiral lactones from achiral ketones has been achieved by the use of enzymes[425] and other asymmetric reactions are known.[426] Chiral Pd complexes have been used, with high enantioselectively.[427] Bacteriogenic iron oxide has been used as a catalyst.[428] Other chiral catalysts are known,[429] including organocatalysts.[430] Baeyer-Villiger oxidation of chiral substrates with *m*-chloroperoxybenzoic acid (mcpba) also leads to chiral lactones.[431]

For acyclic compounds, R′ must usually be secondary, tertiary, or vinylic, although primary R′ has been rearranged with peroxytrifluoroacetic acid,[432] with I_2/H_2O_2,[433] and BF_3/H_2O_2.[434] For unsymmetrical ketones the approximate order of migration is tertiary alkyl > secondary alkyl, aryl > primary alkyl > methyl. Since the methyl group has a low migrating ability, the reaction provides a means of cleaving a methyl ketone (R′COMe) to produce an alcohol or phenol (R′OH) (by hydrolysis of the ester R′OCOMe). The migrating ability of aryl groups is increased by electron-donating substituents and decreased by electron-withdrawing substituents.[435] There is a preference of *anti* over *gauche* migration.[436] Enolizable β-diketones do not react.

The mechanism[437] is similar to those of the analogous reactions with hydrazoic acid (**18-16** with ketones) and diazomethane (**18-8**). Evidence for this mechanism was that benzophenone-^{18}O gave ester entirely labeled in the carbonyl oxygen, with none in the

[420] Alam, M.M.; Varala, R.; Adapa, S.R. *Synth. Commun.* ***2003***, *33*, 3035.

[421] Lambert, A.; Elings, J.A.; Macquarrie, D.J.; Carr, G.; Clark, J.H. *Synlett* ***2000***, 1052. See Hagiwara, H.; Nagatomo, H.; Yoshii, F.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 2645.

[422] Yakura, T.; Kitano, T.; Ikeda, M.; Uenishi, J. *Tetrahedron Lett.* ***2002***, *43*, 6925.

[423] See González-Núñez, M.E.; Mello, R.; Olmos, A.; Asensio, G. *J. Org. Chem.* ***2006***, *71*, 6432.

[424] See Bolm, C.; Frison, J.-C.; Zhang, Y.; Wulff, W.D. *Synlett* ***2004***, 1619; Rodríguez-Mata, M.; Lavandera, I.; Gotor-Fernández, V.; Gotor, V.; García-Cerrada, S.; Mendiola, J.; de Frutos, Ó.; Collado, I. *Tetrahedron* ***2016***, *72*, 7268.

[425] For a review, see Leisch, H.; Morley, K.; Lau, P.C.K. *Chem. Rev.* ***2011***, *111*, 4165. Saß, S.; Kadow, M.; Geitner, K.; Thompson, M.L.; Talmann, L.; Böttcher, D.; Schmidt, M.; Bornscheuer, U.T. *Tetrahedron* ***2012***, *68*, 7575; van Beek, H.L.; Winter, R.T.; Eastham, G.R.; Fraaije, M.W. *Chem. Commun.* ***2014***, *50*, 13034; Drożdż, A.; Erfurt, K.; Bielas, R.; Chrobok, A. *New J. Chem.* ***2015***, 1315; Li, G.; Fürst, M.L.L.J.; Mansouri, H.R.; Ressmann, A.K.; Ilie, A.; Rudroff, F.; Mihovilovic, M.D.; Fraajie, M.W.; Reetz, M.T. *Org. Biomol. Chem.* ***2017***, *15*, 9824.

[426] See Watanabe, A.; Uchida, T.; Ito, K.; Katsuki, T. *Tetrahedron Lett.* ***2002***, *43*, 4481; Murhashi, S.-I.; Ono, S.; Imada, Y. *Angew. Chem. Int. Ed.* ***2002***, *41*, 2366.

[427] Malkov, A.V.; Friscourt, F.; Bell, M.; Swarbrick, M.E.; Koovský, P. *J. Org. Chem.* ***2008***, *73*, 3996; Petersen, K.S.; Stoltz, B.M. *Tetrahedron* ***2011***, *67*, 4352.

[428] Bradley, T.D.; Dragan, A.; Tomkinson, N.C.O. *Tetrahedron* ***2015***, *71*, 8155.

[429] Frison, J.-C.; Palazzi, C.; Bolm, C. *Tetrahedron* ***2006***, *62*, 6700; Romney, D.K.; Colvin, S.M.; Miller, S.J. *J. Am. Chem. Soc.* ***2014***, *136*, 14109.

[430] Xu, H.-J.; Zhu, F.-F.; Shen, Y.-Y.; Wan, X.; Feng, Y.-S. *Tetrahedron* ***2012***, *68*, 4145; Poudel, P.P.; Arimitsu, K.; Yamamoto, K. *Chem. Commun.* ***2016***, *52*, 4163.

[431] Hunt, K.W.; Grieco, P.A. *Org. Lett.* ***2000***, *2*, 1717.

[432] Emmons, W.D.; Lucas, G.B. *J. Am. Chem. Soc.* ***1955***, *77*, 2287.

[433] Gaikwad, D.D.; Dake, S.A.; Kulkarni, R.S.; Jadhav, W.N.; Kakde, S.B.; Pawar, R.P. *Synth. Commun.* ***2007***, *37*, 4093.

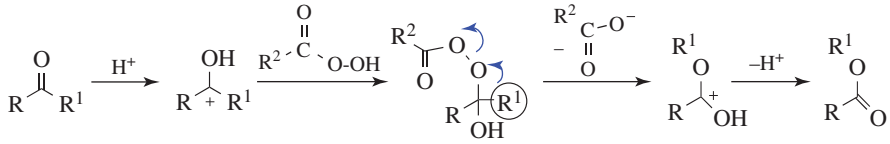
[434] McClure, J.D.; Williams, P.H. *J. Org. Chem.* ***1962***, *27*, 24.

[435] See Noyori, R.; Sato, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 2661.

[436] Snowden, M.; Bermudez, A.; Kelly, D.R.; Radkiewicz-Poutsma, J.L. *J. Org. Chem.* ***2004***, *69*, 7148.

[437] Proposed by Criegee, R. *Liebigs Ann. Chem.* ***1948***, *560*, 127.

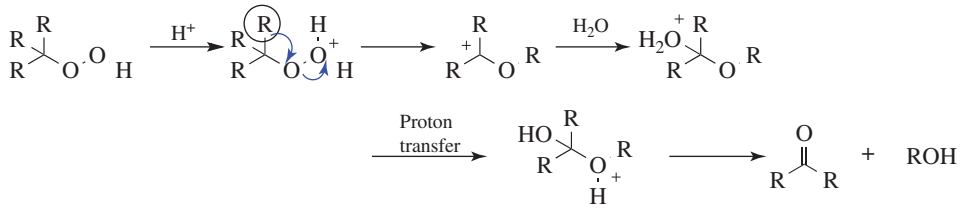
alkoxyl oxygen.[438] Carbon-14 isotope-effect studies on acetophenones have shown that migration of aryl groups takes place in the rate-determining step,[439] demonstrating that the migration is concerted with departure of $OCOR^2$.[440]



It is unlikely that migration would be the slow step if the leaving group departed first to give an ion with a positive charge on an oxygen atom, which would be a highly unstable species.

The reaction of alkenes in aqueous hydrogen peroxide, in the presence of benzonitrile at pH 9.5–10, gave the epoxide, in what is known as *Payne epoxidation*.[441]

18-20 Rearrangement of Hydroperoxides



Hydroperoxides (R = alkyl, aryl, or hydrogen) can be cleaved by proton or Lewis acids in a reaction whose principal step is a rearrangement.[442] The reaction has also been applied to peroxy esters ($R_3COOCOR'$), but less often. When aryl and alkyl groups are both present, migration of aryl dominates. It is not necessary actually to prepare and isolate hydroperoxides. The reaction takes place when the alcohols are treated with H_2O_2 and acids. Migration of an alkyl group of a primary hydroperoxide provides a means for converting an alcohol to its next lower homolog:

$$RCH_2OOH \rightarrow CH_2{=}O + ROH$$

The mechanism is as shown.[443] The last step is hydrolysis of the unstable hemiacetal. Alkoxycarbocation intermediates (an oxocarbenium ion, R = alkyl) have been isolated in

[438] Doering, W. von E.; Dorfman, E. *J. Am. Chem. Soc.* ***1953***, *75*, 5595. Also see Smith, P.A.S. in de Mayo, P. *Molecular Rearrangements*, Vol. 1, Wiley, NY, ***1963***, pp. 578–584.

[439] Palmer, B.W.; Fry, A. *J. Am. Chem. Soc.* ***1970***, *92*, 2580. See Winnik, M.A.; Stoute, V.; Fitzgerald, P. *J. Am. Chem. Soc.* ***1974***, *96*, 1977.

[440] Also see Ogata, Y.; Sawaki, Y. *J. Org. Chem.* ***1972***, *37*, 2953.

[441] For a review, see Wong, O.A.; Shi, Y. *Chem. Rev.* ***2008***, *108*, 3958; Payne, G.B.; Deming, P.H.; Williams, P.H. *J. Org. Chem.* ***1961***, *26*, 659; Okazaki, H.; Hanaya, K.; Shoji, M.; Hada, N.; Sugai, T. *Tetrahedron* ***2013***, *69*, 7931; Burke, C.P.; Shu, L.; Shi, Y. *J. Org. Chem.* ***2007***, *72*, 6320; Bradley, T.D.; Dragan, A.; Tomkinson, N.C.O. *Tetrahedron* ***2015***, *71*, 8155.

[442] Yablokov, V.A. *Russ. Chem. Rev.* ***1980***, *49*, 833; Lee, J.B.; Uff, B.C. *Q. Rev. Chem. Soc.* ***1967***, *21*, 429 (pp. 445–449).

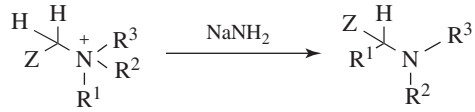
[443] See Wistuba, E.; Rüchardt, C. *Tetrahedron Lett.* ***1981***, *22*, 3389.

superacid solution[444] at low temperatures, and their structures proved by NMR.[445] The protonated hydroperoxides could not be observed in these solutions, evidently reacting immediately on formation.

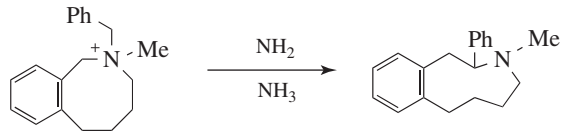
OS **V**, 818.

E. Nitrogen-to-Carbon, Oxygen-to-Carbon, and Sulfur-to-Carbon Migration

18-21 The Stevens Rearrangement



In the *Stevens rearrangement*,[446] a quaternary ammonium salt containing an electron-withdrawing group Z on one of the carbons attached to the nitrogen is treated with a strong base (e.g., NaOR or $NaNH_2$) to give a rearranged tertiary amine. The Z group may be RCO, ROOC, or phenyl.[447] The most common migrating groups are allylic, benzylic, benzhydryl, 3-phenylpropargyl, and phenacyl, although even methyl migrates to a sufficiently negative center. Migration of aryl is rare, but has been reported.[448] When an allylic group migrates, it may or may not involve an allylic rearrangement within the migrating group (see **18-35**), depending on the substrate and reaction conditions. The reaction has been used for ring enlargement, illustrated by the rearrangement of **49** to give the ring-expanded product in 90% yield.[449]

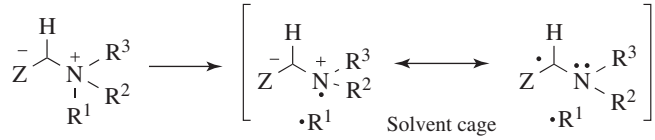


49

The mechanism has been the subject of much study.[450] The rearrangement is intramolecular, as shown by crossover experiments, by ^{14}C labeling,[451] and by the fact that retention of configuration is found at R^1.[452] The first step is loss of the acidic proton to give a

[444] See Olah, G.A.; Parker, D.G.; Yoneda, N. *Angew. Chem. Int. Ed.* ***1978***, *17*, 909.
[445] Sheldon, R.A.; van Doorn, J.A. *Tetrahedron Lett.* ***1973***, 1021.
[446] For syntheses, see Vanecko, J.A.; Wan, H.; West, F.G. *Tetrahedron* ***2006***, *62*, 1043.
[447] Lepley, A.R.; Giumanini, A.G. *Mech. Mol. Migr.* ***1971***, *3*, 297; Pine, S.H. *Org. React.* ***1970***, *18*, 403; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, NJ, ***1973***, pp. 81–116; Wilt, J.W. in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 448–458; Stevens, T.S. *Prog. Org. Chem.* ***1968***, *7*, 48.
[448] Heaney, H.; Ward, T.J. *Chem. Commun.* ***1969***, 810; Truce, W.E.; Heuring, D.L. *Chem. Commun.* ***1969***, 1499.
[449] Elmasmodi, A.; Cotelle, P.; Barbry, D.; Hasiak, B.; Couturier, D. *Synthesis* ***1989***, 327.
[450] See Heard, G.L.; Yates, B.F. *Aust. J. Chem.* ***1994***, *47*, 1685.
[451] See Stevens, T.S. *J. Chem. Soc.* ***1955***, 4487.
[452] Brewster, J.H.; Kline, M.W. *J. Am. Chem. Soc.* ***1952***, *74*, 5179; Schöllkopf, U.; Ludwig, U.; Ostermann, G.; Patsch, M. *Tetrahedron Lett.* ***1969***, 3415.

nitrogen ylid, which has been isolated.[453] The finding[454] that CIDNP is observed[455] in many instances shows that in these cases the product is formed directly from a free-radical precursor and a radical pair mechanism was proposed:[456]



The radicals do not drift apart because the solvent cage holds them together. According to this mechanism, the radicals must recombine rapidly in order to account for the fact that R^1 does not racemize. Other evidence in favor of a radical pair mechanism is that in some cases small amounts of coupling products (R^1—R^1) have been isolated,[457] which would be expected if some $\bullet R^1$ leaked from the solvent cage. However, not all the evidence is easily compatible with the ylid mechanism.[458] It is possible that another mechanism, similar to the radical pair mechanism but involving ion pairs in a solvent cage, operates in some cases. A third possible mechanism would be a concerted 1,2-shift,[459] but the orbital symmetry principle requires that this take place with inversion at R^1 (see **18-30** and [1,5]-migration).[460] Since the actual migration takes place with retention, it *cannot*, according to this argument, proceed by a concerted mechanism. However, in the case where the migrating group is allylic, a concerted mechanism can also operate (**18-35**). An interesting finding compatible with all three mechanisms is that optically active allylbenzylmethylphenylammonium iodide (asymmetric nitrogen, Sec. 4.C, category 3) gave an optically active product.[461] An aryne [2,3]-Stevens' rearrangement is known.[462]

The *Sommelet-Hauser rearrangement* competes when Z is an aryl group (see **13-32**). *Hofmann elimination* competes when one of the R groups contains a β hydrogen atom (**17-6** and **17-2**).

The formation of *o*-benzylbenzyldimethylamine from benzhydryltrimethylammonium bromide, by heating to 180 °C with concentrated hydroxide, illustrates the *Sommelet rearrangement*.[463] Initial deprotonation probably occurred at the benzylic site, but under equilibrium conditions an ylid was generated. Nucleophilic attack at the proximal benzene ring gave led to cleavage of the C—N bond, and subsequent aromatization gave the final product 1-(2-benzylphenyl)-*N*,*N*-dimethylmethanamine. Evidence suggests the mechanism is a

[453] Jemison, R.W.; Mageswaran, S.; Ollis, W.D.; Potter, S.E.; Pretty, A.J.; Sutherland, I.O.; Thebtaranonth, Y. *Chem. Commun.* ***1970***, 1201.

[454] See Lepley, A.R.; Becker, R.H.; Giumanini, A.G. *J. Org. Chem.* ***1971***, *36*, 1222.

[455] For a review of the application of CIDNP to rearrangement reactions, see Lepley, A.R. in Lepley, A.R.; Closs, G.L. *Chemically Induced Magnetic Polarization*, Wiley, NY, ***1973***, pp. 323–384.

[456] Ollis, W.D.; Rey, M.; Sutherland, I.O. *J. Chem. Soc., Perkin Trans. 1* ***1983***, 1009, 1049.

[457] Hennion, G.F.; Shoemaker, M.J. *J. Am. Chem. Soc.* ***1970***, *92*, 1769.

[458] See, for example, Pine, S.H.; Catto, B.A.; Yamagishi, F.G. *J. Org. Chem.* ***1970***, *35*, 3663.

[459] For evidence against this mechanism: Jenny, E.F.; Druey, J. *Angew. Chem. Int. Ed.* ***1962***, *1*, 155.

[460] Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***, p. 131.

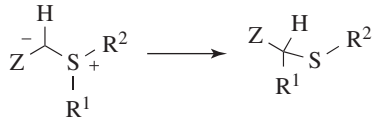
[461] Hill, R.K.; Chan, T. *J. Am. Chem. Soc.* ***1966***, *88*, 866.

[462] Roy, T.; Thangaraj, M.; Kaicharla, T.; Kamath, R.V.; Gonnade, R.G.; Biju, A.T. *Org. Lett.* ***2016***, *18*, 5428.

[463] Sommelet, M. *Compt. Rend.* ***1937***, *205*, 56; Hauser, C.R.; van Eenam, D.N. *J. Am. Chem. Soc.* ***1956***, *78*, 5698; The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, NJ, ***2006***, p ONR-88; Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis*, 2nd ed., Wiley-Interscience, NJ, ***2005***, pp. 608–609.

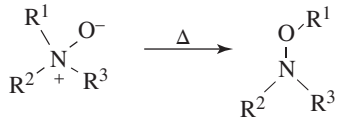
[1,2]-shift of the ylid via a caged radical pair intermediate.[464] Steric effects appear to be less significant than electronic effects for ylid stability.[465] The so-called *ortho substitution rearrangement*[466] involves reaction of the benzyltrimethylammonium salt with $NaNH_2$ to give 2-(dimethylaminomethyl)toluene. This rearrangement is either the same reaction as the Sommelet rearrangement, or it is closely related.[466]

Sulfur ylids containing a Z group give an analogous rearrangement to give the sulfide, as shown, and this has been referred to as a *Stevens rearrangement*.[467]



In this case too, there is much evidence (including CIDNP) that a radical-pair cage mechanism is operating,[468] except that when the migrating group is allylic, the mechanism may be different (see **18-35**).

Another reaction with a similar mechanism[469] is the *Meisenheimer rearrangement*,[470] in which certain tertiary amine oxides rearrange on heating to give substituted hydroxylamines.[471]



The migrating group R^1 is almost always allylic or benzilic.[472] The R^2 and R^3 groups may be alkyl or aryl, but if one of the R groups contains a β hydrogen, *Cope elimination* (**17-7**) often competes. In a related reaction, when 2-methylpyridine *N*-oxides are treated with trifluoroacetic anhydride, the *Boekelheide reaction* occurs to give 2-hydroxymethylpyridines.[473]

[464] Tanaka, T.; Shirai, N.; Sugimori, J.; Sato, Y. *J. Org. Chem.* ***1992***, *57*, 5034; Lepley, A.R.; Giumanini, A.G. in *Mechanism of Molecular Migrations*, Vol. 3, Thyagarajan, B.S. (Ed.), Wiley-Interscience, NY, ***1971***, p. 297.

[465] Heard, G.L.; Yates, B.F. *Aust. J. Chem.* ***1994***, *47*, 1685.

[466] Kantor, S.W.; Hauser, C.R. *J. Am. Chem. Soc.* ***1951***, *73*, 4122; Puterbaugh, W.H.; Hauser, C.R. *J. Am. Chem. Soc.* ***1964***, *86*, 1105.

[467] Olsen, R.K.; Currie Jr., J.O. in Patai, S. *The Chemistry of The Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 561–566. See Okazaki, Y.; Asai, T.; Ando, F.; Koketsu, J. *Chem. Lett.* ***2006***, *35*, 98; Soheili, A.; Tambar, U.K. *J. Am. Chem. Soc.* ***2011***, *133*, 12956.

[468] See Iwamura, H.I.; Iwamura, M.; Nishida, T.; Yoshida, M.; Nakayama, T. *Tetrahedron Lett.* ***1971***, 63.

[469] See Ostermann, G.; Schöllkopf, U. *Liebigs Ann. Chem.* ***1970***, *737*, 170; Lorand, J.P.; Grant, R.W.; Samuel, P.A.; O'Connell, E.; Zaro, J. *Tetrahedron Lett.* ***1969***, 4087.

[470] Meisenheimer, J. *Ber. Dtsch. Chem. Ges.* ***1919***, *52*, 1667; Johnstone, R.A.W. *Mech. Mol. Migr.* ***1969***, *2*, 249. See Buston, J.E.H.; Coldham, I.; Mulholland, K.R. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2327. See Yang, H.; Sun, M.; Zhao, S.; Zhu, M.; Xie, Y.; Niu, C.; Li, C. *J. Org. Chem.* ***2013***, *78*, 339.

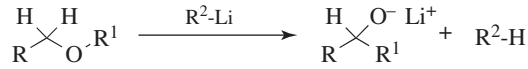
[471] See Buston, J.E.H.; Coldham, I.; Mulholland, K.R. *Tetrahedron: Asymmetry* ***1998***, *9*, 1995.

[472] See Khuthier, A.; Al-Mallah, K.Y.; Hanna, S.Y.; Abdulla, N.I. *J. Org. Chem.* ***1987***, *52*, 1710, and references cited therein.

[473] Boekelheide, V.; Linn, W.J. *J. Am. Chem. Soc.* ***1954***, *76*, 1286. See Fontenas, C.; Bejan, E.; Haddon, H.A.; Balavoine, G.G.A. *Synth. Commun.* ***1995***, *25*, 629.

Isocyanides, when heated in the gas phase or in nonpolar solvents, undergo a 1,2-intramolecular rearrangement to nitriles: RNC → RCN.[474] In polar solvents the mechanism is different.[475]

18-22 The Wittig Rearrangement[476]



The rearrangement of ethers upon treatment with alkyllithium reagents is called the *Wittig rearrangement* (not to be confused with the *Wittig reaction*, **16-44**) and is similar to **18-21**.[454] However, a stronger base is required (e.g., phenyllithium or sodium amide). The R and R^1 groups may be alkyl,[477] aryl, or vinylic.[478] One of the hydrogen atoms may be replaced by an alkyl or aryl group, in which case the product is the salt of a tertiary alcohol. Migratory aptitudes here are allylic, benzylic > ethyl > methyl > phenyl.[479] The stereospecificity of the 1,2-Wittig rearrangement has been discussed.[480]

A radical-pair mechanism[481] (similar to ylid mechanism of **18-21**) is likely, after removal of the proton by the base. One of the radical pair is a ketyl. Evidence for this mechanism includes: (i) the rearrangement is largely intramolecular; (ii) migratory aptitudes are in the order of free-radical stabilities, not of carbanion stabilities[482] (which rules out an ion-pair mechanism); (iii) aldehydes are obtained as side products;[483] (iv) partial racemization of R^1 has been observed[484] (the remainder of the product retained its configuration); (v) crossover products have been detected;[485] and (vi) when ketyl radicals and R• radicals from different precursors were brought together, similar products resulted.[486] However, there is evidence that at least in some cases the radical-pair mechanism accounts for only a portion of the product, and some kind of concerted mechanism can also take place.[487] Most of the above investigations were carried out with systems where R^1 is alkyl, but a radical-pair mechanism has also been suggested for the case where R^1 is aryl.[488] When R^1 is allylic a concerted mechanism can operate (**18-35**).

When R is vinylic it is possible, by using a combination of an alkyllithium and *t*-BuOK, to get migration to the γ carbon (as well as to the α carbon), producing an enolate that,

[474] See Pakusch, J.; Rüchardt, C. *Chem. Ber.* ***1991***, *124*, 971 and references cited therein.
[475] Meier, M.; Rüchardt, C. *Chimia* ***1986***, *40*, 238.
[476] See Hiersemann, M.; Abraham, L.; Pollex, A. *Synlett* ***2003***, 1088.
[477] Bailey, W.F.; England, M.D.; Mealy, M.J.; Thongsornkleeb, C.; Teng, L. *Org. Lett.* ***2000***, *2*, 489.
[478] For migration of vinyl, see Rautenstrauch, V.; Büchi, G.; Wüest, H. *J. Am. Chem. Soc.* ***1974***, *96*, 2576. For rearrangment of an α-trimethylsilyl allyl ether see Maleczka Jr., R.E.; Geng, F. *Org. Lett.* ***1999***, *1*, 1115.
[479] Wittig, G. *Angew. Chem.* ***1954***, *66*, 10; Solov'yanov, A.A.; Ahmed, E.A.A.; Beletskaya, I.P.; Reutov, O.A. *J. Chem. Soc., Chem. Commun.* ***1987***, *23*, 1232.
[480] Maleczka Jr., R.E.; Geng, F. *J. Am. Chem. Soc.* ***1998***, *120*, 8551.
[481] See Schöllkopf, U. *Angew. Chem. Int. Ed.* ***1970***, *9*, 763.
[482] See Schäfer, H.; Schöllkopf, U.; Walter, D. *Tetrahedron Lett.* ***1968***, 2809.
[483] See Cast, J.; Stevens, T.S.; Holmes, J. *J. Chem. Soc.* ***1960***, 3521.
[484] Hebert, E.; Welvart, Z. *J. Chem. Soc., Chem. Commun.* ***1980***, 1035; *Nouv. J. Chim.* ***1981***, *5*, 327.
[485] Lansbury, P.T.; Pattison, V.A. *J. Org. Chem.* ***1962***, *27*, 1933; *J. Am. Chem. Soc.* ***1962***, *84*, 4295.
[486] Garst, J.F.; Smith, C.D. *J. Am. Chem. Soc.* ***1973***, *95*, 6870.
[487] Garst, J.F.; Smith, C.D. *J. Am. Chem. Soc.* ***1976***, *98*, 1526. For evidence against this, see Hebert, E.; Welvart, Z.; Ghelfenstein, M.; Szwarc, H. *Tetrahedron Lett.* ***1983***, *24*, 1381.
[488] Eisch, J.J.; Kovacs, C.A.; Rhee, S. *J. Organomet. Chem.* ***1974***, *65*, 289.

on hydrolysis, gives an aldehyde:[489] An *aza-Wittig rearrangement* is also known.[490] Other [2,3]-rearrangements are discussed in **18-35**.

There are no OS references, but see OS **VIII**, 501, for a related reaction.

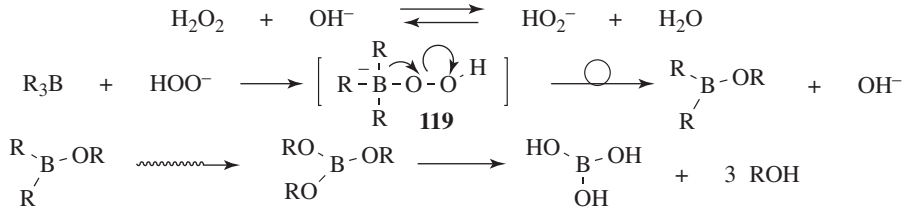
F. Boron-to-Carbon Migrations[491]

For another reaction involving B-to-C migration, see **10-73**.

18-23 Conversion of Boranes to Alcohols

$$R_3B \xrightarrow[NaOH]{H_2O_2} 3\ R\text{-}OH + B(OH)_3$$

Hydroboration (**15-11**) of alkenes leads to organoboranes, which need not be isolated since subsequent reaction with basic hydrogen peroxide gives the anti-Markovnikov alcohol and boric acid. Oxidation of organoboranes (see **15-11**) uses NaOH and hydrogen peroxide, which react to give the hydroperoxide anion, HOO^-. Reaction of the organoborane with basic hydrogen peroxide (via HOO^-) leads to an "ate" complex, and subsequent B → O rearrangement of an alkyl group on boron to a peroxy oxygen, with expulsion of hydroxide, leads to a borate, and then an alcohol after hydrolysis. The proposed mechanism[492] is shown, in which a trialkylborane is converted to 3 molar equivalents of the alcohol, along with boric acid.



As mentioned, if the hydroboration reaction in **15-11** is used then this procedure converts alkenes to an *anti-Markovnikov* borane, and oxidation leads to the anti-Markovnikov alcohol. An example is the conversion of methylcyclopentene to *trans*-2-methylcyclopentanol.[493] Formation of the organoborane proceeds via a *cis* addition of B—H, placing the boron *trans* to the methyl group, and stereoselective oxidation and B → O rearrangement leads to retention of configuration in the alcohol.

[489] Schlosser, M.; Strunk, S. *Tetrahedron* ***1989***, *45*, 2649.

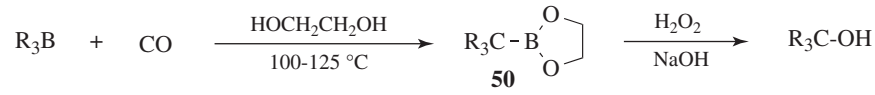
[490] Anderson, J.C.; Siddons, D.C.; Smith, S.C.; Swarbrick, M.E. *J. Chem. Soc., Chem. Commun.* ***1995***, 1835; Ahman, J.; Somfai, P. *J. Am. Chem. Soc.* ***1994***, *116*, 9781.

[491] Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 256–301; Negishi, E.; Idacavage, M.J. *Org. React.* ***1985***, *33*, 1; Suzuki, A. *Top. Curr. Chem.* ***1983***, *112*, 67; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 249–300.

[492] Brown, H.C. *Hydroboration*, W.A. Benjamin, New York, ***1962***. See Kuivila, H.G. *J. Am. Chem. Soc.* ***1954***, *76*, 870; ***1955***, *77*, 4014; See Kuivila, H.G.; Armour, A.G. *J. Am. Chem. Soc.* ***1957***, *79*, 5659; Wechter, W.J. *Chem. & Ind. (London)* ***1959***, 294.

[493] Zweifel, G.; Brown, H.C. *Org. React.* ***1964***, *13*, 1.

Trialkylboranes can be prepared from alkenes by **15-11**, and they react with carbon monoxide[494] at 100–125 °C in the presence of ethylene glycol to give the 2-bora-1,3-dioxolanes (**50**), which are easily oxidized (**12-27**) to tertiary alcohols.[495]



50

The R groups may be primary, secondary, or tertiary, and may be the same or different.[496] Yields are high and the reaction is quite useful, especially for the preparation of sterically hindered alcohols, such as 9-decalol (**51**) and *cis*,*cis*,*trans*-perhydro-9b-phenalenol (**52**), which are difficult to prepare by **16-22**.

51 **52**

The overall conversion of a diene or triene to a cyclic alcohol was described by H.C. Brown as "stitching" with B and "riveting" with C.

The mechanism has been shown to be intramolecular by the failure to find crossover products when mixtures of boranes are used.[497] The mechanistic scheme to form **50** involves formation of a B—$^{+}$C═O intermediate and three boron-to-carbon migrations before reaction with the diol,[497] which otherwise forms polymers that are difficult to oxidize.

There are two other methods for achieving the conversion $R_3B \rightarrow R_3COH$, which often give better results: (i) treatment with α,α-dichloromethyl methyl ether and the base lithium triethylcarboxide[498] and (ii) treatment with a suspension of sodium cyanide in THF followed by reaction of the resulting trialkylcyanoborate with an excess (>2 equivalents) of trifluoroacetic anhydride.[499] All the above migrations take place with retention of configuration at the migrating carbon.[500] Several other methods for the conversion of boranes to tertiary alcohols are also known.[501]

If the reaction between trialkylboranes and carbon monoxide (**18-23**) is carried out in the presence of water followed by addition of NaOH, the product is a secondary alcohol. If H_2O_2 is added along with the NaOH, the corresponding ketone is obtained instead.[502] Various functional groups (e.g., OAc, COOR, CN) may be present in R without being affected,[503] although if they are in the α or β position relative to the boron atom, difficulties

[494] See Negishi, E. *Intra-Sci. Chem. Rep.* ***1973***, *7(1)*, 81; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithica, NY, ***1972***, pp. 343–371; *Acc. Chem. Res.* ***1969***, *2*, 65.

[495] See Brown, H.C.; Cole, T.E.; Srebnik, M.; Kim, K. *J. Org. Chem.* ***1986***, *51*, 4925.

[496] Negishi, E.; Brown, H.C. *Synthesis* ***1972***, 197.

[497] Brown, H.C.; Rathke, M.W. *J. Am. Chem. Soc.* ***1967***, *89*, 4528.

[498] Brown, H.C.; Carlson, B.A. *J. Org. Chem.* ***1973***, *38*, 2422; Brown, H.C.; Katz, J.; Carlson, B.A. *J. Org. Chem.* ***1973***, *38*, 3968.

[499] Pelter, A.; Hutchings, M.G.; Smith, K.; Williams, D.J. *J. Chem. Soc., Perkin Trans. 1* ***1975***, 145, and references cited therein.

[500] See, however, Pelter, A.; Maddocks, P.J.; Smith, K. *J. Chem. Soc., Chem. Commun.* ***1978***, 805.

[501] See Junchai, B.; Hongxun, D. *J. Chem. Soc., Chem. Commun.* ***1990***, 323.

[502] Brown, H.C.; Rathke, M.W. *J. Am. Chem. Soc.* ***1967***, *89*, 2738.

[503] Brown, H.C.; Kabalka, G.W.; Rathke, M.W. *J. Am. Chem. Soc.* ***1967***, *89*, 4530.

may be encountered. The use of an equimolar amount of trifluoroacetic anhydride leads to the ketone rather than the tertiary alcohol.[504] By this procedure thexylboranes (RR^1R^2B, where R^2 = thexyl) can be converted to unsymmetrical ketones ($RCOR^1$).[505] Variations of this methodology have been used to prepare optically active alcohols.[506] See **18-26** for another conversion of trialkylboranes to ketones.[507] It is noted that Oxone was used to oxidize organotrifluoroborates to the corresponding alcohol.[508]

OS **VII**, 427. Also see, OS **VI**, 137.

18-24 Conversion of Boranes to Primary Alcohols, Aldehydes, or Carboxylic Acids

$$R_3B + CO \xrightarrow[2.\ H_2O_2\text{-}OH^-]{1.\ LiBH_4} RCH_2OH$$

$$R_3B + CO \xrightarrow[2.\ H_2O_2\text{-}NaH_2PO_4\text{-}Na_2HPO_4]{1.\ LiAlH(OMe)_3} RCHO$$

When the reaction between a trialkylborane and carbon monoxide (**18-23**) is carried out in the presence of a reducing agent such as lithium borohydride or potassium triisopropoxyborohydride, the reduction agent intercepts the intermediate so that only one B → C migration takes place, and the product is hydrolyzed to a primary alcohol or oxidized to an aldehyde.[509] This procedure wastes two of the three R groups, but this problem can be avoided by the use of *B*-alkyl 9-BBN derivatives (see **15-11**). Since only the 9-alkyl group migrates, this method permits the conversion in high yield of an alkene to a primary alcohol or aldehyde containing one more carbon.[510] When *B*-alkyl 9-BBN derivatives are treated with CO and lithium tri-*tert*-butoxyaluminum hydride,[511] other functional groups (e.g., CN and ester) can be present in the alkyl group without being reduced.[512] Boranes can be directly converted to carboxylic acids by reaction with the dianion of phenoxyacetic acid.[513]

Boronic esters $RB(OR')_2$ react with methoxy(phenylthio)methyllithium, LiCH(OMe)SPh, to give salts, which, after treatment with $HgCl_2$ and then H_2O_2, yields aldehydes.[514] This synthesis has been made enantioselective, with high ee values (>99%), by the use of an optically pure boronic ester.[515]

[504] Pelter, A.; Smith, K.; Hutchings, M.G.; Rowe, K. *J. Chem. Soc., Perkin Trans. 1* ***1975***, 129; See also, Mallison, P.R.; White, D.N.J.; Pelter, A.; Rowe, K.; Smith, K. *J. Chem. Res. (S)* ***1978***, 234.

[505] See Brown, H.C.; Bakshi, R.K.; Singaram, B. *J. Am. Chem. Soc.* ***1988***, *110*, 1529.

[506] See Matteson, D.S. *Mol. Struct. Energ.* ***1988***, *5*, 343; *Acc. Chem. Res.* ***1988***, *21*, 294.

[507] See Pelter, A.; Rao, J.M. *J. Organomet. Chem.* ***1985***, *285*, 65; Brown, H.C.; Bhat, N.G.; Basavaiah, D. *Synthesis* ***1983***, 885; Narayana, C.; Periasamy, M. *Tetrahedron Lett.* ***1985***, *26*, 6361.

[508] Molander, G.A.; Cavalcanti, L.N. *J. Org. Chem.* ***2011***, *76*, 623.

[509] Brown, H.C.; Hubbard, J.L.; Smith, K. *Synthesis* ***1979***, 701, and references cited therein. See Hubbard, J.L.; Smith, K. *J. Organomet. Chem.* ***1984***, *276*, C41.

[510] Brown, H.C.; Knights, E.F.; Coleman, R.A. *J. Am. Chem. Soc.* ***1969***, *91*, 2144.

[511] Brown, H.C.; Coleman, R.A. *J. Am. Chem. Soc.* ***1969***, *91*, 4606.

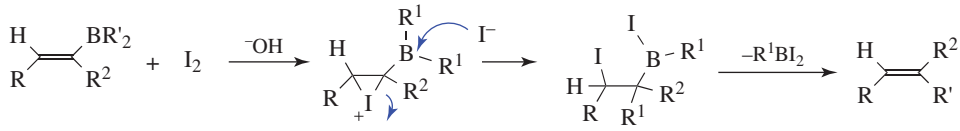
[512] See Negishi, E.; Yoshida, T.; Silveira Jr., A.; Chiou, B.L. *J. Org. Chem.* ***1975***, *40*, 814.

[513] Hara, S.; Kishimura, K.; Suzuki, A.; Dhillon, R.S. *J. Org. Chem.* ***1990***, *55*, 6356. See also, Brown, H.C.; Imai, T. *J. Org. Chem.* ***1984***, *49*, 892.

[514] Brown, H.C.; Imai, T. *J. Am. Chem. Soc.* ***1983***, *105*, 6285. For a related method that produces primary alcohols, see Brown, H.C.; Imai, T.; Perumal, P.T.; Singaram, B. *J. Org. Chem.* ***1985***, *50*, 4032.

[515] Brown, H.C.; Imai, T.; Desai, M.C.; Singaram, B. *J. Am. Chem. Soc.* ***1985***, *107*, 4980.

18-25 Conversion of Vinylic Boranes to Alkenes

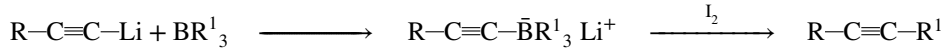


53

The reaction between trialkylboranes and iodine to give alkyl iodides was mentioned at **12-31**. When the substrate contains a vinylic group, the reaction takes a different course,[516] with one of the R′ groups migrating from the boron to the carbon, to give alkenes.[517] The reaction is stereospecific in two senses: (i) if the groups R and R^2 are *cis* in the starting compound, they will be *trans* in the product; (ii) there is retention of configuration within the migrating group R′.[518] Since vinylic boranes can be prepared from alkynes (**15-11**), this is a method for the addition of R′ and H to a triple bond. If R^2 = H, the product is a (*Z*)-alkene. The mechanism is believed to involve an iodonium intermediate, such as **53**, and attack by iodide on boron. When R′ is vinylic, the product is a conjugated diene.[519]

In another procedure, the addition of a dialkylborane to a 1-haloalkyne produces an α-halo vinylic borane.[520] Treatment of the 1-bromovinyl borane with NaOMe gives the rearrangement, and protonolysis of the product produces an (*E*)-alkene.[518] If one of the groups is thexyl, the other migrates.[521] A combination of both of the procedures described above results in the preparation of trisubstituted alkenes.[522]

18-26 Formation of Alkynes, Alkenes, and Ketones from Boranes and Acetylides



A hydrogen directly attached to a triple-bond carbon can be replaced in high yield by an alkyl or an aryl group, by treatment of the lithium acetylide with a trialkyl- or triarylborane, followed by reaction of the lithium alkynyltrialkylborate with iodine.[523] The R′ group may be primary or secondary alkyl as well as aryl, so the reaction has a broader scope than the older reaction **10-74**.[524] The R group may be alkyl, aryl, or hydrogen, although in the last-mentioned case satisfactory yields are obtained only if lithium acetylide-ethylenediamine is used as the starting compound.[525] Optically active alkynes can be prepared by using optically active thexylborinates (RR^2BOR', R^2 = thexyl), where R is

[516] Basavaiah, D.; Kulkarni, S.U.; Bhat, N.G.; Vara Prasad, J.V.N. *J. Org. Chem.* ***1988***, *53*, 239.
[517] For a list of methods of preparing alkenes using boron reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 421–427.
[518] Zweifel, G.; Fisher, R.P.; Snow, J.T.; Whitney, C.C. *J. Am. Chem. Soc.* ***1971***, *93*, 6309.
[519] Hyuga, S.; Takinami, S.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* ***1986***, *27*, 977.
[520] For improvements in this method, see Brown, H.C.; Basavaiah, D.; Kulkarni, S.U.; Lee, H.D.; Negishi, E.; Katz, J. *J. Org. Chem.* ***1986***, *51*, 5270.
[521] Corey, E.J.; Ravindranathan, T. *J. Am. Chem. Soc.* ***1972***, *94*, 4013; Negishi, E.; Katz, J.; Brown, H.C. *Synthesis* ***1972***, 555.
[522] Zweifel, G.; Fisher, R.P. *Synthesis* ***1972***, 557.
[523] See Sikorski, J.A.; Bhat, N.G.; Cole, T.E.; Wang, K.K.; Brown, H.C. *J. Org. Chem.* ***1986***, *51*, 4521. For a review of reactions of organoborates, see Suzuki, A. *Acc. Chem. Res.* ***1982***, *15*, 178.
[524] For a study of the relative migratory aptitudes, see Slayden, S.W. *J. Org. Chem.* ***1981***, *46*, 2311.
[525] Midland, M.M.; Sinclair, J.A.; Brown, H.C. *J. Org. Chem.* ***1974***, *39*, 731.

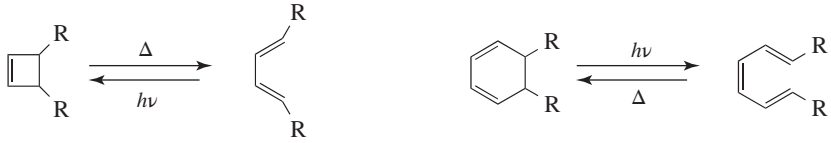
chiral, and LiC≡CSiMe$_3$.[526] The reaction can be adapted to the preparation of alkenes[527] by treatment of the lithium alkynyltrialkylborate with an electrophile such as propanoic acid[528] or tributyltin chloride.[529] The reaction with Bu_3SnCl produces the (*Z*)-alkene stereoselectively.

Treatment of the lithium alkynyltrialkylborate with electrophiles such as methyl sulfate, allyl bromide, or triethyloxonium tetrafluoroborate, followed by oxidation of the resulting vinylic borane, gives a ketone.[530] Note that there are reactions that involve N → O rearrangements, including those mediated by silicon.[531]

18.F.ii. Non 1,2-Rearrangements

A. Electrocyclic Rearrangements

18-27 Electrocyclic Rearrangements of Cyclobutenes and 1,3-Cyclohexadienes

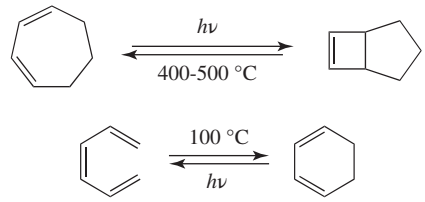


Cyclobutenes and 1,3-dienes can be interconverted by treatment with UV light or with heat.[532] These are 4π electrocyclizations. The thermal reaction is generally not reversible (although exceptions[533] are known), and many cyclobutenes have been converted to 1,3-dienes by heating at temperatures between 100 and 200 °C.[534] Benzocyclobutenes also undergo electrocyclic ring opening,[535] as do benzocyclobutanones.[536] The photochemical conversion can in principle be carried out in either direction, but most often 1,3-dienes are converted to cyclobutenes rather than the reverse, because the dienes are stronger absorbers of light at the wavelengths used.[537] In a similar reaction, 1,3-cyclohexadienes interconvert with 1,3,5-trienes, but in this case the ring-closing process is generally favored thermally and the ring-opening process photochemically, but exceptions are known in both directions.[538] Substituent effects can lead to acceleration of the electrocyclization

[526] Brown, H.C.; Mahindroo, V.K.; Bhat, N.G.; Singaram, B. *J. Org. Chem.* ***1991***, *56*, 1500.
[527] See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 218–222.
[528] Pelter, A.; Gould, K.J.; Harrison, C.R. *Tetrahedron Lett.* ***1975***, 3327.
[529] Wang, K.K.; Chu, K. *J. Org. Chem.* ***1984***, *49*, 5175.
[530] Pelter, A.; Drake, R.A. *Tetrahedron Lett.* ***1988***, *29*, 4181.
[531] Talami, S.; Stirling, C.J.M. *Can. J. Chem.* ***1999***, *77*, 1105.
[532] See Dolbier Jr., W.R.; Koroniak, H.; Houk, K.N.; Sheu, C. *Acc. Chem. Res.* ***1996***, *29*, 471; Niwayama, S.; Kallel, E.A.; Spellmeyer, D.C.; Sheu, C.; Houk, K.N. *J. Org. Chem.* ***1996***, *61*, 2813. The effect of pressure on this reaction has been discussed, see Jenner, G. *Tetrahedron* ***1998***, *54*, 2771.
[533] See Steiner, R.P.; Michl, J. *J. Am. Chem. Soc.* ***1978***, *100*, 6413 and cited references.
[534] See Um, J.M.; Xu, H.; Houk, K.N.; Tang, W. *J. Am. Chem. Soc.* ***2009***, *131*, 6664.
[535] Matsuya, Y.; Ohsawa, N.; Nemoto, H. *J. Am. Chem. Soc.* ***2006***, *128*, 412.
[536] Matsuya, Y.; Ohsawa, N.; Nemoto, H. *J. Am. Chem. Soc.* ***2006***, *128*, 13072.
[537] See Dauben, W.G.; Haubrich, J.E. *J. Org. Chem.* ***1988***, *53*, 600.
[538] See Dauben, W.G.; McInnis, E.L.; Michno, D.M. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 91–129. For an *ab initio* study see Rodríguez-Otero, J. *J. Org. Chem.* ***1999***, *64*, 6842.

process.[539] *Torquoselectivity* in cyclobutene ring-opening reactions[540] and the origins of 1,6-stereoinduction in torquoselective 6π electrocyclizations[541] has been examined.

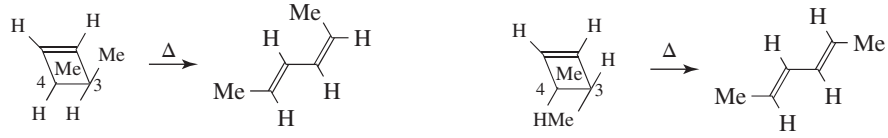
Examples of these types of reactions include:



Ref. 542

An interesting example of 1,3-cyclohexadiene → 1,3,5-triene interconversion is the reaction of norcaradienes to give cycloheptatrienes,[543] a 6π electrocyclization that has been catalyzed by Lewis acids.[544] Norcaradienes[545] (e.g., bicyclo[4.1.0]hepta-2,4-diene to cyclohepta-1,3,5-triene) give this reaction so readily (because they are *cis*-1,2-divinylcyclopropanes, see **18-32**) that they cannot generally be isolated, though some exceptions are known[546] (see also, **15-61**).

These reactions, called *electrocyclic rearrangements*,[547] take place by pericyclic mechanisms and are important in natural product synthesis.[548] The evidence comes from stereochemical studies, which show a remarkable stereospecificity whose direction depends on whether the reaction is induced by heat or light. For example, it was found for the thermal reaction that *cis*-3,4-dimethylcyclobutene gave only *cis*,*trans*-hexa-2,4-diene, while the *trans* isomer gave only the *trans*,*trans* diene:[549]



This experiment is evidence for a four-membered cyclic transition state and arises from conrotatory motion about the C-3—C-4 bond.[550] It is called conrotatory because both

[539] Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* ***2001***, *66*, 3099. See Beaudry, C.M.; Malerich, J.P.; Trauner, D. *Chem. Rev.* ***2005***, *105*, 4757.

[540] See Boon, B.A.; Green, A.G.; Liu, P.; Houk, K.N.; Merlic, C.A. *J. Org. Chem.* ***2017***, *82*, 4613.

[541] Patel, A.; Barcan, G.A.; Kwon, O.; Houk, K.N. *J. Am. Chem. Soc.* ***2013***, *135*, 4878.

[542] Chapman, O.L.; Pasto, D.J.; Borden, G.W.; Griswold, A.A. *J. Am. Chem. Soc.* ***1962***, *84*, 1220.

[543] See Maier, G. *Angew. Chem. Int. Ed.* ***1967***, *6*, 402; Vogel, E. *Pure Appl. Chem.* ***1969***, *20*, 237.

[544] Bishop, L.M.; Barbarow, J.E.; Bergman, R.G.; Trauner, D. *Angew. Chem. Int. Ed.* ***2008***, *47*, 8100.

[545] McNamara, O.A.; Maguire, A.R. *Tetrahedron* ***2011***, *67*, 9.

[546] See Ciganek, E. *J. Am. Chem. Soc.* ***1967***, *89*, 1454; Iyoda, M.; Oda, M. *Angew. Chem. Int. Ed.* ***1987***, *26*, 559.

[547] See Gajewski, J.J. *Hydrocarbon Thermal Isomerizations*, Academic Press, NY, ***1981***; Marvell, E.N. *Thermal Electrocyclic Reactions*, Academic Press, NY, ***1980***; Laarhoven, W.H. *Org. Photochem.* ***1987***, *9*, 129; George, M.V.; Mitra, A.; Sukumaran, K.B. *Angew. Chem. Int. Ed.* ***1980***, *19*, 973; Jutz, J.C. *Top. Curr. Chem.* ***1978***, *73*, 125; Gilchrist, T.L.; Storr, R.C. *Organic Reactions and Orbital Symmetry*, Cambridge University Press, Cambridge, ***1972***, pp. 48–72; Criegee, R. *Angew. Chem. Int. Ed.* ***1968***, *7*, 559. See Schultz, A.G.; Motyka, L. *Org. Photochem.* ***1983***, *6*, 1.

[548] For a review, see Bian, M.; Li, L.; Ding, H. *Synthesis* ***2017***, *49*, 4383.

[549] Winter, R.E.K. *Tetrahedron Lett.* ***1965***, 1207; Criegee, R.; Noll, K. *Liebigs Ann. Chem.* ***1959***, *627*, 1.

[550] Baldwin, J.E.; Gallagher, S.S.; Leber, P.A.; Raghavan, A.S.; Shukla, R. *J. Org. Chem.* ***2004***, *69*, 7212.

movements are clockwise (or both counterclockwise). Because both rotate in the same direction (conrotatory), the *cis* isomer gives the *cis*,*trans* diene.[551] The other possibility (*disrotatory* motion) would have one moving clockwise while the other moves counterclockwise (the groups move in opposite directions); the *cis* isomer would have given the *cis,cis* diene (shown) or the *trans*,*trans* diene. If the motion had been disrotatory, this would still have been evidence for a cyclic mechanism. If the mechanism were a diradical or some other kind of noncyclic process, it is likely that no stereospecificity of either kind would have been observed.

The reverse reaction is also conrotatory. In contrast, the photochemical cyclobutene to 1,3-diene interconversion is *disrotatory* in either direction.[552] Predictions of the stereochemistry are possible.[553] There is evidence, however, that steric effects[554] are an important factor, and that electronic effects also play a role, and their role may be even greater.[555] An electron-donating group stabilizes the transition state when it rotates *outward*, because it mixes with the LUMO; if it rotates *inward*, it mixes with the HOMO, destabilizing the transition state.[556]

The compound 3-formylcyclobutene provided a test. Steric factors would cause the CHO (an electron-withdrawing group) to rotate outward; electronic effects would cause it to rotate inward. The experiment showed inward rotation.[557]

Cyclohexadiene shows precisely the opposite behavior for 1,3,5-triene interconversion. The thermal process is *disrotatory*, while the photochemical process is *conrotatory* (in either direction). These startling results are a consequence of the symmetry rules mentioned in **15-56**, the *Frontier Orbital Method*.[558] As in the case of cycloaddition reactions, the frontier orbital and Möbius-Hückel approaches[559] will be used. Cyclohexadienes are of course 1,3-dienes, and in certain cases it is possible to convert them to cyclobutenes

[551] See Woodward, R.B.; Hoffmann, R. *J. Am. Chem. Soc.* ***1965***, *87*, 395.

[552] See Leigh, W.J.; Zheng, K.; Nguyen, N.; Werstiuk, N.H.; Ma, J. *J. Am. Chem. Soc.* ***1991***, *113*, 4993, and references cited therein.

[553] See Gesche, P.; Klinger, F.; Riesen, A.; Tschamber, T.; Zehnder, M.; Streith, J. *Helv. Chim. Acta* ***1987***, *70*, 2087.

[554] Leigh, W.J.; Postigo, J.A. *J. Am. Chem. Soc.* ***1995***, *117*, 1688.

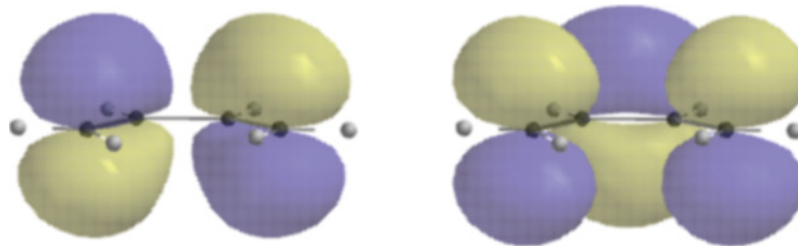
[555] Dolbier Jr., W.R.; Gray, T.A.; Keaffaber, J.J.; Celewicz, L.; Koroniak, H. *J. Am. Chem. Soc.* ***1990***, *112*, 363; Hayes, R.; Ingham, S.; Saengchantara, S.T.; Wallace, T.W. *Tetrahedron Lett.* ***1991***, *32*, 2953.

[556] See Kallel, E.A.; Wang, Y.; Spellmeyer, D.C.; Houk, K.N. *J. Am. Chem. Soc.* ***1990***, *112*, 6759.

[557] Piers, E.; Lu, Y.-F. *J. Org. Chem.* ***1989***, *54*, 2267.

[558] Woodward, R.B.; Hoffmann, R. *J. Am. Chem. Soc.* ***1965***, *87*, 395. See Seeman, J.I. *J. Org. Chem.* ***2015***, *80*, 11632. Also see, Longuet-Higgins, H.C.; Abrahamson, E.W. *J. Am. Chem. Soc.* ***1965***, *87*, 2045; Fukui, K. *Tetrahedron Lett.* ***1965***, 2009.

[559] See Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 352–359; Yates, K. *Hückel Molecular Orbital Theory*, Academic Press, NY, ***1978***, pp. 250–263. Also see, Zimmerman, H.E. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 53–107; Dewar, M.J.S. *Angew. Chem. Int. Ed.* ***1971***, *10*, 761; Jefford, C.W.; Burger, U. *Chimia* ***1971***, *25*, 297; Herndon, W.C. *J. Chem. Educ.* ***1981***, *58*, 371.



HOMO: X_2 LOMO: X_3^*

FIGURE 18.1. Symmetries of the X_2 and X_3* orbitals of a conjugated diene.

instead of to 1,3,5-trienes.[560] An interesting example is found in the pyrocalciferols, where photolysis of the *syn* isomer leads to the corresponding cyclobutene,[561] while photolysis of the *anti* isomers gives the ring-opened 1,3,5-triene. These products are predictable based on a combination of orbital symmetry rules and steric influences.

Heating to >500 °C induced the rearrangement of 6,6-dicyanopentafulvenes to 1,3- and 1,4-dicyanobenzenes in polar aprotic solvents, presumably via a polar "ring-walk" mechanism.[562] The Rh-catalyzed cycloisomerization of 1,6-enynes gave functionalized six-membered carbocyclic systems.[563] Substituents effects for 8π/6π electrocyclization cascade reactions of 1,3,5,7-tetraenes have been studied.[564] A Cu-catalyzed 6π photocyclization of dienynes has been reported.[565] The study of enhanced photochemical 6π electrocyclization in lipophilic proteins has been reported.[566] Substituted naphthylamines were prepared by the 6π/10π electrocyclization of ketene iminium salts.[567] Pyrroles have been prepared by a 4π electrocyclic ring closure of 1-azapentadienyl cations.[568] Pyrrole-2-carboxylates and 2-carboxamides have been prepared via an electrocyclization–oxidation sequence.[569]

The Frontier Orbital Method[570] As applied to these reactions, the frontier orbital method may be expressed in this way: A σ bond will open in such a way that the resulting p orbitals will have the symmetry of the highest occupied π orbital of the product. In the case of cyclobutenes, the HOMO of the product in the thermal reaction is the X_2 orbital (Figure 18.1). Therefore, in a thermal process, the cyclobutene must open so that on one side

[560] See Dauben, W.G.; Kellogg, M.S.; Seeman, J.I.; Vietmeyer, N.D.; Wendschuh, P.H. *Pure Appl. Chem.* ***1973***, *33*, 197.
[561] Dauben, W.G.; Fonken, G.J. *J. Am. Chem. Soc.* ***1959***, *81*, 4060.
[562] Finke, A.D.; Haberland, S.; Schweizer, W.B.; Chen, P.; Diederich, F. *Angew. Chem. Int. Ed.* ***2013***, *52*, 9827.
[563] Matsushima, Y.; Phillips, E.M.; Bergman, R.G.; Ellman, J.A. *Synlett* ***2015***, *26*, 1533.
[564] Patel, A.; Houk, K.N. *J. Org. Chem.* ***2014***, *79*, 11370.
[565] Jin, R.; Chen, J.; Chen, Y.; Liu, W.; Xu, D.; Li, Y.; Ding, A.; Guo, H. *J. Org. Chem.* ***2016***, *81*, 12553.
[566] Marin, M.; Lhiaubet-Vallet, V.; Miranda, M.A. *Org. Lett.* ***2012***, *14*, 1788.
[567] Villedieu-Percheron, E.; Catak, S.; Zurwerra, D.; Staiger, R.; Lachia, M.; De Mesmaeker, A. *Tetrahedron Lett.* ***2014***, *55*, 2446.
[568] Narayan, R.; Fröhlich, R.; Würthwein, E.-U. *J. Org. Chem.* ***2012***, *77*, 1868.
[569] Imbri, D.; Netz, N.; Kucukdisli, M.; Kammer, L.-M.; Jung, P.; Kretzschmann, A.; Opatz, T. *J. Org. Chem.* ***2014***, *79*, 11750.
[570] Fukui, K. *Fortschr. Acc. Chem. Res.* ***1971***, *4*, 57; Houk, K.N. *Acc. Chem. Res.* ***1975***, *8*, 361. See also, Chu, S. *Tetrahedron* ***1978***, *34*, 645; Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, ***1999***; Fukui, K. *Angew. Chem. Int. Ed.* ***1982***, *21*, 801; Houk, K.N. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 181–271.

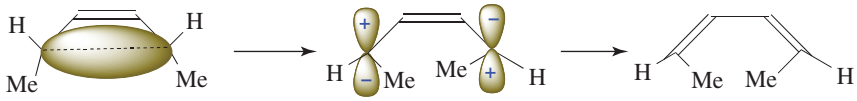


FIGURE 18.2. Thermal opening of 1,2-diethylcyclobutene. The two hydrogens and two methyls are forced into conrotatory motion so that the resulting *p* orbitals have the symmetry of the HOMO of the diene.

the positive lobe lies above the plane, and on the other side below it. Thus the substituents are forced into conrotatory motion (Figure 18.2). On the other hand, in the photochemical process, the HOMO of the product is now the X_3 orbital (Figure 18.1), and in order for the *p* orbitals to achieve this symmetry (the two plus lobes on the same side of the plane), the substituents are forced into disrotatory motion.

This reaction may be considered from the opposite direction (ring closing). For this direction, the rule is that *those lobes of orbitals that overlap (in the HOMO) must be of the same sign*. For thermal cyclization of butadienes, this requires conrotatory motion (Figure 18.3). In the photochemical process the HOMO is the X_3 orbital, so that disrotatory motion is required for lobes of the same sign to overlap.

The Möbius-Hückel Method As seen in **15-56** (the Möbius-Hückel method), a basis set of *p* orbitals is chosen and inspected for sign inversions in the transition state. Figure 18.4 shows a basis set for a 1,3-diene. It is seen that disrotatory ring closing (Figure 18.4*a*) results in overlap of plus lobes only, while in conrotatory closing (Figure 18.4*b*) there is one overlap of a plus with a minus lobe. In the first case, there are zero sign inversions, while in the second there is one sign inversion. With zero (or an even number of) sign inversions, the disrotatory transition state is a *Hückel system,* and so is allowed thermally only if the total number of electrons is $4n + 2$ (**15-56**, the Möbius-Hückel Method). Since the total here is 4, the disrotatory process is not allowed. On the other hand, the conrotatory process, with one sign inversion, is a Möbius system, which is thermally allowed if the total number is $4n$. The conrotatory process is therefore allowed thermally. For the photochemical reactions, the rules are reversed: a reaction with $4n$ electrons requires a Hückel system, so only the disrotatory process is allowed.

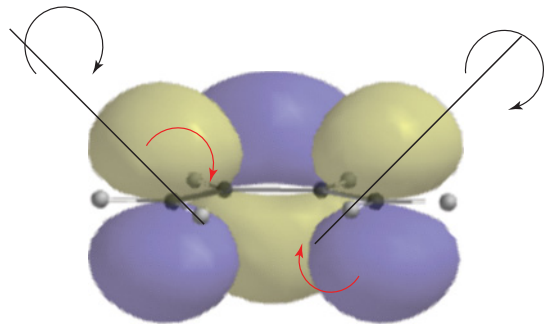


FIGURE 18.3. Thermal ring closing of a 1,3-diene. Conrotatory motion is required for two + lobes to overlap.

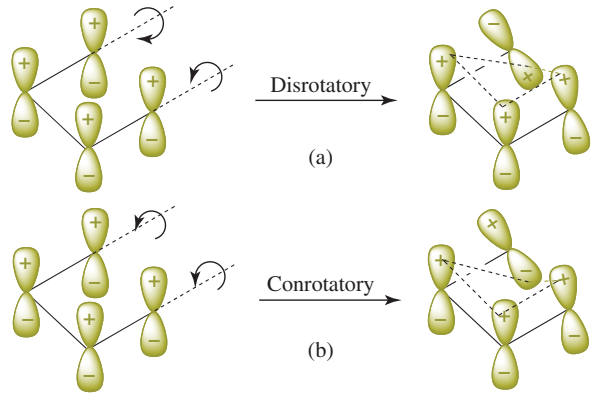
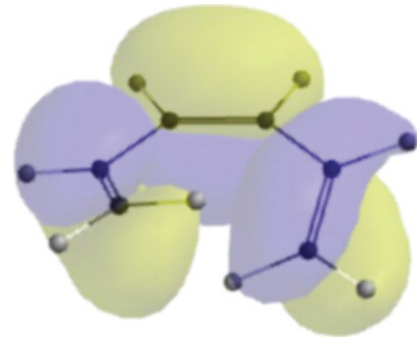
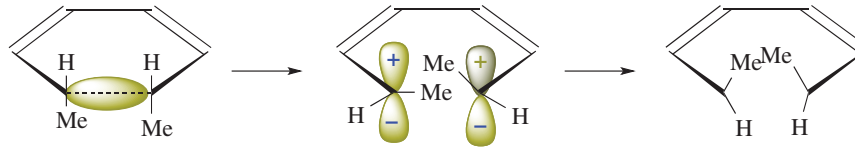


FIGURE 18.4. The 1,3-diene–cyclobutene interconversion. The orbitals shown are *not* molecular orbitals, but a basis set of *p* atomic orbitals. (*a*) Disrotatory ring closure gives zero sign inversion. (*b*) Conrotatory ring closure gives one sign inversion. We could have chosen to show any other basis set (e.g., another basis set would have two plus lobes above the plane and two below, etc.). This would change the number of sign inversion, but the disrotatory mode would still have an even number of sign inversions, and the conrotatory mode an odd number, whichever basis set was chosen.

Both the frontier orbital and the Möbius-Hückel methods can also be applied to the cyclohexadiene to 1,3,5-triene reaction;[571] in either case the predicted result is that for the thermal process, only the disrotatory pathway is allowed, and for the photochemical process, only the conrotatory. For example, for hexa-1,3,5-triene, the symmetry of the HOMO is:

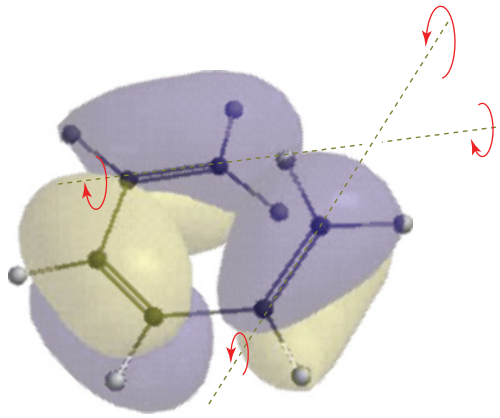


In the thermal cleavage of cyclohexadienes, then, the positive lobes must lie on the same side of the plane, requiring disrotatory motion:



[571] For the transition structures and energy, see Zora, M. *J. Org. Chem.* ***2004***, *69*, 1940.

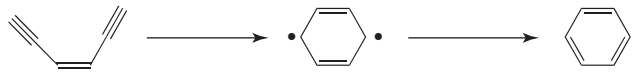
Disrotatory motion is also necessary for the reverse reaction, in order that the orbitals that overlap may be of the same sign:



All these directions are reversed for photochemical processes, because in each case a higher orbital, with inverted symmetry, is occupied.

In the Möbius-Hückel approach, diagrams similar to Figure 18.4 can be drawn for this case. Here too, the disrotatory pathway is a Hückel system and the conrotatory pathway a Möbius system, but since six electrons are now involved, the thermal reaction follows the Hückel pathway and the photochemical reaction follows the Möbius pathway.

A related process is the *Bergmann cyclization*,[572] where an ene-diyne cyclizes to a biradical (**54**) and then aromatizes as shown.



54

Simply heating the ene-diyne will usually lead to aromatization via this pathway.[573] Enediyne dimerization versus Bergman cyclization has been discussed.[574] Quinones can be formed via Bergman cyclization[575] and there are other synthetic applications.[576] The role of vinyl substitution has been examined.[577] An *aza-Bergman cyclization* is known.[578]

The 1,3-diene–cyclobutene interconversion can even be applied to benzene rings.[579] Aromatic compound **55** is converted to **56** by heating to 120 °C,[580] and the Dewar benzene

[572] Bergman, R.G. *Acc. Chem. Res.* ***1973***, *6*, 25; Adam, W.; Krebs, O. *Chem. Rev.* ***2003***, *103*, 4131. See Doubleday, C.; Boguslav, M.; Howell, C.; Korotkin, S.D.; Shaked, D. *J. Am. Chem. Soc.* ***2016***, *138*, 7476; Gomes, G.d.P.; Alabugin, I.V. *J. Am. Chem. Soc.* ***2017***, *139*, 3406.

[573] See Tanaka, H.; Yamada, H.; Matsuda, A.; Takahashi, T. *Synlett* ***1997***, 381.

[574] Haberhauer, G.; Gleiter, R.; Fabig, S. *Org. Lett.* ***2015***, *17*, 1425.

[575] Jones, G.B.; Warner, P.M. *J. Org. Chem.* ***2001***, *66*, 8669.

[576] Bowles, D.M.; Palmer, G.J.; Landis, C.A.; Scott, J.L.; Anthony, J.E. *Tetrahedron* ***2001***, *57*, 3753.

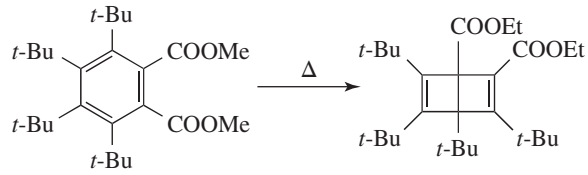
[577] Jones, G.B.; Warner, P.M. *J. Am. Chem. Soc.* ***2001***, *123*, 2134.

[578] Feng, L.; Kumar, D.; Kerwin, S.M. *J. Org. Chem.* ***2003***, *68*, 2234.

[579] See Ward, H.R.; Wishnok, J.S. *J. Am. Chem. Soc.* ***1968***, *90*, 1085; Bryce-Smith, D.; Gilbert, A.; Robinson, D.A. *Angew. Chem. Int. Ed.* ***1971***, *10*, 745. Also see Barlow, M.G.; Haszeldine, R.N.; Hubbard, R. *Chem. Commun.* ***1969***, 202; Lemal, D.M.; Staros, J.V.; Austel, V. *J. Am. Chem. Soc.* ***1969***, *91*, 3373.

[580] Maier, G.; Schneider, K. *Angew. Chem. Int. Ed.* ***1980***, *19*, 1022. See also, Wingert, H.; Maas, G.; Regitz, M. *Tetrahedron* ***1986***, *42*, 5341.

(**56**) is actually more stable than the benzene. In this case thermolysis of the benzene gives the Dewar benzene (rather than the reverse), because of the strain of four adjacent *tert*-butyl groups on the ring.

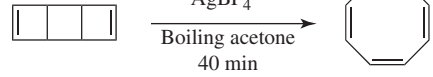


55 **56**

Predictions of the reactions discussed in this section can be summarized according to whether the number of electrons involved in the cyclic process is of the form $4n$ or $4n + 2$ (where n is any integer including zero). Although the orbital symmetry rules predict the stereochemical results in almost all cases, it is necessary to recall (**15-56**, the Möbius-Hückel Method) that they only say what is allowed and what is forbidden, but t*he fact that a reaction is allowed does not necessarily mean that the reaction takes plac*e, and if an allowed reaction does take place, it does not *necessarily* follow that a concerted pathway is involved, since other pathways of lower energy may be available.[581] Furthermore, a "forbidden" reaction might still be made to go, if a method of achieving its high activation energy can be found. This was, in fact, done for the cyclobutene–butadiene interconversion (*cis*-3,4-dichlorocyclobutene gave the forbidden *cis*,*cis*- and *trans*,*trans*-1,4-dichlorobuta-1,3-dienes, as well as the allowed *cis*,*trans* isomer) by the use of IR laser light.[582] This is a thermal reaction. The laser light excites the molecule to a higher vibrational level (Sec. 7.A.i), but not to a higher electronic state.

	Thermal reaction	Photochemical reaction
$4n$	Conrotatory	Disrotatory
$4n + 2$	Disrotatory	Conrotatory

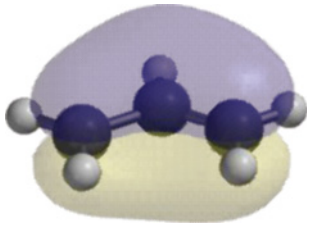
As is the case for [2 + 2] cycloaddition reactions (**15-59**), certain forbidden electrocyclic reactions can be made to take place by the use of metallic catalysts.[583] An example is the silver ion-catalyzed conversion of tricyclo[4.2.0.$0^{2,5}$]octa-3,7-diene to cyclooctatetraene:[584]



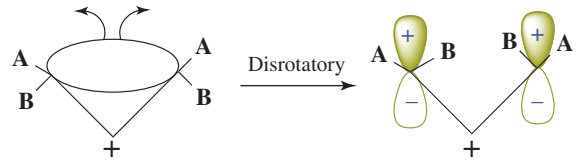
This conversion is very slow thermally (i.e., without the catalyst) because the reaction must take place by a disrotatory pathway, which is disallowed thermally.[585]

[581] See Baldwin, J.E.; Andrist, A.H.; Pinschmidt Jr., R.K. *Acc. Chem. Res.* ***1972***, *5*, 402.
[582] Mao, C.; Presser, N.; John, L.; Moriarty, R.M.; Gordon, R.J. *J. Am. Chem. Soc.* ***1981***, *103*, 2105.
[583] Pettit, R.; Sugahara, H.; Wristers, J.; Merk, W. *Discuss. Faraday Soc.* ***1969***, *47*, 71. See also, Labunskaya, V.I.; Shebaldova, A.D.; Khidekel, M.L. *Russ. Chem. Rev.* ***1974***, *43*, 1; Mango, F.D. *Top. Curr. Chem.* ***1974***, *45*, 39; Mango, F.D.; Schachtschneider, J.H. *J. Am. Chem. Soc.* ***1971***, *93*, 1123.
[584] Merk, W.; Pettit, R. *J. Am. Chem. Soc.* ***1967***, *89*, 4788.
[585] See Pinhas, A.R.; Carpenter, B.K. *J. Chem. Soc., Chem. Commun.* ***1980***, 15.

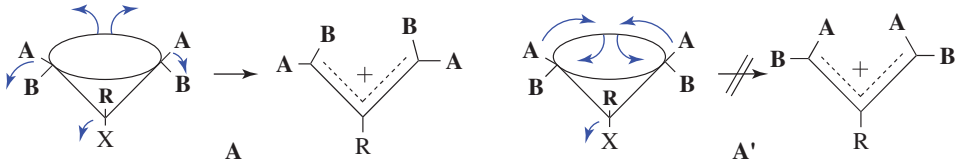
The ring opening of cyclopropyl cations (Sec. 10.G.i, category 7 and **18-3**) is an electrocyclic reaction and is governed by the orbital symmetry rules.[586] For this case, the rule is invoked that the σ bond opens in such a way that the resulting *p* orbitals have the symmetry of the highest occupied orbital of the product, in this case, an allylic cation. Recall that an allylic system has three molecular orbitals (Sec. 2.C, category 3). For the cation, with only two electrons, the highest occupied orbital is the one of the lowest energy (HOMO). Thus, the cyclopropyl cation must undergo a disrotatory ring opening in order to maintain the symmetry.



HOMO



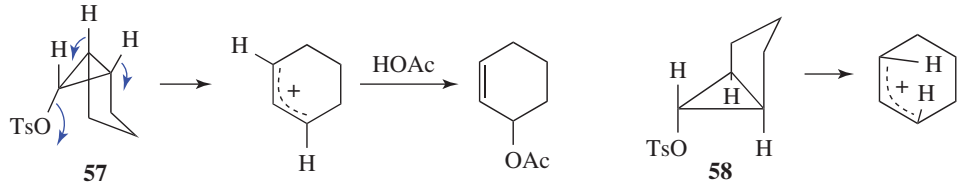
Note that, in contrast, ring opening of the cyclopropyl *anion* must be conrotatory,[587] since in this case it is the next orbital of the allylic system that is the highest occupied, and this has the opposite symmetry.[588] However, it is difficult to generate a free cyclopropyl cation (Sec. 10.G.i, category 7), and it is likely that in most cases, cleavage of the σ bond is concerted with departure of the leaving group in the original cyclopropyl substrate. This fact, of course, means that the σ bond provides anchimeric assistance to the removal of the leaving group (an S_N2 -type process), and it is expected that such assistance should come from the back side, which has an important effect on the direction of ring opening. The orbital symmetry rules require that the ring opening is disrotatory, but as seen above, there are two disrotatory pathways and the rules do not indicate which is preferred. But the fact that the σ orbital provides assistance from the backside means that the two substituents that are *trans* to the leaving group must move *outward*, not inward.[589]



Thus, the disrotatory pathway that is followed is the one shown in **A**, not the one shown in **A′**, because the former puts the electrons of the σ bond on the side opposite that of the leaving group.[590] Strong confirmation of this picture[591] comes from acetolysis of *endo*- (**57**)

[586] DePuy, C.H. *Acc. Chem. Res.* ***1968***, *1*, 33; Schöllkopf, U. *Angew. Chem. Int. Ed.* ***1968***, *7*, 588.
[587] See Boche, G. *Top. Curr. Chem.* ***1988***, *146*, 1.
[588] See Coates, R.M.; Last, L.A. *J. Am. Chem. Soc.* ***1983***, *105*, 7322. For a review of the analogous ring opening of epoxides, see Huisgen, R. *Angew. Chem. Int. Ed.* ***1977***, *16*, 572.
[589] DePuy, C.H.; Schnack, L.G.; Hausser, J.W.; Wiedemann, W. *J. Am. Chem. Soc.* ***1965***, *87*, 4006.
[590] It has been suggested that the pathway shown in **C** is possible in certain cases: Hausser, J.W.; Grubber, M.J. *J. Org. Chem.* ***1972***, *37*, 2648; Hausser, J.W.; Uchic, J.T. *J. Org. Chem.* ***1972***, *37*, 4087.
[591] Also see Reese, C.B.; Shaw, A. *J. Am. Chem. Soc.* ***1970***, *92*, 2566; Dolbier Jr., W.R.; Phanstiel, O. *Tetrahedron Lett.* ***1988***, *29*, 53, and references in these papers.

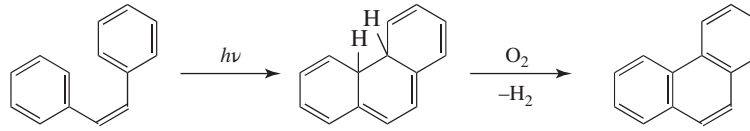
and *exo*-bicyclo[3,1,0]hexyl-6-tosylate (**58**). The groups *trans* to the tosylate must move outward. For **57** this means that the two hydrogen atoms can go outside the framework of the six-membered ring, but for **58** they are forced to go inside.



Consequently, it is not surprising that the rate ratio for solvolysis of **57**/**58** was found to be $> 2.5 \times 10^6$ and that at 150 °C **58** did not solvolyze at all.[592] This evidence is kinetic. Unlike the cases of the cyclobutene (1,3-diene and cyclohexadiene) 1,3,5-triene interconversions, the direct product here is a cation, which is not stable but reacts with a nucleophile and loses some of its steric integrity in the process, so that much of the evidence has been of the kinetic type rather than from studies of product stereochemistry. However, it has been shown by investigations in superacids (Sec. 5.A.ii), where it is possible to keep the cations intact and to study their structures by NMR, that in all cases studied the cation that is predicted by these rules is in fact formed.[593]

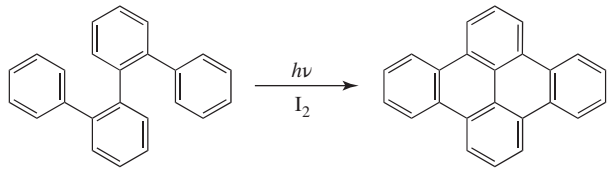
OS **V**, 235, 277, 467; **VI**, 39, 145, 196, 422, 427, 862; **IX**, 180.

18-28 Conversion of One Aromatic Compound to Another



Stilbenes can be converted to phenanthrenes by irradiation with UV light[594] in the presence of an oxidizing agent, such as dissolved molecular oxygen, $FeCl_3$, or iodine.[595] The reaction is a photochemically allowed conrotatory[596] conversion of a 1,3,5-hexatriene to a cyclohexadiene, followed by removal of two hydrogen atoms by the oxidizing agent. The intermediate dihydrophenanthrene has been isolated.[597] The actual reacting species must be the *cis*-stilbene, but *trans*-stilbenes can often be used, because they are isomerized to the *cis* isomers under the reaction conditions. The reaction can be extended to the preparation of many fused aromatic systems, as in the conversion of 1,1′:2′,1″:2″,1‴-quaterphenyl to dibenzo[*fg*,*op*]tetracene.[598]

[592] Schöllkopf, U.; Fellenberger, K.; Patsch, M.; Schleyer, P.v.R.; Su, T.M.; van Dine, G.W. *Tetrahedron Lett.* ***1967***, 3639.
[593] Schleyer, P.v.R.; Su, T.M.; Saunders, M.; Rosenfeld, J.C. *J. Am. Chem. Soc.* ***1969***, *91*, 5174.
[594] Mallory, F.B.; Mallory, C.W. *Org. React.* ***1984***, *30*, 1; Blackburn, E.V.; Timmons, C.J. *Q. Rev. Chem. Soc.* ***1969***, *23*, 482. See Laarhoven, W.H. *Org. Photochem.* ***1989***, *10*, 163.
[595] See Liu, L.; Yang, B.; Katz, T.J.; Poindexter, M.K. *J. Org. Chem.* ***1991***, *56*, 3769.
[596] Cuppen, T.J.H.M.; Laarhoven, W.H. *J. Am. Chem. Soc.* ***1972***, *94*, 5914.
[597] Doyle, T.D.; Benson, W.R.; Filipescu, N. *J. Am. Chem. Soc.* ***1976***, *98*, 3262.
[598] Sato, T.; Shimada, S.; Hata, K. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 2484.

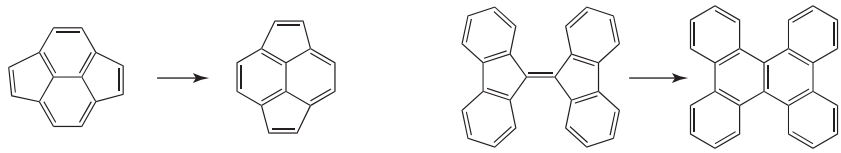


1,1':2',1":2",1"'-quaterphenyl dibenzo[*fg*,*op*]tetracene

Not all such systems give this reaction.[599] The use of substrates containing heteroatoms (e.g., PhN=NPh) allows the formation of heterocyclic ring systems.

Isomerization of biphenylene to benzo[*a*]pentalene[600] is a well-known benzene ring contraction rearrangement,[601] driven by relief of strain in the four-membered ring. Related to this process is the flash vacuum pyrolysis (FVP) of the alternant polycyclic aromatic hydrocarbon benzo[*b*]biphenylene at 1100 °C, which gives fluoranthene, a nonalternant polycyclic aromatic hydrocarbon, as the major product at 1100 °C in the gas phase.[602] The mechanism used to explain this isomerization involves equilibrating diradicals of 2-phenylnaphthalene, which rearrange by the net migration of a phenyl group to give equilibrating diradicals of 1-phenylnaphthalene, one isomer of which then cyclizes to fluoranthene.

Another transformation of one aromatic compound to another is the *Stone-Wales rearrangement* of pyracyclene (**59**),[603] which is a bond-switching reaction. The rearrangement of bifluorenylidene (**60**) to dibenzo[*g*,*p*]chrysene (**61**) occurs at temperatures as low as 400 °C and is accelerated in the presence of decomposing iodomethane, a convenient source of methyl radicals.[604]



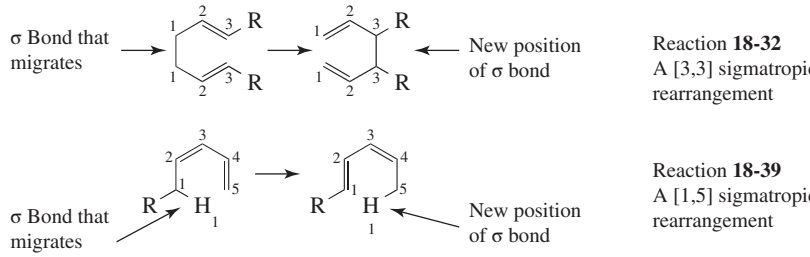
59 **60** **61**

This result suggested a radical rearrangement. This rearrangement is believed to occur by a radical-promoted mechanism consisting of a sequence of homoallyl–cyclopropylcarbinyl rearrangement steps.[605]

B. Sigmatropic Rearrangements

A sigmatropic rearrangement is defined[606] as migration, in an uncatalyzed intramolecular process, of a σ bond, adjacent to one or more π systems, to a new position in a molecule, with the π systems becoming reorganized in the process. Examples are shown here.

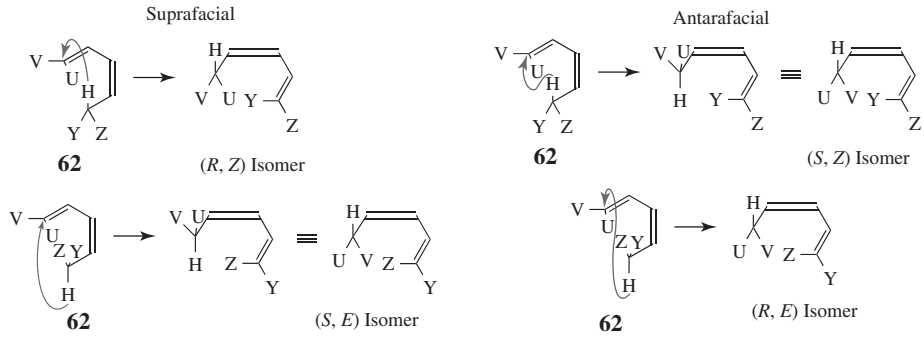
[599] See Laarhoven, W.H. *Recl. Trav. Chim. Pays-Bas* ***1983***, *102*, 185 (pp. 185–204).
[600] Wiersum, U.E.; Jenneskens, L.W. *Tetrahedron Lett.* ***1993***, *34*, 6615; Brown, R.F.C.; Choi, N.; Coulston, K.J.; Eastwood, F.W.; Wiersum, U.E.; Jenneskens, L.W. *Tetrahedron Lett.* ***1994***, *35*, 4405.
[601] See Brown, R F.C.; Eastwood, F.W.; Wong, N.R. *Tetrahedron Lett.* ***1993***, *34*, 3607.
[602] Preda, D.V.; Scott, L.T. *Org. Lett.* ***2000***, *2*, 1489.
[603] Stone, A.J.; Wales, D.J. *Chem. Phys. Lett.* ***1986***, *128*, 501.
[604] Alder, R.W.; Whittaker, G. *J. Chem. Soc., Perkin Trans. 2* ***1975***, 712.
[605] Alder, R.W.; Harvey, J.N. *J. Am. Chem. Soc.* ***2004***, *126*, 2490.
[606] Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***, p. 114. See Tantillo, D.J. *Acc. Chem. Res.* ***2016***, *49*, 741.



The *order* of a sigmatropic rearrangement is expressed by two numbers set in brackets: [*i*,*j*]. These numbers can be determined by counting the atoms over which each end of the σ bond has moved. Each of the original termini is given the number 1. Thus in the first example above, each terminus of the σ bond has migrated from C-1 to C-3, so the order is [3,3]. In the second example the carbon terminus has moved from C-1 to C-5, but the hydrogen terminus has not moved at all, so the order is [1,5].

18-29 [1,*j*]-Sigmatropic Migrations of Hydrogen

Many examples of thermal or photochemical rearrangements in which a hydrogen atom migrates from one end of a system of π bonds to the other have been reported,[607] although the reaction is subject to geometrical constraints. Isotope effects play a role in sigmatropic rearrangements, and there is evidence for a kinetic silicon isotope effect.[608] Pericyclic mechanisms are involved,[609] and the hydrogen must, in the transition state, be in contact with both ends of the chain at the same time. This means that for [1,5] and longer rearrangements, the molecule must be able to adopt the *s-cis* conformation. Furthermore, there are two geometrical pathways by which any sigmatropic rearrangement can take place, illustrated for the case of a [1,5]-sigmatropic rearrangement,[610] starting with a substrate of the form **62**, where the migration origin is an asymmetric carbon atom and U ≠ V.



[607] Gajewski, J.J. *Hydrocarbon Thermal Isomerizations*, Academic Press, NY, ***1981***; Mironov, V.A.; Fedorovich, A.D.; Akhrem, A.A. *Russ. Chem. Rev.* ***1981***, *50*, 666; Spangler, C.W. *Chem. Rev.* ***1976***, *76*, 187.

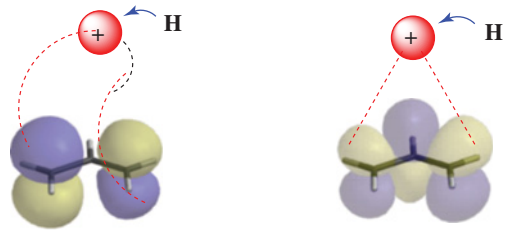
[608] Lin, Y.-L.; Turos, E. *J. Am. Chem. Soc.* ***1999***, *121*, 856.

[609] Moss, S.; King, B.T.; de Meijere, A.; Kozhushkov, S.I.; Eaton, P.E.; Michl, J. *Org. Lett.* ***2001***, *3*, 2375.

[610] Note that a [1,5] sigmatropic rearrangement of hydrogen is also an internal ene synthesis (**15-15**).

In one of the two pathways, the hydrogen moves along the top or bottom face of the π system. This is called *suprafacial migration*. In the other pathway, the hydrogen moves *across* the π system, from top to bottom, or vice versa. This is *antarafacial* migration. Altogether, a single isomer like **62** (different rotamers) can give four products. In a suprafacial migration, H can move across the top of the π system (as drawn above) to give the (*R*,*Z*) isomer, or it can rotate 180° and move across the bottom of the π system to give the (*S*,*E*) isomer.[611] The antarafacial migration can similarly lead to two diastereomers, in this case the (*S*,*Z*) and (*R*,*E*) isomers.

In any given sigmatropic rearrangement, only one of the two pathways is allowed by the orbital symmetry rules; the other is forbidden. To analyze this situation, first use a modified frontier orbital approach.[612] Imagine that, in the transition state, the migrating H atom breaks away from the rest of the system, which is treated as if it were a free radical. Note that this is not what actually takes place; it is *imagined* in order to analyze the process. In a [1,3]-sigmatropic rearrangement, the imaginary transition state consists of a hydrogen atom and an allyl radical. The latter species (Sec. 2.C, category 3) has three π orbitals, but the only one that is of concern, the HOMO, which, in a thermal rearrangement is **B**. The electron of the hydrogen atom is of course in a 1 *s* orbital, which has only one lobe. The rule governing sigmatropic migration of hydrogen is *the H must move from a plus to a plus or from a minus to a minus lobe, of the HOMO; it cannot move to a lobe of opposite sign*.[613] The only way this can happen in a thermal [1,3]-sigmatropic rearrangement is by an antarafacial migration. Consequently, the rule predicts that antarafacial thermal [1,3]-sigmatropic rearrangements are allowed, but the suprafacial pathway is forbidden. However, in a photochemical reaction, promotion of an electron means that **C** is now the HOMO; the suprafacial pathway is now allowed and the antarafacial pathway forbidden.



B **C**

A similar analysis of [1,5]-sigmatropic rearrangements shows that in this case the thermal reaction must be suprafacial and the photochemical process antarafacial. For the general case, with odd-numbered *j*, [1,*j*]-suprafacial migrations are allowed thermally when *j* is of the form $4n + 1$, and photochemically when *j* has the form $4n - 1$; the opposite is true for antarafacial migrations.

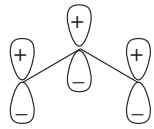
As expected, the Möbius-Hückel method leads to the same predictions. Here, examine the basis set of orbitals shown in **D** and **E** for [1,3]- and [1,5]-rearrangements, respectively. A [1,3]-shift involves four electrons, so an allowed thermal pericyclic reaction must be a

[611] The designations U, V, Y, and Z are arbitrary, so which isomer is (*R*,*Z*) and which is (*S*,*E*) is arbitrary.

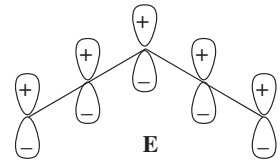
[612] See Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***, pp. 114–140.

[613] This statement follows from the principle that bonds are formed only by overlap of orbitals of the same sign. Since this is a concerted reaction, the hydrogen orbital in the transition state must overlap simultaneously with one lobe from the migration origin and one from the terminus. It is obvious that both of these lobes must have the same sign.

Möbius system (**15-56**, the Möbius-Hückel Method) with one or an odd number of sign inversions. As can be seen in **D**, only an antarafacial migration can achieve this. A [1,5]-shift, with six electrons, is allowed thermally only when it is a Hückel system with zero or an even number of sign inversions; hence it requires a suprafacial migration.[614]

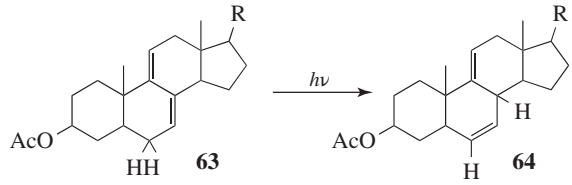


D



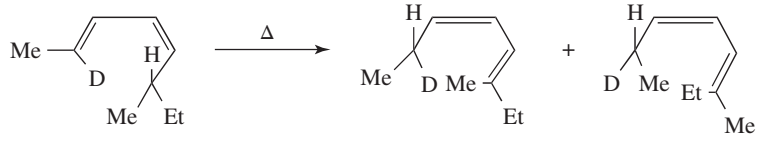
E

The actual reported results bear out this analysis. Thus a thermal [1,3]-migration is allowed to take place only antarafacially, but such a transition state would be extremely strained, and thermal [1,3]-sigmatropic migrations of hydrogen are unknown.[615] On the other hand, the photochemical pathway allows suprafacial [1,3]-shifts, and a few such reactions are known, an example being the photochemical rearrangement of **63** to **64**.[616]

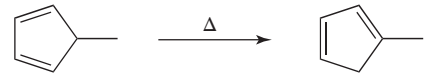


Substituents influence the efficacy of the [1,3]-hydrogen shift.[617] Hot water was used as a mildly acidic catalyst that promoted 1,*n*-rearrangement ($n = 3, 5, 7, 9$) of allylic alcohols to give a new allylic alcohol.[618] An Ir-catalyzed [1,3]-hydrogen shift involving allylic alcohols was reported.[619] The heterocyclization of sulfur and 1,3-migration of silicon has been reported.[620]

The situation is reversed for [1,5]-hydrogen shifts. In this case the thermal rearrangements, being suprafacial, are quite common, while photochemical rearrangements are rare.[621] Two examples of the thermal reaction are shown:



Ref. 622



Ref. 623

[614] See Kless, A.; Nendel, M.; Wilsey, S.; Houk, K.N. *J. Am. Chem. Soc.* ***1999***, *121*, 4524.
[615] See, however, Yeh, M.; Linder, L.; Hoffman, D.K.; Barton, T.J. *J. Am. Chem. Soc.* ***1986***, *108*, 7849. See also, Pasto, D.J.; Brophy, J.E. *J. Org. Chem.* ***1991***, *56*, 4554.
[616] Dauben, W.G.; Wipke, W.T. *Pure Appl. Chem.* ***1964***, *9*, 539 (p. 546). See Kropp, P.J.; Fravel Jr., H.G.; Fields, T.R. *J. Am. Chem. Soc.* ***1976***, *98*, 840.
[617] Hudson, C.E.; McAdoo, D.J. *J. Org. Chem.* ***2003***, *68*, 2735.
[618] Li, P.-F.; Wang, H.-L.; Qu, J. *J. Org. Chem.* ***2014***, *79*, 3955.
[619] Ahlsten, N.; Gómez, A.B.; Martín-Matute, B. *Angew. Chem. Int. Ed.* ***2013***, *52*, 6273.
[620] Tang, J.; Ming, L.; Zhao, X. *Synthesis* ***2013***, *45*, 1713.
[621] See Dauben, W.G.; Poulter, C.D.; Suter, C. *J. Am. Chem. Soc.* ***1970***, *92*, 7408.
[622] Roth, W.R.; König, J.; Stein, K. *Chem. Ber.* ***1970***, *103*, 426.
[623] See Klärner, F. *Top. Stereochem.* ***1984***, *15*, 1; Hess Jr., B.A.; Baldwin, J.E. *J. Org. Chem.* ***2002***, *67*, 6025.

Note that the first example bears out the stereochemical prediction made earlier. Only the two isomers shown were formed. In the second example, migration can continue around the ring, which is common for substituted cyclopentadiene derivatives. Migrations of this kind are called *circumambulatory rearrangements*,[624] and such migrations are known for cyclopentadiene,[625] pyrrole, and phosphole derivatives.[626] Geminal bond participation has been observed in pentadienes,[627] the effects of phenyl substituents have been studied,[628] and the kinetics and activation parameters of [1,5]-hydrogen shifts have been examined.[629] The [1,5]-hydrogen shifts are also known with vinyl aziridines.[630] A Ru-catalyzed cycloisomerization of en-1-ynes leads to cyclic dienes.[631] Highly substituted naphthylamine derivatives were prepared via a Pd-catalyzed [1,5]-sigmatropic hydrogen shift and cyclization reaction of propargyl esters.[632] The Pt-catalyzed cycloisomerization involved the 1,5-acyl migration of benzoendiynyl esters.[633] The competition between 6π electrocyclization and [1,5]-H sigmatropic shifts in tetrahydro-1*H*-cyclobuta[*e*]indene derivatives has been studied.[634] The Co-catalyzed synthesis of tetrahydroquinolines involved 1,5-hydride transfer/cyclization.[635] The [1,5]-shift of aldehyde hydrogen in dienal compounds gave ketenes.[636] An azo-hydrazo conversion involved [1,5]-hydrogen shifts.[637]

The rare [1,4]-hydrogen transfer has been observed in radical cyclizations.[638] With respect to [1,7]-hydrogen shifts, the rules predict the thermal reaction to be antarafacial.[639] Unlike the case of [1,3]-shifts, the transition state is not too greatly strained.[640] Photochemical [1,7]-shifts are suprafacial and, not surprisingly, many of these have been observed.[641] The orbital symmetry rules also help to explain the unexpected stability of certain compounds (see **15-59**, the text immediately preceding **15-60**, and **18-27**, the Möbius-Hückel Method).

[624] Childs, R.F. *Tetrahedron* ***1982***, *38*, 567. See also, Minkin, V.I.; Mikhailov, I.E.; Dushenko, G.A.; Yudilevich, J.A.; Minyaev, R.M.; Zschunke, A.; Mügge, K. *J. Phys. Org. Chem.* ***1991***, *4*, 31. For a study of [1,5]-sigmatropic shiftamers, see Tantillo, D.J.; Hoffmann, R. *Acc. Chem. Res.* ***2006***, *39*, 477.

[625] Shelton, G.R.; Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* ***2007***, *129*, 164.

[626] Bachrach, S.M. *J. Org. Chem.* ***1993***, *58*, 5414.

[627] Ikeda, H.; Ushioda, N.; Inagaki, S. *Chem. Lett.* ***2001***, 166.

[628] Hayase, S.; Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* ***2004***, *126*, 10028.

[629] See Baldwin, J.E.; Raghavan, A.S.; Hess, Jr., B.A.; Smentek, L. *J. Am. Chem. Soc.* ***2006***, *128*, 14854. See also Peles, D.N.; Thoburn, J.D. *J. Org. Chem.* ***2008***, *73*, 3135.

[630] Somfai, P.; Åhman, J. *Tetrahedron Lett.* ***1995***, *36*, 1953.

[631] Datta, S.; Odedra, A.; Liu, R.-S. *J. Am. Chem. Soc.* ***2005***, *127*, 11606.

[632] Zhao, S.-C.; Shu, X.-Z.; Ji, K-G.; Zhou, A.-X.; He, T.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* ***2011***, *76*, 1941.

[633] Chen, Z.; Jia, X.; Huang, J.; Yuan, J. *J. Org. Chem.* ***2014***, *79*, 10674.

[634] Karmakar, S.; Datta, A. *J. Org. Chem.* ***2017***, *82*, 1558.

[635] Cao, W.; Liu, X.; Wang, W.; Lin, L.; Feng, X. *Org. Lett.* ***2011***, *13*, 600.

[636] Sakaguchi, T.; Okuno, Y.; Tsutsumi, Y.; Tsuchikawa, H.; Katsumura, S. *Org. Lett.* ***2011***, *13*, 4292.

[637] Brasil, E.M.; Borges, R.S.; Romero, O.A.S.; Alves, C.N.; Sáez, J.A.; Domingo, L.R. *Tetrahedron* ***2012***, *68*, 6902.

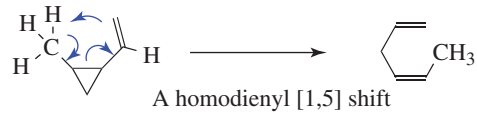
[638] Journet, M.; Malacria, M. *Tetrahedron Lett.* ***1992***, *33*, 1893.

[639] See Hess Jr., B.A. *J. Org. Chem.* ***2001***, *66*, 5897.

[640] Gurskii, M.E.; Gridnev, I.D.; Il'ichev, Y.V.; Ignatenko, A.V.; Bubnov, Y.N. *Angew. Chem. Int. Ed.* ***1992***, *31*, 781; Baldwin, J.E.; Reddy, V.P. *J. Am. Chem. Soc.* ***1988***, *110*, 8223.

[641] See ter Borg, A.P.; Kloosterziel, H. *Recl. Trav. Chim. Pays-Bas* ***1969***, *88*, 266; Tezuka, T.; Kimura, M.; Sato, A.; Mukai, T. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 1120.

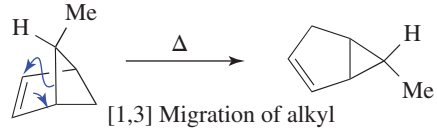
Analogs of sigmatropic rearrangements in which a cyclopropane ring replaces one of the double bonds are also known, as in the reaction shown.[642]



A homodienyl [1,5] shift

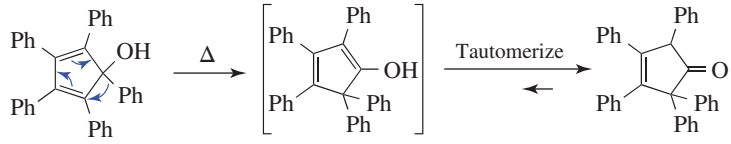
The reverse reaction has also been reported.[643] 2-Vinylcycloalkanols[644] undergo an analogous reaction, as do cyclopropyl ketones (see **18-33**, the text immediately preceding **18-34**, for this reaction).

18-30 [1,*j*]-Sigmatropic Migrations of Carbon



[1,3] Migration of alkyl

Ref. 645



[1,5] Migration of phenyl

Ref. 646

Sigmatropic migrations of alkyl or aryl groups[647] are less common than the corresponding hydrogen migrations.[648] When they do take place, there is an important difference. Unlike a hydrogen atom, whose electron is in a 1 *s* orbital with only one lobe, a carbon free radical has its odd electron in a *p* orbital that has *two lobes of opposite sign*. Therefore, if the imaginary transition states for this case are drawn, a thermal suprafacial [1,5]-process (Figure 18.5) is observed, and symmetry can be conserved only if the migrating carbon moves in such a way that the lobe which was originally attached to the π system remains attached to the π system.

This can happen only if configuration is *retained within the migrating group*. On the other hand, thermal suprafacial [1,3]-migration (Figure 18.6) *can* take place if the migrating carbon switches lobes. If the migrating carbon was originally bonded by its minus lobe, it

[642] See Parziale, P.A.; Berson, J.A. *J. Am. Chem. Soc.* ***1990***, *112*, 1650; Pegg, G.G.; Meehan, G.V. *Aust. J. Chem.* ***1990***, *43*, 1009, 1071.
[643] Roth, W.R.; König, J. *Liebigs Ann. Chem.* ***1965***, *688*, 28. See, Grimme, W. *Chem. Ber.* ***1965***, *98*, 756.
[644] Arnold, R.T.; Smolinsky, G. *J. Am. Chem. Soc.* ***1960***, *82*, 4918; Leriverend, P.; Conia, J.M. *Tetrahedron Lett.* ***1969***, 2681; Conia, J.M.; Barnier, J.P. *Tetrahedron Lett.* ***1969***, 2679.
[645] Roth, W.R.; Friedrich, A. *Tetrahedron Lett.* ***1969***, 2607.
[646] Youssef, A.K.; Ogliaruso, M.A. *J. Org. Chem.* ***1972***, *37*, 2601.
[647] See Mironov, V.A.; Fedorovich, A.D.; Akhrem, A.A. *Russ. Chem. Rev.* ***1981***, *50*, 666; Spangler, C.W. *Chem. Rev.* ***1976***, *76*, 187.
[648] See Shen, K.; McEwen, W.E.; Wolf, A.P. *Tetrahedron Lett.* ***1969***, 827; Miller, L.L.; Greisinger, R.; Boyer, R.F. *J. Am. Chem. Soc.* ***1969***, *91*, 1578.

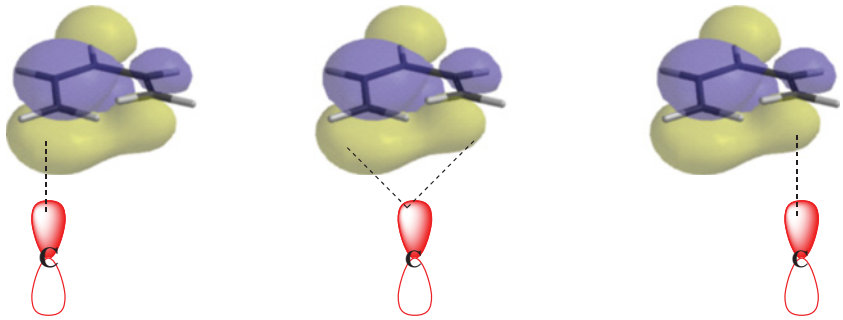


FIGURE 18.5. Hypothetical orbital movement for a thermal [1,5]-sigmatropic migration of carbon. To move from one negative lobe, the migrating carbon uses only its own negative lobe, retaining its configuration.

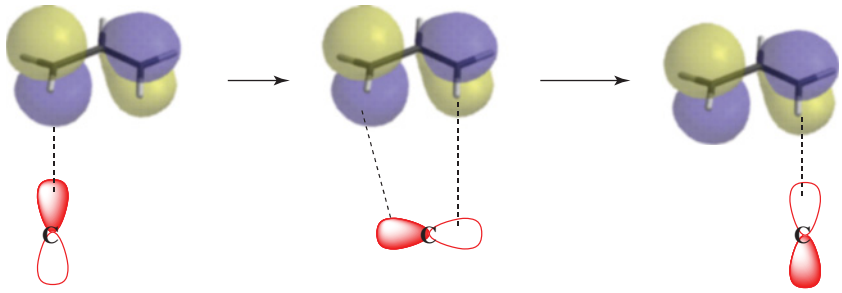


FIGURE 18.6. Hypothetical orbital movement for a thermal [1,3]-sigmatropic migration of carbon. The migrating carbon moves a negative to a positive lobe, requiring it to switch its own bonding lobe from negative to positive, inverting its configuration.

must now use its plus lobe to form the new C—C bond. Thus, configuration in the migrating group will be *inverted*.

From these considerations, suprafacial [1,*j*]-sigmatropic rearrangements in which carbon is the migrating group should always be allowed, both thermally and photochemically, but thermal [1,3]-migrations[649] will proceed with inversion, and thermal [1,5]-migrations will proceed with retention of configuration within the migrating group. More generally, suprafacial [1,*j*]-migrations of carbon in systems where $j = 4n - 1$ proceed with inversion thermally and retention photochemically, while systems where $j = 4n + 1$ show the opposite behavior. Where antarafacial migrations take place, all these predictions are of course reversed. A Au-catalyzed [1,3]-O → C rearrangement of allenyl ethers was reported.[650]

The first laboratory test of these predictions was the pyrolysis of deuterated *endo*-bicyclo[3.2.0]hept-2-en-6-yl acetate, which gave the *exo*-deuterio-*exo*-norbornyl acetate.[651] Thus, as predicted by the orbital symmetry rules, this thermal suprafacial [1,3]-sigmatropic reaction took place with complete inversion at C-7. Similar results have been obtained in a number of other cases.[652] Other cases of lack of complete inversion are also known.[653]

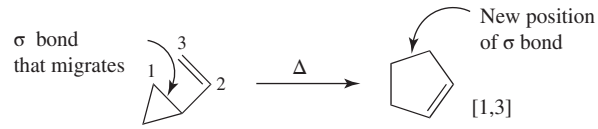
[649] See Baldwin, J.E.; Leber, P.A. *Org. Biomol. Chem.* ***2008***, *6*, 35.
[650] Kona, C.N.; Ramana, C.V. *Chem. Commun.* ***2014***, *50*, 2152.
[651] Berson, J.A. *Acc. Chem. Res.* ***1968***, *1*, 152.
[652] See Berson, J.A. *Acc. Chem. Res.* ***1972***, *5*, 406; Klärner, F.; Adamsky, F. *Angew. Chem. Int. Ed.* ***1979***, *18*, 674.
[653] See Pikulin, S.; Berson, J.A. *J. Am. Chem. Soc.* ***1988***, *110*, 8500.

A diradical mechanism has been invoked to explain such cases.[653,654] There is strong evidence for a radical mechanism for some [1,3]-sigmatropic rearrangements.[655] Photochemical suprafacial [1,3]-migrations of carbon have been shown to proceed with retention, as predicted.[656] Although allylic vinylic ethers generally undergo [3,3]-sigmatropic rearrangements (**18-33**), they can be made to give the [1,3] kind, to give aldehydes. An example is the reaction of 1-(vinyloxy)-2,3,4,5,6,7-hexahydro-1*H*-indene with $LiClO_4$ in diethyl ether to give 2-(2,3,4,5,6,7-hexahydro-1*H*-inden-1-yl)acetaldehyde.[657] In this case, the C—O bond undergoes a 1,3-migration from the O to the end vinylic carbon. When the vinylic ether is of the type $ROCR'{=}CH_2$, ketones RCH_2COR' are formed. There is evidence that this [1,3]-sigmatropic rearrangement is not concerted, but involves dissociation of the substrate into ions.[657] Thermal suprafacial [1,5]-migrations of carbon have been found to take place with retention,[658] but also with inversion.[659] A diradical mechanism has been suggested for the latter case.[659] The effect of ring size and the nature of the migratory groups on [1,*n*]-suprafacial shifts were examined vis-à-vis aromatic and antiaromatic transition states via ring current analysis.

Simple nucleophilic, electrophilic, and free-radical 1,2-shifts can also be regarded as sigmatropic rearrangements (in this case, [1,2]-rearrangements). As previously discussed (see discussion preceding Sec. 18.A) similar principles applied to such rearrangements show that nucleophilic 1,2-shifts are allowed, but the other two types are forbidden unless the migrating group has some means of delocalizing the extra electron or electron pair. The mechanism of the forbidden [3 *s*,5 *s*]-sigmatropic shift has been examined.[660]

Substituted pyrroles were prepared via [3,3]- or [1,3]-rearrangements of *O*-vinyl oximes.[661]

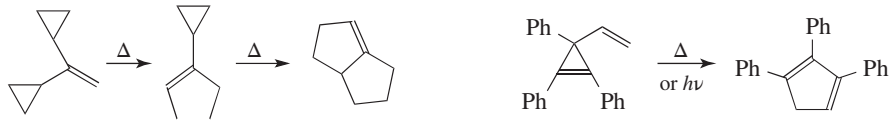
18-31 Vinylcyclopropane Rearrangements



The thermal expansion of a vinylcyclopropane to a cyclopentene ring[662] is a special case of a [1,3]-sigmatropic migration of carbon, although it can also be considered an internal [$_\pi$2 + $_\sigma$2]-cycloaddition reaction (see **15-59**). It is known as a *vinylcyclopropane*

[654] Berson, J.A. *Chemtracts: Org. Chem.* ***1989***, *2*, 213.
[655] See Dolbier, W.B.; Phanstiel IV, O. *J. Am. Chem. Soc.* ***1989***, *111*, 4907.
[656] Cookson, R.C.; Hudec, J.; Sharma, M. *Chem. Commun.* ***1971***, 107, 108.
[657] Grieco, P.A.; Clark, J.D.; Jagoe, C.T. *J. Am. Chem. Soc.* ***1991***, *113*, 5488; Palani, N.; Balasubramanian, K.K. *Tetrahedron Lett.* ***1995***, *36*, 9527.
[658] Boersma, M.A.M.; de Haan, J.W.; Kloosterziel, H.; van de Ven, L.J.M. *Chem. Commun.* ***1970***, 1168.
[659] See Gajewski, J.J.; Gortva, A.M.; Borden, J.E. *J. Am. Chem. Soc.* ***1986***, *108*, 1083.
[660] Leach, A.G.; Catak, S.; Houk, K.N. *Chem. Eur. J.* ***2002***, *8*, 1290.
[661] Wang, H.-Y.; Mueller, D.S.; Sachwani, R.M.; Kapadia, R.; Londino, H.N.; Anderson, L.L. *J. Org. Chem.* ***2011***, *76*, 3203.
[662] See Baldwin, J.E. *Chem. Rev.* ***2003***, *103*, 1197; Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165, pp. 169–172; Hudlicky, T.; Kutchan, T.M.; Naqvi, S.M. *Org. React.* ***1985***, *33*, 247; Hudlicky, T.; Reed, J.W. *Angew. Chem. Int. Ed.* ***2010***, *49*, 4864. See Hay, E.B.; Zhang, H.; Curran, D.P. *J. Am. Chem. Soc.* ***2015***, *137*, 322.

rearrangement.[663] The reaction has been carried out on many vinylcyclopropanes bearing various substituents in the ring[664] or on the vinyl group and has been extended to 1,1-dicyclopropylethene[665] and (both thermally[666] and photochemically[667]) to vinylcyclopropenes.



This rearrangement can be catalyzed by Rh and Ag compounds, and has been used to form rings.[668] Two competing reactions are the homodienyl [1,5]-shift (if a suitable H is available, see **18-29**), and simple cleavage of the cyclopropane ring, leading in this case to a diene (see **18-3**).

Flash vacuum pyrolysis of the trimethylsilyl ether of cyclopropylcarbinyl alcohols gives ring-expanded ketones.[669] Various heterocyclic analogs[670] are also known, as in the rearrangement of aziridinyl amides [such as aziridin-1-yl(phenyl)methanone], which gave 2-phenyl-4,5-dihydrooxazole when heated.[671] Cyclopropyl ketones can be treated with tosylamine and a Zr catalyst, which converts the imine formed *in situ* to a pyrroline.[672] *N*-Cyclopropylimines undergo rearrangement to cyclic imines (pyrrolines) under photochemical conditions.[673] Vinylcyclobutanes can be converted to cyclohexenes,[674] but larger ring compounds do not generally give the reaction.[675]

The CuCN-mediated rearrangement reaction of allenylcyclopropanols gave 5-alkyl or 4-alkyl cyclopentenone regioisomers, depending reaction conditions.[676] Alkynylcyclopropanol derivatives were rearranged to cyclopentenones using a Ru catalyst.[677] The ring expansion of alkenyl cyclobutanols by reaction with ethynylbenziodoxolones gave β-alkynylated cyclopentanones.[678] The visible light-mediated, Ru-catalyzed photocatalytic reaction of alkenylcyclobutanols with aryldiazonium salts gave cyclopentanones.[679] The

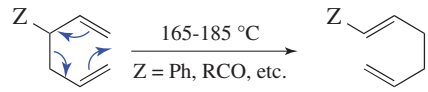
[663] Armesto, D.; Ramos, A.; Mayoral, E.P.; Ortiz, M.J.; Agarrabeitia, A.R. *Org. Lett.* ***2000***, *2*, 183.
[664] For a study of substituent effects, see McGaffin, G.; Grimm, B.; Heinecke, U.; Michaelsen, H.; de Meijere, A.; Walsh, R. *Eur. J. Org. Chem.* ***2001***, 3559.
[665] Ketley, A.D. *Tetrahedron Lett.* ***1964***, 1687; Branton, G.R.; Frey, H.M. *J. Chem. Soc. A* ***1966***, 1342.
[666] Small, A.; Breslow, R. cited in Breslow, R. in de Mayo, P. *Molecular Rearrangments*, Vol. 1, Wiley, NY, ***1963***, p. 236.
[667] Zimmerman, H.E.; Kreil, D.J. *J. Org. Chem.* ***1982***, *47*, 2060.
[668] Wender, P.A.; Husfeld, C.O.; Langkopf, E.; Love, J.A. *J. Am. Chem. Soc.* ***1998***, *120*, 1940.
[669] Rüedi, G.; Nagel, M.; Hansen, H.-J. *Org. Lett.* ***2004***, *6*, 2989.
[670] See Boeckman Jr., R.K.; Walters, M.A. *Adv. Heterocycl. Nat. Prod. Synth.* ***1990***, *1*, 1.
[671] Heine, H.W. *Mech. Mol. Migr.* ***1971***, *3*, 145; Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, ***1969***, pp. 282–290. See also, Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165 (pp. 190–192).
[672] Shi, M.; Yang, Y.-H.; Xu, B. *Synlett* ***2004***, 1622.
[673] Campos, P.J.; Soldevilla, A.; Sampedro, D.; Rodrguez, M.A. *Org. Lett.* ***2001***, *3*, 4087.
[674] See Baldwin, J.E.; Fedé, J.-M. *J. Am. Chem. Soc.* ***2006***, *128*, 5608; Northrop, B.H.; Houk, K.N. *J. Org. Chem.* ***2006***, *71*, 3; Leber, P.A.; Baldwin, J.E. *Acc. Chem. Res.* ***2002***, *35*, 279.
[675] See Thies, R.W. *J. Am. Chem. Soc.* ***1972***, *94*, 7074.
[676] Tumma, N.; Gyanchander, E.; Cha, J.-K. *J. Org. Chem.* ***2017***, *82*, 4379.
[677] Gyanchander, E.; Ydhyam, S.; Tumma, N.; Belmore, K.; Cha, J.K. *Org. Lett.* ***2016***, *18*, 6098.
[678] Zhang, R.-Y.; Xi, L.-Y.; Shi, L.; Zhang, X.-Z.; Chen, S.-Y.; Yu, X.-Q. *Org. Lett.* ***2016***, *18*, 4024.
[679] Kwon, S.J.; Kim, D.Y. *Org. Lett.* ***2016***, *18*, 4562.

Cu-catalyzed ring expansion of vinyl oxetanes gave 3,6-dihydro-2*H*-pyrans.[680] A ring expansion–oxidative arylation reaction via visible light photocatalysis and Au-catalyzed[681] coupling of alkenyl and allenyl cycloalkanols with aryl diazonium salts gave cyclobutanone derivatives.[682]

The reaction rate has also been greatly increased by the addition of a one-electron oxidant tris-(4-bromophenyl)aminium hexafluoroantimonate $Ar_3N^{\bullet+}$ SbF_6^- (Ar = *p*-bromophenyl).[683] This reagent converts the substrate to a cation radical, which undergoes ring expansion much faster.[684] The mechanisms of these ring expansions are not certain. Both concerted[685] and diradical[686] pathways have been proposed,[687] and it is possible that both pathways operate, in different systems. Density functional theory computations were reported for the Cu-catalyzed ring expansion of vinyloxiranes to 2,5-dihydrothiophene derivatives via a Cu catalyst mechanism.[688]

The Cu-catalyzed reaction of chiral vinyl aziridines gave the chiral 2,5-*cis*- or 2,5-*trans*-3-pyrroline.[689] Vinylidenecyclopropanes gave the corresponding alkylidenecyclobutanone derivatives in the presence of an Au/Ag catalyst system and a substituted pyridine *N*-oxide.[690]

18-32 The Cope Rearrangement[691]

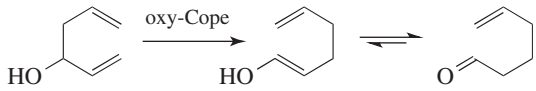


When 1,5-dienes are heated, a [3,3]-sigmatropic rearrangement, known as the *Cope rearrangement* (not to be confused with the *Cope elimination* reaction, **17-7**), occurs to generate an isomeric 1,5-diene.[692] When the diene is symmetrical about the 3,4-bond, the reaction gives a product identical with the starting material.[693] Therefore, a Cope rearrangement can be detected only when the diene is not symmetrical about this bond. The 1,5-diene 3-methylhexa-1,5-diene was heated to 300 °C and gave hepta-1,5-diene.[694] The

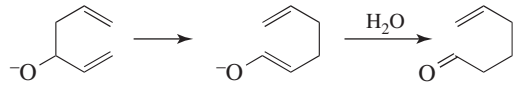
[680] Guo, B.; Schwarzwalder, G.; Njardarson, J.T. *Angew. Chem. Int. Ed.* ***2012***, *51*, 5675.
[681] See Obradors, C.; Echavarren, A.M. *Acc. Chem. Res.* ***2014***, *47*, 902.
[682] Shu, X.-z.; Zhang, M.; He, Y.; Frei, H.; Toste, F.D. *J. Am. Chem. Soc.* ***2014***, *136*, 5844.
[683] Dinnocenzo, J.P.; Conlan, D.A. *J. Am. Chem. Soc.* ***1988***, *110*, 2324.
[684] See Bauld, N.L. *Tetrahedron* ***1989***, *45*, 5307. For a rearrangement of a housane cation radical, see Gerken, J.B.; Wang, S.C.; Preciado, A.B.; Park, Y.S.; Nishiguchi, G.; Tantillo, D.J.; Little, R.D. *J. Org. Chem.* ***2005***, *70*, 4598.
[685] See Gajewski, J.J.; Olson, L.P. *J. Am. Chem. Soc.* ***1991***, *113*, 7432.
[686] See de Meijere, A.; Walsh, R. *Chem. Ber.* ***1991***, *124*, 939. See Roth, W.R.; Lennartz, H.; Doering, W. von E.; Birladeanu, L.; Guyton, C.A.; Kitagawa, T. *J. Am. Chem. Soc.* ***1990***, *112*, 1722 and references cited therein.
[687] See Gajewski, J.J.; Olson, L.P.; Willcott III, M.R. *J. Am. Chem. Soc.* ***1996***, *118*, 299. For a discussion of the mechanism of this reaction, see Su, M.-D. *Tetrahedron* ***1995***, *51*, 5871.
[688] Mustard, T.J.L.; Mack, D.J.; Njardarson, J.T.; Cheong, P.H.-Y. *J. Am. Chem. Soc.* ***2013***, *135*, 471.
[689] Brichacek, M.; Villalobos, M.N.; Plichta, A.; Njardarson, J.T. *Org. Lett.* ***2011***, *13*, 1110.
[690] Yuan, W.; Dong, X.; Wei, Y.; Shi, M. *Chem. Eur. J.* ***2012***, *18*, 10501.
[691] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 838–844.
[692] Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2 (pp. 28–39); Rhoads, S.J.; Raulins, N.R. *Org. React.* ***1975***, *22*, 1; Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* ***1971***, *8*, 75 (pp. 153–201); DeWolfe, R.H., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 455–461.
[693] Note that the same holds true for [1,*j*]-sigmatropic reactions of symmetrical substrates.
[694] Levy, H.; Cope, A.C. *J. Am. Chem. Soc.* ***1944***, *66*, 1684.

reaction takes place more easily (lower temperature required) when there is a group on the 3- or 4-carbon (of the original diene) that leads to the new double bonds being more substituted. An organocatalytic Cope rearrangement has been reported.[695] A theoretical investigation of the thermal rearrangements of hex-1-en-5-yne, hexa-1,2,5-triene, and 2-methylenebicyclo[2.1.0]pentane used density functional theory (DFT) and high level *ab initio* methods.[696] Some concerted Cope rearrangements can be promoted by noncovalent association of their transition state structures with ammonium cations, according to a theoretical investigation of concerted and stepwise Cope rearrangements of natural products.[697]

The reaction is reversible[698] and produces an equilibrium mixture of the two 1,5-dienes that is *richer in the thermodynamically more stable isomer.* However, the equilibrium is shifted to the right for 3-hydroxy-1,5-dienes,[699] because the enol product tautomerizes to the ketone or aldehyde. The rearrangement of 3-hydroxy-1,5-dienes is called the *oxy-Cope rearrangement*,[700] and has proved highly useful in synthesis.[701]



An oxy-Cope rearrangement using microflow conditions (Sec. 7.D) gave cycloheptane derivatives.[702] The oxy-Cope rearrangement is greatly accelerated (by factors of 10^{10}–10^{17}) if the alkoxide is used rather than the alcohol (the *anionic oxy-Cope rearrangement*),[703] where the direct product is the enolate ion, which is hydrolyzed to the ketone.



Anionic-oxy-Cope

A metal-free reaction using a phosphazene base has been reported.[704]

aza-Cope rearrangements are also known,[705] and there is an enantioselective aza-Cope rearrangement.[706] In *amino-Cope rearrangements*, the solvent plays a role in the regioselectivity of the reaction.[707] It has been suggested that this latter reaction does not proceed

[695] Kaldre, D.; Gleason, J.L. *Angew. Chem. Int. Ed.* ***2016***, *55*, 11557; Gebauer, K.; Schneider, C. *Angew. Chem. Int. Ed.* ***2016***, *55*, 14208.
[696] Bozkaya, U.; Özkan, I. *J. Org. Chem.* ***2012***, *77*, 2337.
[697] Painter, P.P.; Wong, B.M.; Tantillo, D.J. *Org. Lett.* ***2014***, *16*, 4818.
[698] See Cooper, N.J.; Knight, D.W. *Tetrahedron* ***2004***, *60*, 243.
[699] See Elmore, S.W.; Paquette, L.A. *Tetrahedron Lett.* ***1991***, *32*, 319.
[700] Paquette, L.A. *Angew. Chem. Int. Ed.* ***1990***, *29*, 609; Marvell, E.N.; Whalley, W. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 2, Wiley, NY, ***1971***, pp. 738–743; see Jung, M.E.; Nishimura, N.; Novack, A.R. *J. Am. Chem. Soc.* ***2005***, *127*, 11206.
[701] For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1306–1307.
[702] Haraguchi, R.; Takada, Y.; Matsubara, S. *Chem. Lett.* ***2012***, *41*, 628.
[703] See Gajewski, J.J.; Gee, K.R. *J. Am. Chem. Soc.* ***1991***, *113*, 967. See also, Schulze, S.M.; Santella, N.; Grabowski, J.J.; Lee, J.K. *J. Org. Chem.* ***2001***, *66*, 7247.
[704] Mamdani, H.T.; Hartley, R.C. *Tetrahedron Lett.* ***2000***, *41*, 747.
[705] See Yadav, J.S.; Reddy, B.V.S.; Rasheed, M.A.; Kumar, H.M.S. *Synlett* ***2000***, 487.
[706] Rueping, M.; Antonchick, A.P. *Angew. Chem. Int. Ed.* ***2008***, *47*, 10090.
[707] Dobson, H.K.; LeBlanc, R.; Perrier, H.; Stephenson, C.; Welch, T.R.; Macdonald, D. *Tetrahedron Lett.* ***1999***, *40*, 3119.

solely by a concerted [3,3]-sigmatropic rearrangement.[708] An asymmetric 2-aza-Cope rearrangement was used for the dynamic kinetic resolution of α-stereogenic-β-formyl amides using a chiral phosphoric acid catalyst to give β-imino amides.[709] There is also a 1,2-oxaza-Cope rearrangement that involves esters and alkyl nitrites.[710]

The 1,5-diene system may be inside a ring or part of an allenic system.[711] When the two double bonds are in vinylic groups attached to adjacent ring positions, the product is a ring four carbons larger. This fact has been applied to Cope rearrangement of divinylcyclopropanes and divinylcyclobutanes, as shown.[712]

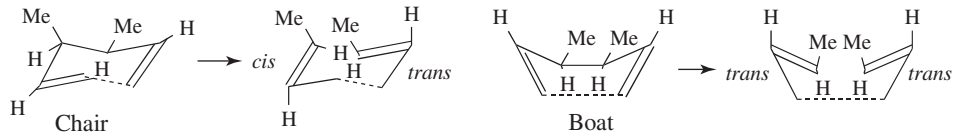
Indeed, *cis*-1,2-divinylcyclopropanes rearrange so rapidly that they generally cannot be isolated at room temperature,[713] but exceptions are known.[714] It is noted that divinyloxiranes, divinylphosphiranes, and divinylthiiranes undergo similar rearrangements.[715] When heated, 1,5-diynes are converted to 3,4-dimethylenecyclobutenes.[716] A rate-determining Cope rearrangement is followed by a very rapid electrocyclic (**18-27**) reaction. Note that the reaction does not take place when one of the double bonds is part of an aromatic system (e.g., 4-phenylbut-1-ene).[717]

The interconversion of 1,3,5-trienes and cyclohexadienes (in **18-27**) is very similar to the Cope rearrangement, but in **18-27**, the 3,4-bond goes from a double bond to a single bond rather than from a single bond to no bond. Like [2 + 2] cycloadditions (**15-59**), Cope rearrangements of simple 1,5-dienes can be catalyzed by certain transition metal compounds. For example, the addition of a Pd catalyst causes the reaction to take place at room temperature.[718]

As indicated with the electron transfer arrows, the mechanism of the uncatalyzed Cope rearrangement is a simple six-centered pericyclic process.[719] Since the mechanism is so simple, it has been possible to study some rather subtle points, among them the question of whether the six-membered transition state is in the boat or the chair form.[720] For the case

[708] Allin, S.M.; Button, M.A.C. *Tetrahedron Lett.* ***1999***, *40*, 3801.
[709] Goodman, C.G.; Johnson, J.S. *J. Am. Chem. Soc.* ***2015***, *137*, 14574.
[710] Zakarian, A.; Lu, C.-D. *J. Am. Chem. Soc.* ***2006***, *128*, 5356.
[711] Duncan, J.A.; Azar, J.K.; Beatle, J.C.; Kennedy, S.R.; Wulf, C.M. *J. Am. Chem. Soc.* ***1999***, *121*, 12029.
[712] Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165 (see pp. 172–174); Mil'vitskaya, E.M.; Tarakanova, A.V.; Plate, A.F. *Russ. Chem. Rev.* ***1976***, *45*, 469 (see pp. 475–476).
[713] See Schneider, M.P.; Rebell, J. *J. Chem. Soc., Chem. Commun.* ***1975***, 283.
[714] See Schneider, M.P.; Rau, A. *J. Am. Chem. Soc.* ***1979***, *101*, 4426.
[715] Zora, M. *J. Org. Chem.* ***2005***, *70*, 6018.
[716] Viola, A.; Collins, J.J.; Filipp, N. *Tetrahedron* ***1981***, *37*, 3765; Théron F.; Verny, M.; Vessière, R. in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 381–445 (pp. 428–430); Huntsman, W.D. *Intra-Sci. Chem. Rep.* ***1972***, *6*, 151.
[717] See Newcomb, M.; Vieta, R.S. *J. Org. Chem.* ***1980***, *45*, 4793. Also see Yasuda, M.; Harano, K.; Kanematsu, K. *J. Org. Chem.* ***1980***, *45*, 2368.
[718] Siebert, M.R.; Tantillo, D.J. *J. Am. Chem. Soc.* ***2007***, *129*, 8686. Lutz, R.P. *Chem. Rev.* ***1984***, *84*, 205. See Overman, L.E.; Renaldo, A.F. *J. Am. Chem. Soc.* ***1990***, *112*, 3945.
[719] See Poupko, R.; Zimmermann, H.; Müller, K.; Luz, Z. *J. Am. Chem. Soc.* ***1996***, *118*, 7995.
[720] See Shea, K.J.; Stoddard, G.J.; England, W.P.; Haffner, C.D. *J. Am. Chem. Soc.* ***1992***, *114*, 2635. See also, Tantillo, D.J.; Hoffmann, R. *J. Org. Chem.* ***2002***, *67*, 1419.

of 3,4-dimethylhexa-1,5-diene, it was demonstrated conclusively that the transition state is in the chair form. This fact was shown by the stereospecific nature of the reaction: The *meso* isomer gave the *cis*,*trans* product, while the (±) diastereomer gave the *trans*,*trans* diene.[721]



If the transition state is in the chair form (taking the *meso* isomer, for example), one methyl must be "axial" and the other "equatorial" and the product must be the *cis*,*trans* alkene. There are two possible boat forms for the transition state of the *meso* isomer. One leads to a *trans*,*trans* product; the other to a *cis*,*cis* alkene. For the (±) pair the predictions are just the opposite. There is just one boat form, and it leads to the *cis*,*trans* alkene, while one chair form ("diaxial" methyls) leads to the *cis*,*cis* product and the other ("diequatorial" methyls) predicts the *trans*,*trans* product. Thus the nature of the products obtained demonstrates that the transition state is a chair and not a boat.[722] While 3,4-dimethylhexa-1,5-diene is free to assume either the chair or boat (it prefers the chair), other compounds are not so free. Thus 1,2-divinylcyclopropane (see above) can react *only* in the boat form, demonstrating that such reactions are possible.[723]

Because of the nature of the transition state[724] in the pericyclic mechanism, optically active substrates with a stereogenic carbon at C-3 or C-4 transfer the chirality to the product. (For an example in the mechanistically similar *Claisen rearrangement*, see **18-33**.)[725] There are many examples of asymmetric [3,3]-sigmatropic rearrangements.[726]

Not all Cope rearrangements proceed by the cyclic six-centered mechanism.[727] Thus *cis*-1,2-divinylcyclobutane rearranges smoothly to cycloocta-1,5-diene, since the geometry is favorable. The *trans* isomer also gives this product, but the main product is 4-vinylcyclohexene (resulting from **18-31**). This reaction can be rationalized as proceeding by a diradical mechanism,[728] although it is possible that at least part of the cyclooctadiene produced comes from a prior epimerization of the *trans*- to the *cis*-divinylcyclobutane followed by Cope rearrangement of the latter.[729]

[721] Doering, W. von E.; Roth, W.R. *Tetrahedron* ***1962***, *18*, 67. See also, Paquette, L.A.; DeRussy, D.T.; Cottrell, C.E. *J. Am. Chem. Soc.* ***1988***, *110*, 890.

[722] See Hoffmann, R.; Woodward, R.B. *J. Am. Chem. Soc.* ***1965***, *87*, 4389; Fukui, K.; Fujimoto, H. *Tetrahedron Lett.* ***1966***, 251.

[723] See Gajewski, J.J.; Jimenez, J.L. *J. Am. Chem. Soc.* ***1986***, *108*, 468.

[724] See Özkan, I.; Zora, M. *J. Org. Chem.* ***2003***, *68*, 9635.

[725] See Hill, R.K. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1984***, pp. 503–572 (pp. 503–545).

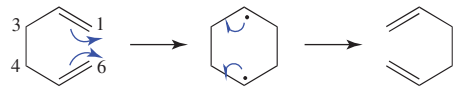
[726] For a review, see Nubbemeyer, U. *Synthesis* ***2003***, 961.

[727] See Navarro-Vázquez, A.; Prall, M.; Schreiner, P.R. *Org. Lett.* ***2004***, *6*, 2981.

[728] Hammond, G.S.; De Boer, C.D. *J. Am. Chem. Soc.* ***1964***, *86*, 899; Trecker, D.J.; Henry, J.P. *J. Am. Chem. Soc.* ***1964***, *86*, 902. Also see, Kessler, H.; Ott, W. *J. Am. Chem. Soc.* ***1976***, *98*, 5014. Also see Berson, J.A. in de Mayo, P. *Rearrangements in Ground and Excited States*, Academic Press, NY, ***1980***, pp. 358–372.

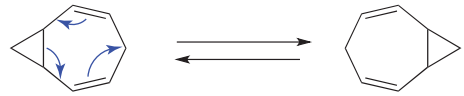
[729] See Baldwin, J.E.; Gilbert, K.E. *J. Am. Chem. Soc.* ***1976***, *98*, 8283. For a similar result in the 1,2-divinylcyclopropane series, see Baldwin, J.E.; Ullenius, C. *J. Am. Chem. Soc.* ***1984***, *96*, 1542.

It has been suggested that another type of diradical two-step mechanism may be preferred by some substrates.[730] Indeed, a nonconcerted Cope rearrangement has been reported.[731] In this pathway,[732] the 1,6-bond is formed before the 3,4-bond breaks:



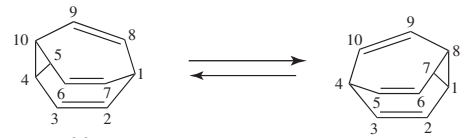
This rearrangement is related to the *Bergman cyclization* that was introduced in **18-27**.

It was pointed out earlier that a Cope rearrangement is degenerate for the symmetrical hexa-1,5-diene that gives back hexa-1,5-diene (Sec. 18.A.ii). Bicyclo[5.1.0]octadiene (**65**) undergoes a similar rearrangement.[733] At room temperature, the NMR spectrum of **65** is in accord with the two structures shown.



65 **65**

At 180 °C, it is converted by a Cope reaction to a compound equivalent to itself. The interesting thing is that at 180 °C the NMR spectrum shows that what exists is an equilibrium mixture of the two structures. That is, at this temperature the molecule rapidly (faster than 10^3 times per second) changes back and forth between the two structures. This is called *valence tautomerism* and is quite distinct from resonance, even though only electrons shift[734] (Sec. 2.N for other types of tautomerism). The positions of the nuclei are not the same in the two structures.



66

The molecule could also have undergone rearrangements to put this ring at 1,2,8 or 1,2,7.

Any of these could then undergo several Cope rearrangements. In all, there are $\frac{10!}{3}$ or more than 1.2 million tautomeric forms, and the cyclopropane ring can be at any three carbons that are adjacent. Since each of these tautomers is equivalent to all the others, this has been called an *infinitely degenerate Cope rearrangement*. Bullvalene (**66**) has been synthesized and its ^{1}H NMR spectrum determined.[735,736] At − 25 °C, there are two peaks

[730] Kaufmann, D.; de Meijere, A. *Chem. Ber.* ***1984***, *117*, 1128. See Dewar, M.J.S.; Jie, C. *J. Chem. Soc., Chem. Commun.* ***1989***, 98. For evidence against this view, see Halevi, E.A.; Rom, R. *Isr. J. Chem.* ***1989***, *29*, 311; Owens, K.A.; Berson, J.A. *J. Am. Chem. Soc.* ***1990***, *112*, 5973.

[731] See Roth, W.R.; Gleiter, R.; Paschmann, V.; Hackler, U.E.; Fritzsche, G.; Lange, H. *Eur. J. Org. Chem.* ***1998***, 961.

[732] For a report of still another mechanism, see Gompper, R.; Ulrich, W. *Angew. Chem. Int. Ed.* ***1976***, *15*, 299. See McGuire, M.J.; Piecuch, P. *J. Am. Chem. Soc.* ***2005***, *127*, 2608.

[733] Doering, W. von E.; Roth, W.R. *Tetrahedron* ***1963***, *19*, 715.

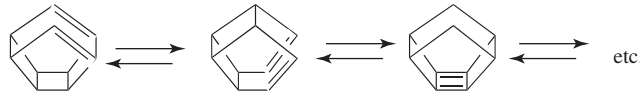
[734] See Decock-Le Révérend, B.; Goudmand, P. *Bull. Soc. Chim. Fr.* ***1973***, 389; Gajewski, J.J. *Mech. Mol. Migr.* ***1971***, *4*, 1 (see pp. 32–49); Paquette, L.A. *Angew. Chem. Int. Ed.* ***1971***, *10*, 11; Schröder, G.; Oth, J.F.M.; Merényi, R. *Angew. Chem. Int. Ed.* ***1965***, *4*, 752.

[735] See Oth, J.F.M.; Schröder, G. *Chem. Ber.* ***1964***, *97*, 3150.

[736] For a review of bullvalenes, see Schröder, G.; Oth, J.F.M. *Angew. Chem. Int. Ed.* ***1967***, *6*, 414.

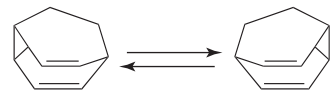
with an area ratio of 6:4, in accord with a single nontautomeric structure. The six protons are the vinylic protons and the four protons are the allylic ones. But at 100 °C the compound shows only one NMR peak, indicating that the compound rapidly interchanges its structure among 1.2 million equivalent forms.[737] The ^{13}C NMR spectrum of bullvalene also shows only one peak at 100 °C.[738]

Another compound for which degenerate Cope rearrangements result in equivalence for all the carbons is *hypostrophene* (**67**).[739]



67

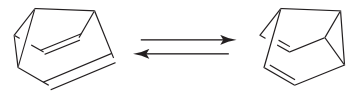
In the case of the compound *barbaralane* (**68**)[740] (bullvalene in which one CH═CH has been replaced by a CH_2): there are only two equivalent tautomers.[741]



68

However, NMR spectra indicate that even at room temperature a rapid interchange of both tautomers is present, although by about − 100 °C this has slowed to the point where the spectrum is in accord with a single structure.

In the case of *semibullvalene* (**69**) (barbaralane in which the CH_2 has been removed), not only is there a rapid interchange at room temperature, but even at − 110 °C.[742]



69

Compound **69** has the lowest energy barrier of any known compound capable of undergoing the Cope rearrangement.[743] The role of strain in the homoaromatization of

[737] See Paquette, L.A.; Malpass, J.R.; Krow, G.R.; Barton, T.J. *J. Am. Chem. Soc.* ***1969***, *91*, 5296.

[738] Oth, J.F.M.; Müllen, K.; Gilles, J.; Schröder, G. *Helv. Chim. Acta* ***1974***, *57*, 1415; Günther, H.; Ulmen, J. *Tetrahedron* ***1974***, *30*, 3781. See Luger, P.; Buschmann, J.; McMullan, R.K.; Ruble, J.R.; Matias, P.; Jeffrey, G.A. *J. Am. Chem. Soc.* ***1986***, *108*, 7825.

[739] McKennis, J.S.; Brener, L.; Ward, J.S.; Pettit, R. *J. Am. Chem. Soc.* ***1971***, *93*, 4957; Paquette, L.A.; Davis, R.F.; James, D.R. *Tetrahedron Lett.* ***1974***, 1615.

[740] For a study of sigmatropic shiftamers in extended barbaralanes, see Tantillo, D.J.; Hoffmann, R.; Houk, K.N.; Warner, P.M.; Brown, E.C.; Henze, D.K. *J. Am. Chem. Soc.* ***2004***, *126*, 4256.

[741] Biethan, U.; Klusacek, H.; Musso, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 176; Doering, W. von E.; Ferrier, B.M.; Fossel, E.T.; Hartenstein, J.H.; Jones Jr., M.; Klumpp, G.W.; Rubin, R.M.; Saunders, M. *Tetrahedron* ***1967***, *23*, 3943; Henkel, J.G.; Hane, J.T. *J. Org. Chem.* ***1983***, *48*, 3858.

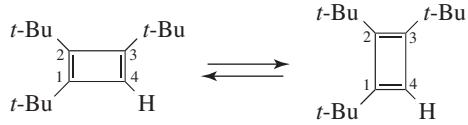
[742] See Meinwald, J.; Schmidt, D. *J. Am. Chem. Soc.* ***1969***, *91*, 5877; Seefelder, M.; Heubes, M.; Quast, H.; Edwards, W.D.; Armantrout, J.R.; Williams, R.V.; Cramer, C.J.; Goren, A.C.; Hrovat, D.A.; Borden, W.T. *J. Org. Chem.* ***2005***, *70*, 3437.

[743] Moskau, D.; Aydin, R.; Leber, W.; Günther, H.; Quast, H.; Martin, H.-D.; Hassenrück, K.; Miller, L.S.; Grohmann, K. *Chem. Ber.* ***1989***, *122*, 925. For a discussion whether semibullvalenes are homoaromatic, see Williams, R.V.; Gadgil, V.R.; Chauhan, K.; Jackman, L.M.; Fernandes, E. *J. Org. Chem.* ***1998***, *63*, 3302.

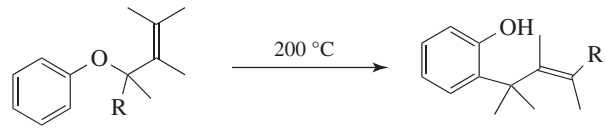
semibullvalene has been discussed.[744] The molecules taking part in a valence tautomerization need not be equivalent. The interconversion benzene oxide[745] and oxepin, for example, exist in a tautomeric equilibrium at room temperature.[746]

Bullvalene and hypostrophene are members of a group of compounds all of whose formulas can be expressed by the symbol $(CH)_{10}$.[747] Many other members of this group are known. Similar groups of $(CH)_n$ compounds exist for other even-numbered values of "*n*".[747] For example, there are 20 possible $(CH)_8$[748] compounds,[749] and five possible $(CH)_6$ compounds,[750] all of which are known: benzene, prismane (Sec. 4.Q.i), Dewar benzene (see **18-27**, the Möbius-Hückel Method), bicyclopropenyl,[751] and benzvalene.[752]

An interesting example of valence tautomerism is the case of 1,2,3-tri-*tert*-butylcyclobutadiene (Sec. 2.K.ii). There are two isomers, both rectangular, and ^{13}C NMR spectra show that they exist in a dynamic equilibrium, even at − 185 °C.[753]



18-33 The Claisen Rearrangement[754]



Allylic aryl ethers, when heated, rearrange to *o*-allylphenols in a reaction called the *Claisen rearrangement*.[755] If both *ortho* positions are filled, the allylic group migrates to the *para*

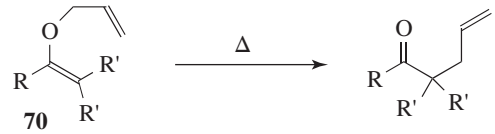
[744] Williams, R.V.; Al-Sehemi, A.G.; Meier, A.K.; Brown, Z.Z.; Armantrout, J.R. *J. Org. Chem.* ***2017***, *82*, 4136.
[745] See Shirwaiker, G.S.; Bhatt, M.V. *Adv. Heterocycl. Chem.* ***1984***, *37*, 67.
[746] Vogel, E. *Pure Appl. Chem.* ***1969***, *20*, 237. See also, Boyd, D.R.; Stubbs, M.E. *J. Am. Chem. Soc.* ***1983***, *105*, 2554.
[747] See Balaban, A.T.; Banciu, M. *J. Chem. Educ.* ***1984***, *61*, 766; Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, ***1978***, pp. 203–215; Scott, L.T.; Jones Jr., M. *Chem. Rev.* ***1972***, *72*, 181. See also, Maier, G.; Wiegand, N.H.; Baum, S.; Wüllner, R. *Chem. Ber.* ***1989***, *122*, 781.
[748] See Hassenrück, K.; Martin, H.; Walsh, R. *Chem. Rev.* ***1989***, *89*, 1125.
[749] See Balaban, A.T.; Banziu, M. *J. Chem. Educ.* ***1984***, *61*, 766; Banciu, M.; Popa, C.; Balaban, A.T. *Chem. Scr.* ***1984***, *24*, 28.
[750] Kobayashi, Y.; Kumadaki, I. *Top. Curr. Chem.* ***1984***, *123*, 103; Bickelhaupt, F.; de Wolf, W.H. *Recl. Trav. Chim. Pays-Bas* ***1988***, *107*, 459.
[751] See Davis, J.H.; Shea, K.J.; Bergman, R.G. *J. Am. Chem. Soc.* ***1977***, *99*, 1499.
[752] See Christl, M. *Angew. Chem. Int. Ed.* ***1981***, *20*, 529; Burger, U. *Chimia* ***1979***, 147.
[753] Maier, G.; Kalinowski, H.; Euler, K. *Angew. Chem. Int. Ed.* ***1982***, *21*, 693.
[754] Castro, A.M.M. *Chem. Rev.* ***2004***, *104*, 2939; Hiersemann, M.; Nubbemeyer, U *The Claisen Rearrangement: Methods and Applications*, Wiley-VCH, ***2007***.
[755] Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, ***1999***, pp. 71–83; Moody, C.J. *Adv. Heterocycl. Chem.* ***1987***, *42*, 203; Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2 (see pp. 28–39); Ziegler, F.E. *Acc. Chem. Res.* ***1977***, *10*, 227; Bennett, G.B. *Synthesis* ***1977***, 589; Rhoads, S.J.; Raulins, N.R. *Org. React.* ***1975***, *22*, 1; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1969***, pp. 89–120; Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* ***1971***, *8*, 75 (pp. 153–201); Jefferson, A.; Scheinmann, F. *Q. Rev. Chem. Soc.* ***1968***, *22*, 391. See Rehbein, J.; Hiersemann, M. *Synthesis* ***2013***, *45*, 1121. See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 844–851.

position (this has been called the *para-Claisen rearrangement*).[756] There is no reaction when the *para* and both *ortho* positions are filled. Migration to the *meta* position has not been observed. In the *ortho* migration, the allylic group always undergoes an allylic shift. As shown, a substituent α to the oxygen is now γ to the ring (and vice versa). On the other hand, in the *para* migration there is never an allylic shift: e.g., the allylic group is found exactly as it was in the original ether. Compounds with propargylic groups (i.e., groups with a triple bond in the appropriate position) do not generally give the corresponding products. The Claisen rearrangement of benzyl vinyl ethers was reported.[757] The impact of Novel Process Windows (Sec. 7.D) on the Claisen rearrangement has been discussed.[758]

The mechanism is a concerted pericyclic [3,3]-sigmatropic rearrangement[759] and accounts for all these facts. For the *ortho* rearrangement there is a fast tautomerization of the initially formed cyclohexa-2,4-dien-1-one to the phenol. Evidence is the lack of a catalyst, the fact that the reaction is first order in the ether, the absence of crossover products when mixtures are heated, and the presence of the allylic shift, which is required by this mechanism. The allylic shift for the *ortho* rearrangement (and the absence of one for the *para*) has been demonstrated by ^{14}C labeling, even when no substituents are present. Studies of the transition-state geometry have shown that, like the *Cope rearrangement*, the Claisen rearrangement usually prefers a chair-like transition state.[760] A *retro-Claisen rearrangement* is known and its mechanism has been examined.[761]

When the *ortho* positions have no hydrogen, a second [3,3]-sigmatropic migration (a Cope reaction) follows to give the *para*-substituted product. Intermediates in such reactions have been trapped by means of a *Diels-Alder reaction* (**15-56**).[762] The rearrangement of aryl allyl ethers is facilitated by Ag/KI in hot acetic acid,[763] and by $AlMe_3$ in water.[764] A solid phase reaction of polymer-bound substrate undergoes the Claisen rearrangement with microwave irradiation.[765]

Allylic ethers of enols (allylic vinylic ethers, **70**) also undergo the Claisen rearrangement;[766] in fact, it was discovered with these compounds first.[767] In these cases, the final tautomerization does not take place even when R′ = H, since *there is no aromaticity to restore*, and *ketones are more stable than enols.*[768]



70

[756] See Gozzo, F.C.; Fernandes, S.A.; Rodrigues, D.C.; Eberlin, M.N.; Marsaioli, A.J. *J. Org. Chem.* ***2003***, *68*, 5493.
[757] Krenski, E.H.; Burns, J.M.; McGeary, R.P. *Org. Biomol. Chem.* ***2017***, *15*, 7887.
[758] Kobayashi, H.; Driessen, B.; van Osch, D.J.P.; Talla, A.; Ookawara, S.; Noël, T.; Hessel, V. *Tetrahedron* ***2013***, *69*, 2885.
[759] Kupczyk-Subotkowska, L.; Saunders Jr., W.H.; Shine, H.J. *J. Am. Chem. Soc.* ***1988***, *110*, 7153.
[760] Copley, S.D.; Knowles, J.R. *J. Am. Chem. Soc.* ***1985***, *107*, 5306. Also see, Yoo, H.Y.; Houk, K.N. *J. Am. Chem. Soc.* ***1994***, *116*, 12047.
[761] Boeckman Jr., R.K.; Shair, M.D.; Vargas, J.R.; Stolz, L.A. *J. Org. Chem.* ***1993***, *58*, 1295.
[762] Conroy, H.; Firestone, R.A. *J. Am. Chem. Soc.* ***1956***, *78*, 2290.
[763] Sharghi, H.; Aghapour, G. *J. Org. Chem.* ***2000***, *65*, 2813.
[764] Wipf, P.; Ribe, S. *Org. Lett.* ***2001***, *3*, 1503.
[765] Kumar, H.M.S.; Anjaneyulu, S.; Reddy, B.V.S.; Yadav, J.C. *Synlett* ***2000***, 1129.
[766] See Ziegler, F.E. *Chem. Rev.* ***1988***, *88*, 1423.
[767] Claisen, L. *Ber.* ***1912***, *45*, 3157.
[768] See Boeckman Jr., R.K.; Flann, C.J.; Poss, K.M. *J. Am. Chem. Soc.* ***1985***, *107*, 4359.

Catalytic Claisen rearrangements of allyl vinyl ethers are well known.[769] The use of water as solvent accelerates the reaction.[770] Microwave-induced reactions on silica gel[771] and in ionic liquids[772] are known. The mechanism is similar to that with allylic aryl ethers.[773] In the presence of a chiral Cu complex, Claisen rearrangements proceed with good enantioselectivity.[774] *N*-Heterocyclic carbenes catalyzed an enantioselective Claisen rearrangement.[775] Using a Cu complex catalyst, a Claisen rearrangement of allyl vinyl ethers was reported.[776] A Rh-catalyzed rearrangement of propargyl vinyl ethers has been reported.[777] A Au-catalyzed Claisen rearrangement of allenyl vinyl ethers has been reported.[778] A chiral hydrogen bond donor has been used for enantioselective Claisen rearrangements.[779] A chiral allylic ether gave an enantioselective Claisen rearrangement with an Ir catalyst.[780]

Since the Claisen rearrangement mechanism does not involve ions, it should not be greatly dependent on the presence or absence of substituent groups on the ring,[781] and this is the case. Electron-donating groups increase the rate and electron-withdrawing groups decrease it, but the effect is small, with the *p*-amino compound reacting only ~10–20 times faster than the *p*-nitro compound.[782] However, solvent effects[783] are greater, and rates varied over a 300-fold range when the reaction was run in 17 different solvents.[784] An especially good solvent is trifluoroacetic acid, in which the reaction can be carried out at room temperature.[785] Most Claisen rearrangements are performed without a catalyst, but $AlCl_3$ or BF_3 are sometimes used.[786]

Allyl allene ethers undergo a Claisen rearrangement when heated in DMF to give the expected diene with a conjugated aldehyde unit.[787] Butenolides with a β-allylic ether unit undergo a *Claisen rearrangement-Conia reaction*[788] cascade to give an oxaspiroheptane

[769] For reviews, see Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* ***2002***, 1461; Majumdar, K.C.; Alam, S.; Chattopadhyay, B. *Tetrahedron* ***2008***, *64*, 597.

[770] Grieco, P.A.; Brandes, E.B.; McCann, S.; Clark, J.D. *J. Org. Chem.* ***1989***, *54*, 5849. See Guest, J.M.; Craw, J.S.; Vincent, M.A.; Hillier, I.H. *J. Chem. Soc., Perkin Trans. 2* ***1997***, 71; Sehgal, A.; Shao, L.; Gao, J. *J. Am. Chem. Soc.* ***1995***, *117*, 11337.

[771] Kotha, S.; Mandal, K.; Deb, A.C.; Banerjee, S. *Tetrahedron Lett.* ***2004***, *45*, 9603.

[772] Lin, Y.-L.; Cheng, J.-Y.; Chu, Y.-H. *Tetrahedron* ***2007***, *63*, 10949.

[773] See Dewar, M.J.S.; Jie, C. *J. Am. Chem. Soc.* ***1989***, *111*, 511.

[774] Balta, B.; Öztürk, C.; Aviyente, V.; Vincent, M.A.; Hillier, I.H. *J. Org. Chem.* ***2008***, *73*, 4800.

[775] Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J.W. *J. Am. Chem. Soc.* ***2010***, *132*, 8810.

[776] Becker, J.; Butt, L.; von Kiedrowski, V.; Mischler, E.; Quentin, F.; Hiersemann, M. *J. Org. Chem.* ***2014***, *79*, 3040.

[777] Vidhani, D.V.; Krafft, M.E.; Alabugin, I.V. *Org. Lett.* ***2013***, *15*, 4462.

[778] Krafft, M.E.; Hallal, K.M.; Vidhani, D.V.; Cran, J.W. *Org. Biomol. Chem.* ***2011***, *9*, 7535.

[779] Uyeda, C.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2008***, *130*, 9228.

[780] Nelson, S.G.; Wang, K. *J. Am. Chem. Soc.* ***2006***, *128*, 4232.

[781] For substituent effects, see Aviyente, V.; Yoo, H.Y.; Houk, K.N. *J. Org. Chem.* ***1997***, *62*, 6121.

[782] See Zahl, G.; Kosbahn, W.; Kresze, G. *Liebigs Ann. Chem.* ***1975***, 1733. See also, Desimoni, G.; Faita, G.; Gamba, A.; Righetti, P.P.; Tacconi, G.; Toma, L. *Tetrahedron* ***1990***, *46*, 2165; Gajewski, J.J.; Gee, K.R.; Jurayj, J. *J. Org. Chem.* ***1990***, *55*, 1813.

[783] See Gajewski, J.J. *Acc. Chem. Res.* ***1997***, *30*, 219.

[784] White, W.N.; Wolfarth, E.F. *J. Org. Chem.* ***1970***, *35*, 2196. See also, Brandes, E.; Greico, P.A.; Gajewski, J.J. *J. Org. Chem.* ***1989***, *54*, 515.

[785] Svanholm, U.; Parker, V.D. *J. Chem. Soc., Perkin Trans. 2* ***1974***, 169.

[786] See Lutz, R.P. *Chem. Rev.* ***1984***, *84*, 205.

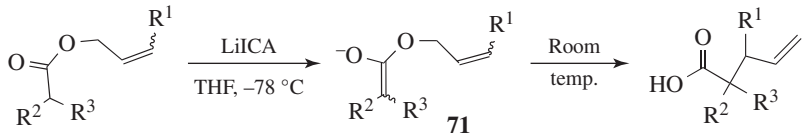
[787] Parsons, P.J.; Thomson, P.; Taylor, A.; Sparks, T. *Org. Lett.****2000***, *2*, 571.

[788] For a review of the *Conia-ene reaction*, see Conia, J.M.; Le Perchec, P. *Synthesis* ***1975***, 1.

with β-keto lactone comprising the five-membered ring.[789] Allylic esters of β-keto acids undergo a Claisen rearrangement in what is known as the *Carroll rearrangement*[790] (also called the *Kimel-Cope rearrangement*[791]), and the reaction can be catalyzed by a Ru complex.[792] An asymmetric Carroll rearrangement was catalyzed by a chiral Pd complex.[793] The ketene-Claisen rearrangement has been reviewed.[794]

Heating an allylic alcohol with *N*,*N*-dimethylacetamide dimethyl acetal gave a transient intermediate, and subsequent Claisen rearrangement gave an amide in a sequence that is known as the *Eschenmoser variant* or the *Eschenmoser-Claisen rearrangement*.[795] This reaction has also been called the *Meerwein-Eschenmoser Claisen rearrangement*.[796] An enantioselective version has been reported using a chiral Pd complex.[797]

Allylic esters can be converted to their enolate anions (**71**) by treatment of the esters with LICA, and a Claisen rearrangement then leads to a γ,δ-unsaturated acid.[798]



71

Alternatively, the silylketene acetal $R^3R^2C{=}C(OSiR_3)OCH_2CH{=}CHR^1$ may be used instead of **71**.[799] This rearrangement also proceeds at room temperature. By either procedure, the reaction is called the *Ireland-Claisen rearrangement*.[800] Note the presence of the negative charge in **71**. As with the oxy-Cope rearrangement (in **18-34**), negative charges generally accelerate the Claisen reaction,[801] although the extent of the acceleration can depend on the identity of the positive counterion.[802] The reaction proceeds with good *syn* selectivity in many cases.[803] The Ireland-Claisen rearrangement has been made enantioselective by converting **71** to an enol borinate in which the boron is attached to a chiral group.[804] The Ireland-Claisen rearrangement can be done with amide derivatives also.[805] A spontaneous [3,3]-sigmatropic rearrangement for the enolate of

[789] Schobert, R.; Siegfried, S.; Gordon, G.; Nieuwenhuyzen, M.; Allenmark, S. *Eur. J. Org. Chem.* ***2001***, 1951.
[790] Carroll, M.F. *J. Chem. Soc.* ***1941***, 507; Ziegler, F.E. *Chem. Rev.* ***1988***, *88*, 1423.
[791] Kimel, W.; Cope, A.C. *J. Am. Chem. Soc.* ***1943***, *65*, 1992.
[792] Burger, E.C.; Tunge, J.A. *Org. Lett.* ***2004***, *6*, 2603.
[793] Kuwano, R.; Ishida, N.; Murakami, M. *Chem. Commun.* ***2005***, 3951.
[794] Mahmood, A. *Tetrahedron* ***2017***, *73*, 2173.
[795] Felix, D.; Gschwend-Steen, K.; Wick, A.E.; Eschenmoser, A. *Helv. Chim. Acta* ***1969***, *52*, 1030.
[796] Gradl, S.N.; Trauner, D. *The Meerwein-Eschenmoser-Claisen Rearrangement*, in *The Claisen Rearrangement*, Hiersemann, M.; Nubbemeyer, U. (Eds.), Wiley-VCH, Weinheim, ***2007***, pp. 367–396.
[797] Linton, E.C.; Kozlowski, M.C. *J. Am. Chem. Soc.* ***2008***, *130*, 16162.
[798] See Cameron, A.G.; Knight, D.W. *J. Chem. Soc., Perkin Trans. 1* ***1986***, 161. See Wilcox, C.S.; Babston, R.E. *J. Am. Chem. Soc.* ***1986***, *108*, 6636.
[799] Ireland, R.E.; Wipf, P.; Armstrong III, J.D. *J. Org. Chem.* ***1991***, *56*, 650 (see p. 783).
[800] See Chai, Y.; Hong, S.-p.; Lindsay, H.A.; McFarland, C.; McIntosh, M.C. *Tetrahedron* ***2002***, *58*, 2905.
[801] See Denmark, S.E.; Harmata, M.A.; White, K.S. *J. Am. Chem. Soc.* ***1989***, *111*, 8878.
[802] See Kirchner, J.J.; Pratt, D.V.; Hopkins, P.B. *Tetrahedron Lett.* ***1988***, *29*, 4229.
[803] Mohamed, M.; Brook, M.A. *Tetrahedron Lett.* ***2001***, *42*, 191. See Khaledy, M.M.; Kalani, M.Y.S.; Khuong, K.S.; Houk, K.N.; Aviyente, V.; Neier, R.; Soldermann, N.; Velker, J. *J. Org. Chem.* ***2003***, *68*, 572.
[804] Corey, E.J.; Lee, D. *J. Am. Chem. Soc.* ***1991***, *113*, 4026.
[805] Tsunoda, T.; Tatsuki, S.; Shiraishi, Y.; Akasaka, M.; Itô, S. *Tetrahedron Lett.* ***1993***, *34*, 3297; Walters, M.A.; Hoem, A.B.; Arcand, H.R.; Hegeman, A.D.; McDonough, C.S. *Tetrahedron Lett.* ***1993***, *34*, 1453.

2-vinyl-6-acyldihydropyran gave a cyclooctadienone via an anionic oxy-Claisen rearrangement.[806]

As just mentioned, asymmetric Claisen rearrangement reactions are well known.[807] Chiral Lewis acids have been designed for this purpose.[808] In general, asymmetric [3,3]-sigmatropic rearrangements are well known.[809]

A number of analogs of the Claisen rearrangement are known, for example rearrangement of $ArNHCH_2CH{=}CH_2$[810] and of $RCH{=}NRCHRCH_2CH{=}CH_2$. These rearrangements of nitrogen-containing compounds can be called *aza-Claisen rearrangements*[811] but are sometimes called *aza-Cope rearrangements.*[812] There is a catalytic enantioselective aza-Cope rearrangement.[813] A Pd-catalyzed aza-Claisen has been reported.[814] The use of excess base was shown to promote an asymmetric aza-Claisen rearrangement.[815] An important contribution to this variation is the rearrangement of trichloroacetimidate derivatives of prochiral (*Z*)-2-alken-1-ols, usually with a Pd catalyst, to give chiral allylic esters.[816] The Claisen rearrangement of allylic alcohols that leads to allylic trichloroacetamides via an intermediate imidate is known as the *Overman rearrangement*.[817] A so-called amine-Claisen rearrangement was reported for *N*-allyl indoles, when heated in the presence of $BF_3{\bullet}OEt_2$.[818] In a related reaction, allylic phorphorimidates undergo [3,3]-sigmatropic rearrangement.[819]

The conversion of allylic aryl thioethers, $ArSCH_2CH{=}CH_2$, to *o*-allylic thiophenols is not feasible, because the latter are not stable[820] but react to give bicyclic compounds.[821] However, many allylic vinylic sulfides do give the rearrangement (the *thio-Claisen rearrangement*).[822] Allylic vinylic sulfones such as $H_2C{=}CRCH_2{-}SO_2{-}CH{=}CH_2$ rearrange, when heated in the presence of ethanol and pyridine, to unsaturated sulfonate salts $CH_2{=}CRCH_2CH_2CH_2SO_3^-$, produced by reaction of the reagents with the unstable sulfene intermediates $CH_2{=}CRCH_2CH_2CH{=}SO_2$.[823] Allylic vinylic sulfoxides rapidly rearrange

[806] Jansma, M.J.; Hoye, T.R. *Org. Lett.* ***2012***, *14*, 4738.

[807] See Zumpe, F.L.; Kazmaier, U. *Synlett* ***1998***, 434; Ito, H.; Sato, A.; Taguchi, T. *Tetrahedron Lett.* ***1997***, *38*, 4815. For asymmetric induction in the thio-Claisen rearrangement, see Reddy, K.V.; Rajappa, S. *Tetrahedron Lett.* ***1992***, *33*, 7957.

[808] See Miller, S.P.; Morken, J.P. *Org. Lett.* ***2002***, *4*, 2743.

[809] For a review, see Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* ***1996***, *7*, 1847.

[810] Jolidon, S.; Hansen, H. *Helv. Chim. Acta* ***1977***, *60*, 978.

[811] For a review, see Majumdar, K.C.; Bhattacharyya, T.; Chattopadhyay, B.; Sinha, B. *Synthesis* ***2009***, 2117. See also, Forte, L.; Lafortune, M.C.; Bierzynski, I.R.; Duncan, J.A. *J. Am. Chem. Soc.* ***2010***, *132*, 2196.

[812] Blechert, S. *Synthesis* ***1989***, 71; Heimgartner, H.; Hansen, H.; Schmid, H. *Adv. Org. Chem.* ***1979***, *9*, pt. 2, 655.

[813] Rueping, M.; Antonchick, A.P. *Angew. Chem. Int. Ed.* ***2008***, *47*, 10090.

[814] See Eitel, S.H.; Bauer, M.; Schweinfurth, D.; Deibel, N.; Sarkar, B.; Harld Kelm, H.; Krüger, H.-J.; Frey, W.; Peters, R. *J. Am. Chem. Soc.* ***2012***, *134*, 4683.

[815] Yoshizuka, M.; Nishii, T.; Sasaki, H.; Kitakado, J.; Ishigaki, N.; Okugawa, S.; Kaku, H.; Horikawa, M.; Inai, M.; Tsunoda, T. *Synlett* ***2011***, *22*, 2967.

[816] See Watson, M.P.; Overman, L.E.; Bergman, R.G. *J. Am. Chem. Soc.* ***2007***, *129*, 5031. See Howard, J.K.; Amin, C.; Lainhart, B.; Smith, J.A.; Rimington, J.; Hyland, C.J.T. *J. Org. Chem.* ***2014***, *79*, 8462.

[817] Overman, L.E. *J. Am. Chem. Soc.* ***1976***, *98*, 2901; Overman, L.E. *Acc. Chem. Res.* ***1980***, *13*, 218; Clizbe, L.A.; Overman, L.E. *Org. Syn. Coll. Vol. 6*. p. 507; *Org. Synth.* ***1978***, *58*, 4.

[818] Anderson, W.K.; Lai, G. *Synthesis* ***1995***, 1287.

[819] Chen, B.; Mapp, A.K. *J. Am. Chem. Soc.* ***2005***, *127*, 6712.

[820] They have been trapped: see Kwart, H.; Schwartz, J.L. *J. Org. Chem.* ***1974***, *39*, 1575.

[821] See Makisumi, Y.; Murabayashi, A. *Tetrahedron Lett.* ***1969***, 1971, 2449.

[822] For a review, see Majumdar, K.C.; Ghosh, S.; Ghosh, M. *Tetrahedron* ***2003***, *59*, 7251.

[823] King, J.F.; Harding, D.R.K. *J. Am. Chem. Soc.* ***1976***, *98*, 3312.

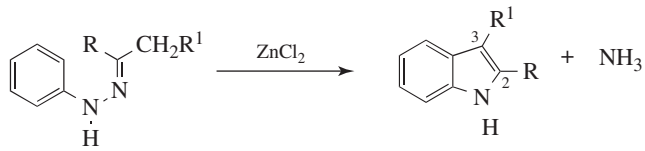
at room temperature or below.[824] Chiral vinyl sulfoxides undergo Claisen rearrangement with good enantioselectivity.[825]

Medium-ring cyclic amines were prepared by conjugate addition/[3,3]-sigmatropic shifts.[826] Butenolides were prepared from allylic cyclopropenecarboxylates via ring expansion [3,3]-sigmatropic rearrangement.[827] (*E*)-1*H*-Inden-1-one derivatives were prepared by Au-catalyzed [3,3]-propargyl ester rearrangement.[828]

Ethers with an alkyl group in the γ position (ArO—C—C=C—R systems) sometimes give abnormal products, with the β carbon becoming attached to the ring.[829] It has been established that these abnormal products do not arise directly from the starting ether but are formed by a further rearrangement of the normal product via a cyclopropyl intermediate.[830] This rearrangement, which has been called an *enolene rearrangement*, a *homodienyl* [1,5]-*sigmatropic hydrogen shift* (see **18-29**), and a [1,5]-*homosigmatropic rearrangement*, involves a shift of three electron pairs over *seven* atoms. It has been found that this "abnormal" Claisen rearrangement is general.

OS **III**, 418; **V**, 25; **VI**, 298, 491, 507, 584, 606; **VII**, 177; **VIII**, 251, 536.

18-34 The Fischer Indole Synthesis

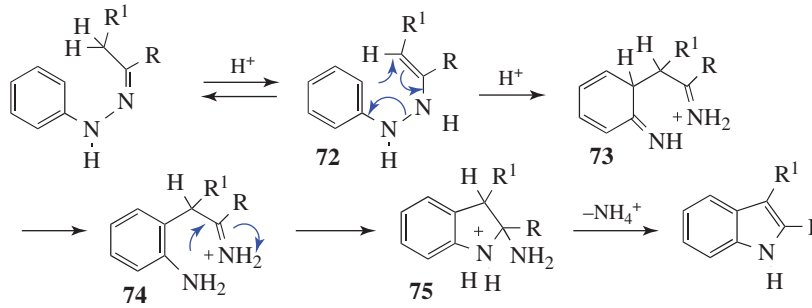


When arylhydrazones of aldehydes or ketones are treated with a catalyst, elimination of ammonia takes place and an indole is formed; this is the *Fischer indole synthesis*.[831] Zinc chloride is a commonly used catalyst, but dozens of others, including other metal halides, proton and Lewis acids, and certain transition metals, have also been used. Microwave irradiation has been used to facilitate this reaction.[832] The reaction has been done using an $AlCl_3$ complex as an ionic liquid,[833] and solid-phase Fischer indole syntheses are known.[834] Arylhydrazones are easily prepared by the treatment of aldehydes or ketones with phenylhydrazine (**16-2**) or by aliphatic diazonium coupling (**12-7**). However, it is not necessary to

[824] Block, E.; Ahmad, S. *J. Am. Chem. Soc.* ***1985***, *107*, 6731.
[825] de la Pradilla, R.F.; Montero, C.; Tortosa, M.; Viso, A. *Chem. Eur. J.* ***2009***, *15*, 697.
[826] Painter, P.P.; Siebert, M.R.; Tantillo, D.J. *J. Org. Chem.* ***2015***, *80*, 11699.
[827] Xie, X.; Li, Y.; Fox, J.M. *Org. Lett.* ***2013***, *15*, 1500.
[828] Wang, L.-J.; Zhu, H.T.; Wang, A.-Q.; Qiu, Y.-F.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* ***2014***, *79*, 204.
[829] For abnormal Claisen rearrangements, Hansen, H. *Mech. Mol. Migr.* ***1971***, *3*, 177; Marvell, E.N.; Whalley, W. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 2, Wiley, NY, ***1971***, pp. 743–750.
[830] Lauer, W.M.; Johnson, T.A. *J. Org. Chem.* ***1963***, *28*, 2913; Marvell, E.N.; Schatz, B. *Tetrahedron Lett.* ***1967***, 67; Watson, J.M.; Irvine, J.L.; Roberts, R.M. *J. Am. Chem. Soc.* ***1973***, *95*, 3348.
[831] Robinson, B. *The Fischer Indole Synthesis*, Wiley, NY, ***1983***; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1969***, pp. 190–207; Sundberg, R.J. *The Chemistry of Indoles*, Academic Press, NY, ***1970***, pp. 142–163; Robinson, B. *Chem. Rev.* ***1969***, *69*, 227. For reviews of so-called abnormal Fischer indole syntheses, see Ishii, H. *Acc. Chem. Res.* ***1981***, *14*, 275. See Susick, R.B.; Morrill, L.A.; Picazo, E.; Garg, N.K. *Synlett* ***2017***, *28*, 1.
[832] Lipinska, T.; Guibé-Jampel, E.; Petit, A.; Loupy, A. *Synth. Commun.* ***1999***, *29*, 1349.
[833] Rebeiro, G.L.O.; Khadilkar, B.M. *Synthesis* ***2001***, 370.
[834] Rosenbaum, C.; Katzka, C.; Marzinzik, A.; Waldmann, H. *Chem. Commun.* ***2003***, 1822.

isolate the arylhydrazone. The aldehyde or ketone can be treated with a mixture of phenylhydrazine and the catalyst; this is now common practice. In order to obtain an indole, the aldehyde or ketone must be of the form $RCOCH_2R'$ (R = alkyl, aryl, or hydrogen). Vinyl ethers, such as dihydrofuran, serve as an aldehyde surrogate when treated with phenylhydrazine and a catalytic amount of aqueous sulfuric acid to give an 3-substituted indole.[835] The benzyne Fisher indole reaction has been reported.[836] A microwave-assisted, propyphosphonic anhydride-mediated reaction has been reported.[837] The catalytic asymmetric Fisher indole synthesis has been discussed.[838] Rhodium catalysts have been used in this reaction.[839] Isothioureas catalyzed the asymmetric [2,3]-rearrangement of allylic ammonium ylids.[840]

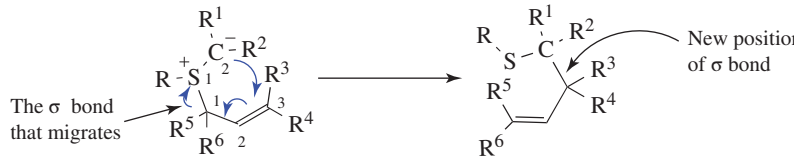
At first glance, the reaction does not seem to be a rearrangement. However, the key step of the mechanism[841] is a [3,3]-sigmatropic rearrangement.[842]



There is much evidence for this mechanism. The main function of the catalyst seems to be to speed the conversion of the hydrazine: (i) the isolation of side products that could only have come from **73**,[843] (ii) the detection of **74** by ^{13}C and ^{15}N NMR,[844] (iii) the isolation of **75**,[845] and (iv) ^{15}N labeling experiments that showed that it was the nitrogen farther from the ring that is eliminated as ammonia.[846]

OS **III**, 725; **IV**, 884. Also see, OS **IV**, 657.

18-35 [2,3]-Sigmatropic Rearrangements



[835] Campos, K.R.; Woo, J.C.S.; Lee, S.; Tillyer, R.D. *Org. Lett.* ***2004***, *6*, 79.
[836] McAusland, D.; Seo, S.; Pintori, D.G.; Finlayson, J.; Greaney, M.F. *Org. Lett.* ***2011***, *13*, 3667.
[837] Desroses, M.; Wieckowski, K.; Stevens, M.; Odell, L.R. *Tetrahedron Lett.* ***2011***, *52*, 4417.
[838] Müller, S.; Webber, M.J.; List, B. *J. Am. Chem. Soc.* ***2011***, *133*, 18534.
[839] Harrison, J.G.; Gutierrez, O.; Jana, N.; Driver, T.G.; Tantillo, D.J. *J. Am. Chem. Soc.* ***2016***, *138*, 487.
[840] West, T.H.; Daniels, D.S.B.; Slawin, A.Z.; Smith, A.D. *J. Am. Chem. Soc.* ***2014***, *136*, 4476.
[841] For a mechanistic study, see Hughes, D.L.; Zhao, D. *J. Org. Chem.* ***1993***, *58*, 228.
[842] This mechanism was proposed by Robinson, G.M.; Robinson, R. *J. Chem. Soc.* ***1918***, *113*, 639.
[843] Bajwa, G.S.; Brown, R.K. *Can. J. Chem.* ***1969***, *47*, 785; ***1970***, *48*, 2293 and references cited therein.
[844] Douglas, A.W. *J. Am. Chem. Soc.* ***1978***, *100*, 6463; ***1979***, *101*, 5676.
[845] See Forrest, T.P.; Chen, F.M.F. *J. Chem. Soc., Chem. Commun.* ***1972***, 1067.
[846] Clausius, K.; Weisser, H.R. *Helv. Chim. Acta* ***1952***, *35*, 400.

Sulfur ylids bearing an allylic group are converted to unsaturated sulfides on heating.[847] This is a concerted [2,3]-sigmatropic rearrangement[848] and has also been demonstrated for the analogous cases of nitrogen ylids[849] and the conjugate bases of allylic ethers. In this last case it is called a *[2,3]-Wittig rearrangement* (**18-22**).[850]

The reaction has been extended to certain other systems,[851] even to an all-carbon system.[852] A phase transfer-catalyzed [2,3]-rearrangement has been reported.[853]

Treatment of an α-(*N*-allylic amino) ketone with NaH led to 2-allylic α-amino ketones via a [2,3]-rearrangement.[854] In the presence of a chiral ligand on nitrogen,[854] or with a chiral additive,[855] good asymmetric induction is possible. Vinylaziridines undergo [2,3]-sigmatropic rearrangement.[856] The Pd-catalyzed, enantioselective [2,3]-rearrangement of amine *N*-oxides has been discussed.[857] Both H bond catalysis and Ca catalytic methods have been developed.[858] The biocatalyst cytochrome $P411_{BM3}$ variants promoted a sulfimidation/[2,3]-rearrangement sequence in whole cells.[859] The [2,3]-Wittig rearrangement in particular has often been used as a means of transferring chirality.[860] If a suitable stereogenic center is present, then stereocontrol over three contiguous stereogenic centers can be achieved. Stereocontrol of the new double bond (*E* or *Z*) has also been accomplished.

Since the reactions involve migration of an allylic group from a sulfur, nitrogen, or oxygen atom to an adjacent negatively charged carbon atom, they are special cases of the *Stevens or Wittig rearrangements* (**18-21**, **18-22**). However, in this case the migrating group *must* be allylic while in **18-21** and **18-22** other groups can also migrate. Thus, when the migrating group is allylic, there are two possible pathways: (i) the radical-ion

[847] See Ma, M.; Peng, L.; Li, C.; Zhang, X.; Wang, J. *J. Am. Chem. Soc.* ***2005***, *127*, 15106. For a review as applied to ring expansions, see Vedejs, E. *Acc. Chem. Res.* ***1984***, *17*, 358.

[848] See Hoffmann, R.W. *Angew. Chem. Int. Ed.* ***1979***, *18*, 563.

[849] See Honda, K.; Inoue, S.; Sato, K. *J. Am. Chem. Soc.* ***1990***, *112*, 1999.

[850] Nakai, T.; Mikami, K. *Chem. Rev.* ***1986***, *86*, 885. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1063–1067. See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 836–838.

[851] See Murata, Y.; Nakai, T. *Chem. Lett.* ***1990***, 2069. Also see Reich, H.J. in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 365–393; Reich, H.J. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 102–111.

[852] Baldwin, J.E.; Urban, F.J. *Chem. Commun.* ***1970***, 165.

[853] Denmark, S.E.; Cullen, L.R. *J. Org. Chem.* ***2015***, *80*, 11818.

[854] Workman, J.A.; Garrido, N.P.; Sançon, J.; Roberts, E.; Wessel, H.P.; Sweeney, J.B. *J. Am. Chem. Soc.* ***2005***, *127*, 1066.

[855] Blid, J.; Panknin, O.; Somfai, P. *J. Am. Chem. Soc.* ***2005***, *127*, 9352.

[856] Somfai, P.; Panknin, O. *Synlett* ***2007***, 1190.

[857] Bao, H.; Qi, X.; Tambar, U.K. *J. Am. Chem. Soc.* ***2011***, *133*, 1206; Bao, H.; Qi, X.; Tambar, U.K. *Synlett* ***2011***, *22*, 1789.

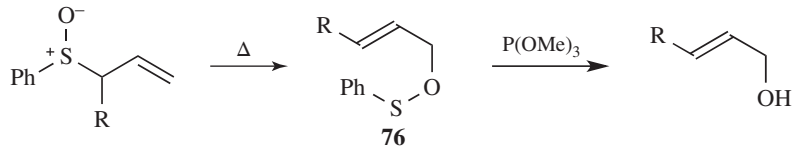
[858] Ošeka, M.; Kimm, M.; Järving, I.; Lippur, K.; Kanger, T. *J. Org. Chem.* ***2017***, *82*, 2889.

[859] Prier, C.K.; Hyster, T.K.; Farwell, C.C.; Huang, A.; Arnold, F.H. *Angew. Chem. Int. Ed.* ***2016***, *55*, 4711.

[860] Mikami, K.; Nakai, T. *Synthesis* ***1991***, 594; Nakai, T.; Mikami, K. *Chem. Rev.* ***1986***, *86*, 885 (pp. 888–895). See also, Scheuplein, S.W.; Kusche, A.; Brückner, R.; Harms, K. *Chem. Ber.* ***1990***, *123*, 917; Wu, Y.; Houk, K.N.; Marshall, J.A. *J. Org. Chem.* ***1990***, *55*, 1421; Marshall, J.A.; Wang, X. *J. Org. Chem.* ***1990***, *55*, 2995.

or ion-pair mechanisms (**18-21**, **18-22**) and (ii) the concerted pericyclic [2,3]-sigmatropic rearrangement. These are easily distinguished since the latter always involves an allylic shift (as in the *Claisen rearrangemen*t), while the former pathway does not.

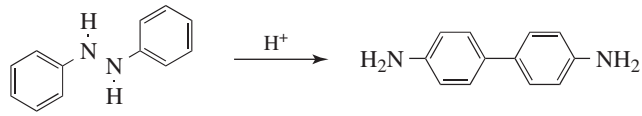
A [2,3]-sigmatropic rearrangement of allylic selenimides has been discussed.[861] The Rh-catalyzed [2,3]-sigmatropic rearrangement of sulfur ylids was reported,[862] as has the Cu-catalyzed rearrangement of propargylic sulfinates.[863] Another [2,3]-sigmatropic rearrangement, called the *Mislow-Evans rearrangement*,[864] converts allylic sulfoxides to **76**, and subsequently a rearranged allylic alcohol by treatment with a thiophilic reagent such as trimethyl phosphite.[865] In this case, the migration is from sulfur to oxygen.



76

[2,3]-Oxygen-to-sulfur migrations are also known.[866]
OS **VIII**, 427.

18-36 The Benzidine Rearrangement



Hydrazobenzene Benzidine

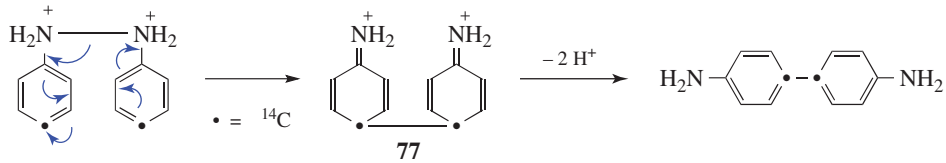
When hydrazobenzene is treated with acids, it rearranges to give ~70% 4,4′-diaminobiphenyl (benzidine) and ~30% 2,4′-diaminobiphenyl. This reaction is called the *benzidine rearrangement* and is general for *N*,*N*′-diarylhydrazines.[867] Usually, the major product is the 4,4′-diaminobiaryl, but four other products may also be produced: the 2,4′-diaminobiaryl (already referred to), the 2,2′-diaminobiaryl, and the *o*- and *p*-arylaminoanilines (called *semidines*). The 2,2′- and *p*-arylaminoaniline compounds are formed less often and in smaller amounts than the other two side products. Usually, the 4,4′-diaminobiaryl predominates, except when one or both *para* positions of the

[861] Armstrong, A.; Emmerson, D.P.G.; Milner, H.J.; Sheppard, R.J. *J. Org. Chem.* ***2014***, *79*, 3895.
[862] Zhang, H.; Wang, B.; Yi, H.; Zhang, Y.; Wang, J. *Org. Lett.* ***2015***, *17*, 3322.
[863] Hampton, C.S.; Harmata, M. *Tetrahedron Lett.* ***2015***, *56*, 3243.
[864] Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis*, 2nd ed., Wiley-Interscience, NJ, ***2005***, pp. 430–431. See Kleimark, J.; Prestat, G.; Poli, G.; Norrby, P.-O. *Chem. Eur. J.* ***2011***, *17*, 13963.
[865] Evans, D.A.; Andrews, G.C. *Acc. Chem. Res.* ***1974***, *7*, 147; Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* ***1989***, *54*, 2779; Bickart, P.; Carson, F.W.; Jacobus, J.; Miller, E.G.; Mislow, K. *J. Am. Chem. Soc.* ***1968***, *90*, 4869; Hoffmann, R.W. *Angew. Chem. Int. Ed.* ***1979***, *18*, 563.
[866] See Tamaru, Y.; Nagao, K.; Bando, T.; Yoshida, Z. *J. Org. Chem.* ***1990***, *55*, 1823.
[867] In Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, see the reviews by Cox, R.A.; Buncel, E., pp. 775–807 and Koga, G.; Koga, N.; Anselme, J., pp. 914–921. See Williams, D.L.H. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, Vol. 13, ***1972***, pp. 437–448. See Ghigo, G.; Maranzana, A.; Tonachini, G. *Tetrahedron* ***2012***, *68*, 2161; Ghigo, G.; Osella, S.; Maranzana, A.; Tonachini, G. *Eur. J. Org. Chem.* ***2011***, 2326.

diarylhydrazine are occupied. However, the 4,4′-diamine may still be produced even if the *para* positions are occupied. If SO_3H, CO_2H, or Cl (but not R, Ar, or NR_2) is present in the *para* position, that group may be ejected. With dinaphthylhydrazines, the major products are not the 4,4′-diaminobinaphthyls, but the 2,2′ isomers. Another side reaction is disproportionation to $ArNH_2$ and ArN=NAr. For example, *p*,*p*′-$PhC_6H_4NHNHC_6H_4Ph$ gives 88% disproportionation products at 25 °C.[868]

The mechanism has been exhaustively studied and several mechanisms have been proposed.[869] At one time it was believed that NHAr broke away from ArNHNHAr and became attached to the *para* position to give the semidine, which then went on to product, but this theory was disproved. An important discovery was the fact that, although the reaction is always first order in substrate, it can be either first[870] or second[871] order in $[H^+]$ but fractional orders can often be observed;[872] this is because at intermediate acidities, both first order and second order processes take place simultaneously. These kinetic results seem to indicate that the actual reacting species can be either the monoprotonated substrate $ArNHNH_2Ar$ or the diprotonated $ArNH_2NH_2Ar$.

Most of the proposed mechanisms[873] attempted to show how all five products could be produced by variations of a single process. An important breakthrough was the discovery that the two main products are formed in entirely different ways, as shown by isotope effect studies.[874] When the reaction was run with hydrazobenzene labeled with ^{15}N at both nitrogen atoms, the isotope effect was 1.022 for formation of benzidine, but 1.063 for formation of 2,4′-diaminobiphenyl. This showed that the N—N bond is broken in the rate-determining step in both cases, but the steps themselves are obviously different. When the reaction was run with hydrazobenzene labeled with ^{14}C at a *para* position, there was an isotope effect of 1.028 for formation of benzidine, but essentially no isotope effect (1.001) for formation of 2,4′-diaminobiphenyl. This can only mean that for the formation of benzidine the new C—C bond *and* breaking of the N—N bond both take place in the rate-determining step; in other words, the mechanism is concerted. The [5,5]-sigmatropic rearrangement shown accounts for this.[875] The diion **77** was obtained as a stable species in superacid solution at − 78 °C by treatment of hydrazobenzene with FSO_3H/SO_2 (SO_2ClF).[876]



77

[868] Shine, H.J.; Stanley, J.P. *J. Org. Chem.* ***1967***, *32*, 905. For investigations of the mechanism of the disproportionation reactions, see Rhee, E.S.; Shine, H.J. *J. Am. Chem. Soc.* ***1986***, *108*, 1000; ***1987***, *109*, 5052.

[869] For a history, see Shine, H.J. *J. Phys. Org. Chem.* ***1989***, *2*, 491.

[870] See Banthorpe, D.V.; O'Sullivan, M. *J. Chem. Soc. B* ***1968***, 627.

[871] Banthorpe, D.V.; Cooper, A.; O'Sullivan, M. *J. Chem. Soc. B* ***1971***, 2054.

[872] See Banthorpe, D.V.; Ingold, C.K.; O'Sullivan, M. *J. Chem. Soc. B* ***1968***, 624.

[873] Banthorpe, D.V.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1964***, 2864; Dewar, M.J.S. in de Mayo, P. *Molecular Rearrangments*, Vol. 1, Wiley, NY, ***1963***, pp. 323–344.

[874] Shine, H.J.; Zmuda, H.; Park, K.H.; Kwart, H.; Horgan, A.J.; Brechbiel, M. *J. Am. Chem. Soc.* ***1982***, *104*, 2501.

[875] This step was also part of the "polar-transition-state mechanism." See also reference 870.

[876] Olah, G.A.; Dunne, K.; Kelly, D.P.; Mo, Y.K. *J. Am. Chem. Soc.* ***1972***, *94*, 7438.

Although the results just given were obtained with hydrazobenzene, which reacts by the diprotonated pathway, monoprotonated substrates have been found to react by the same [5,5]-sigmatropic mechanism.[877] Some of the other rearrangements in this section are also sigmatropic. Thus, formation of the *p*-semidine takes place by a [1,5]-sigmatropic rearrangement,[878] and the conversion of 2,2′-hydrazonaphthalene to 2,2′-diamino-1,1′-binaphthyl takes place by a [3,3]-sigmatropic rearrangement.[879]

2,4′-Diaminobiphenyl is formed by a completely different mechanism, although the details are not known. There is rate-determining breaking of the N—N bond, but the C—C bond is not formed during this step.[880] The formation of the *o*-semidine also takes place by a nonconcerted pathway.[881] Under certain conditions, benzidine rearrangements have been found to go through radical cations.[882]

C. Other Cyclic Rearrangements

18-37 Metathesis of Alkenes (Alkene or Olefin Metathesis)[883]

$$CH_3CH{=}CHCH_2CH_3 \xrightarrow[WCl_6\text{-}EtOH]{EtAlCl_2} CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CHCH_2CH_3$$

When alkenes are treated with certain catalysts they are converted to other alkenes in an equilibrium reaction in which one set of alkylidene groups ($R^1R^2C{=}$) have become interchanged with other alkylidene groups ($R^3R^4C{=}$) by a process schematically illustrated by the equilibrium reaction shown. In the early example shown, pent-2-ene (either *cis*, *trans*, or a *cis-trans* mixture) is converted to a mixture of ~50% pent-2-ene, 25% but-2-ene, and 25% hex-3-ene. Nowadays, superior catalysts and experimental procedures have made this reaction synthetically useful (see below). The reaction is reversible,[884] so the alkene starting material and products exist in equilibrium.[885] In the example cited, the same mixture can be obtained by starting with equimolar quantities of but-2-ene and hex-3-ene. The reaction is called *metathesis* of alkenes or *alkene metathesis* (*olefin metathesis*).[886]

[877] Shine, H.J.; Park, K.H.; Brownawell, M.L.; San Filippo Jr., J. *J. Am. Chem. Soc.* ***1984***, *106*, 7077.

[878] See Shine, H.J.; Zmuda, H.; Kwart, H.; Horgan, A.G.; Brechbiel, M. *J. Am. Chem. Soc.* ***1982***, *104*, 5181.

[879] Shine, H.J.; Gruszecka, E.; Subotkowski, W.; Brownawell, M.; San Filippo Jr., J. *J. Am. Chem. Soc.* ***1985***, *107*, 3218.

[880] See Rhee, E.S.; Shine, H.J. *J. Am. Chem. Soc.* ***1986***, *108*, 1000; ***1987***, *109*, 5052.

[881] Rhee, E.S.; Shine, H.J. *J. Org. Chem.* ***1987***, *52*, 5633.

[882] See Nojima, M.; Ando, T.; Tokura, N. *J. Chem. Soc., Perkin Trans. 1* ***1976***, 1504.

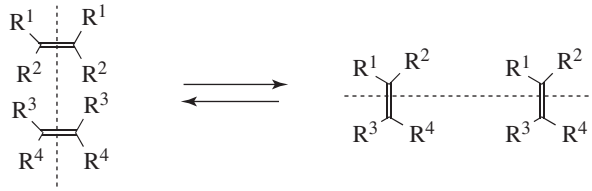
[883] Grubbs, R.H. *Tetrahedron* ***2004***, *60*, 7117; Wakamatsu, H.; Blechert, S. *Angew. Chem. Int. Ed.* ***2002***, *41*, 2403; Schrock, R.R.; Hoveyda, A.H. *Angew. Chem. Int. Ed.* ***2003***, *42*, 4592. See Chauvin, Y. *Angew. Chem. Int. Ed.* ***2006***, *45*, 3740; Schrock, R.R. *Angew. Chem. Int. Ed.* ***2006***, *45*, 3748; Grubbs, R.H. *Angew. Chem. Int. Ed.* ***2006***, *45*, 3760. See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 1002–1008.

[884] Smith III, A.B.; Adams, C.M.; Kozmin, S.A. *J. Am. Chem. Soc.* ***2001***, *123*, 990.

[885] See Hughes, W.B. *J. Am. Chem. Soc.* ***1970***, *92*, 532.

[886] *Olefin Metathesis: Theory and Practice*, Grela, K. (Ed.), Wiley, Hoboken, ***2014***; Dragutn, V.; Balaban, A.T.; Dimonie, M. *Olefin Metathesis and Ring-Opening Polymerization of Cyclo-Olefins*, Wiley, NY, ***1985***; Ivin, K.J. *Olefin Metathesis*, Academic Press, NY, ***1983***; Schrock, R.R. *J. Organomet. Chem.* ***1986***, *300*, 249; Grubbs, R.H. in Wilkinson, G. *Comprehensive Organometallic Chemistry*, Vol. 8, Pergamon, Elmsford, NY, ***1982***, pp. 499–551; Grubbs, R.H. *Prog. Inorg. Chem.* ***1978***, *24*, 1; Calderon N. *Acc. Chem. Res.* ***1972***, *5*, 127; Katz, T.J. *Adv. Organomet. Chem.* ***1977***, *16*, 283; Haines, R.J.; Leigh, G.J. *Chem. Soc. Rev.* ***1975***, *4*, 155.

In an example, a mixture of $R^1R^2C{=}CR^1R^2$ and $R^3R^4C{=}CR^3R^4$ gives rise to only one new alkene ($R^1R^2C{=}CR^3R^4$), while in the most general case, the reaction of two alkenes $R^1R^2C{=}CR^3R^4$ and $R^5R^6C{=}CR^7R^8$ can give a mixture of 10 alkenes: the original 2 + 8 new ones.



In early work, W, Mo,[887] or Re complexes were used. With simple alkenes the proportions of products are generally statistical,[888] which limited the synthetic utility of the reaction since the yield of any one product is low. In some cases one alkene may be more or less thermodynamically stable than the rest, so that the proportions are not statistical in all cases. Work has been done toward a model for alkene ring-closing metathesis.[889]

It is possible to shift the equilibrium to favor certain products. For example, 2-methylbut-1-ene gives rise to ethylene and 3,4-dimethylhex-3-ene. By allowing the gaseous ethylene to escape, the yield of 3,4-dimethylhex-3-ene can be raised to 95%.[890] This example shows that it is possible to tailor the substrate to include two terminal alkenes that then lead to ethylene as a product, whose escape from the reaction drives the equilibrium to product. Copper iodide is an effective co-catalyst for alkene cross metathesis.[891]

The generally accepted mechanism is a chain mechanism,[892] involving the intervention of a metal-carbene complex (**78** and **79**)[893] and a four-membered ring containing a metal[894] (**80**–**83**).[895]

[887] See Crowe, W.E.; Zhang, Z.J. *J. Am. Chem. Soc.* ***1993***, *115*, 10998. Fu, G.C.; Grubbs, R.H. *J. Am. Chem. Soc.* ***1993***, *115*, 3800. See Kotha, S.; Dipak, M.K. *Tetrahedron* ***2012***, *68*, 397.

[888] Calderon, N.; Ofstead, E.A.; Ward, J.P.; Judy, W.A.; Scott, K.W. *J. Am. Chem. Soc.* ***1968***, *90*, 4133.

[889] Nelson, D.J.; Ashworth, D.C.W.A.; Percy, J.M. *J. Org. Chem.* ***2011***, *76*, 8386.

[890] Knoche, H. *Ger. Pat.* (*Offen.*) 2024835, ***1970*** (*Chem. Abstr.* ***1971***, *74*, 44118b). See also, Ichikawa, K.; Fukuzumi, K. *J. Org. Chem.* ***1976***, *41*, 2633; Baker, R.; Crimmin, M.J. *Tetrahedron Lett.* ***1977***, 441.

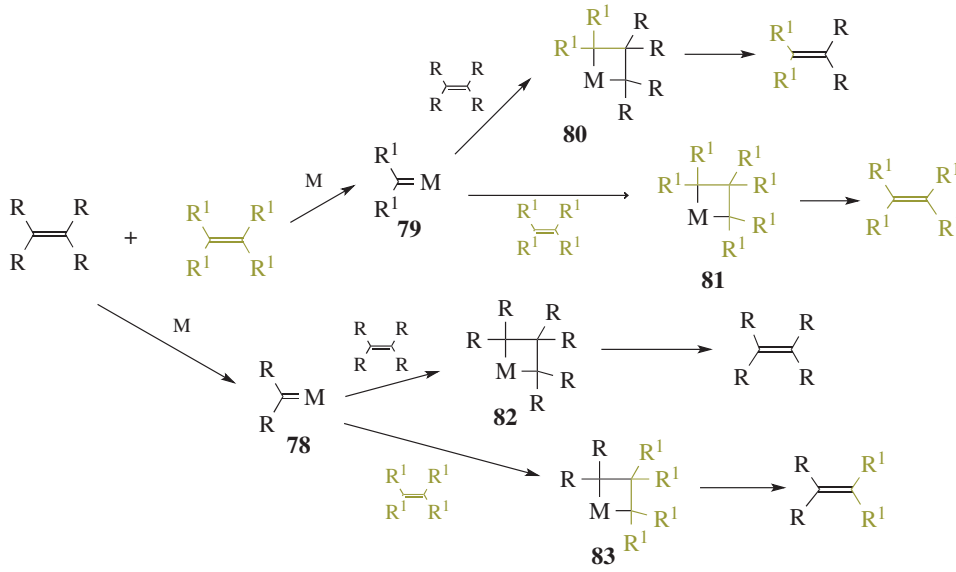
[891] Voigtritter, K.; Ghorai, S.; Lipshutz, B.H. *J. Org. Chem.* ***2011***, *76*, 4697.

[892] See Sanford, M.S.; Love, J.A.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2001***, *123*, 6543; Cavallo, L. *J. Am. Chem. Soc.* ***2002***, *124*, 8965; Adlhart, C.; Chen, P. *J. Am. Chem. Soc.* ***2004***, *126*, 3496.

[893] See Crabtree, R.H. *The Organometallic Chemistry of the Transition Metals*, Wiley, NY, ***1988***, pp. 244–267; Kingsbury, J.S.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2005***, *127*, 4510; Poater, A.; Solans-Monfort, X.; Clot, E.; Copéret, C.; Eisenstein, O. *J. Am. Chem. Soc.* ***2007***, *129*, 8207; Vyboishchikov, S.F.; Thiel, W. *Chem. Eur. J.* ***2005***, *11*, 3921.

[894] See Collman, J.C.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA, ***1987***, pp. 459–520; Lindner, E. *Adv. Heterocycl. Chem.* ***1986***, *39*, 237. See Romero, P.E.; Piers, W.E. *J. Am. Chem. Soc.* ***2007***, *129*, 1698.

[895] See Grubbs, R.H. *Prog. Inorg. Chem.* ***1978***, *24*, 1; Katz, T.J. *Adv. Organomet. Chem.* ***1977***, *16*, 283. See also, Kress, J.; Osborn, J.A.; Greene, R.M.E.; Ivin, K.J.; Rooney, J.J. *J. Am. Chem. Soc.* ***1987***, *109*, 899; Feldman, J.; Davis, W.M.; Schrock, R.R. *Organometallics* ***1989***, *8*, 2266.



In the cross-metathesis reaction shown as an example, $R_2C{=}CR_2$ reacts with $R^1{}_2C{=}CR^1{}_2$ in the presence of a metal catalyst, M. Initial reaction with the catalyst leads to the two expected metal carbenes, **78** and **79**. Metal carbene **79** can react with both alkenes to form metallocyclobutanes **80** and **81**. Each of these intermediates loses the metal to form alkenes, either the product of metathesis $R_2C{=}CR^1{}_2$ or one of the original alkenes. In a likewise manner, **78** reacts with each alkene to form metallocyclobutanes **82** and **83**, which decompose to $R_2C{=}CR_2$ (one of the original alkenes) and the metathesis product. It has been shown that the phosphine-containing methylidene complexes decompose to methylphosphonium salts.[896]

The development of better catalysts has revolutionized this reaction,[897] making it one of the most important methods available for modern synthesis. Both homogeneous[898] and heterogeneous[899] catalysts have been used for this reaction. Of the many homogeneous catalysts, Ru complexes are the most important,[900] and important heterogeneous catalysts include oxides of Mo, W, and Re deposited on alumina or silica gel.[901] The major

[896] Hong, S.H.; Wenzel, A.G.; Salguero, T.T.; Day, M.W.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2007***, *129*, 7961.

[897] Amakawa, K.; Wrabetz, S.; Kröhnert, J.; Tzolova-Müller, G.; Schlögl, R.; Trunschke, A. *J. Am. Chem. Soc.* ***2012***, *134*, 11462. See Inagaki, S.; Ikeda, H. *Tetrahedron Lett.* ***2014***, *55*, 6435; Skowerski, K.; Kasprzycki, P.; Bieniek, M.; Olszewski, T.K. *Tetrahedron* ***2013***, *69*, 7408; Khumsubdee, S.; Burgess, K. *Tetrahedron* ***2014***, *70*, 1326; Chen, S.-W.; Zhang, Z.-C.; Zhai, N.-N.; Zhong, C.-M.; Lee, S.-g. *Tetrahedron* ***2015***, *71*, 648; Szadkowska, A.; Samojłowicz, C.; Grela, K. *Pure Appl. Chem.* ***2011***, *83*, 553.

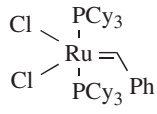
[898] Calderon N.; Chen, H.Y.; Scott, K.W. *Tetrahedron Lett.* ***1967***, 3327. See Hughes, W.B. *Organomet. Chem. Synth.* ***1972***, *1*, 341 (see pp. 362–368). Toreki, R.; Schrock, R.R. *J. Am. Chem. Soc.* ***1990***, *112*, 2448.

[899] Banks, R.L.; Bailey, G.C. *Ind. Eng. Chem. Prod. Res. Dev.* ***1964***, *3*, 170. See also, Banks, R.L. *CHEMTECH* ***1986***, 112.

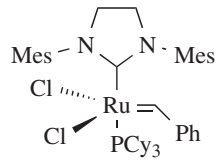
[900] Gilbertson, S.R.; Hoge, G.S.; Genov, D.G. *J. Org. Chem.* ***1998***, *63*, 10077; Maier, M.E.; Bugl, M. *Synlett* ***1998***, 1390; Stefinovic, M.; Snieckus, V. *J. Org. Chem.* ***1998***, *63*, 2808.

[901] See Banks, R.L. *Fortschr. Chem. Forsch.* ***1972***, *25*, 39 (pp. 41–46).

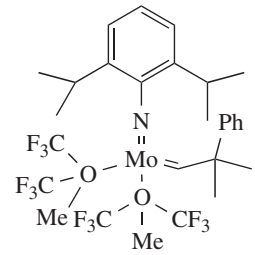
breakthrough in these catalysts was the development of catalysts that are relatively air stable. Three important catalysts are metal carbene complexes **84**[902] and **85**[903] (*Grubbs catalyst I and II*, respectively; Mes = mesityl), and **86** (the *Shrock catalyst*).[904] Catalyst **85** can be generated *in situ* from air-stable precursors.[905]



84



85



86

The exploration of Ru catalysts continues to be an important area of research. The synthetic importance[906] of ring-closing and ring-opening[907] metathesis reactions has, in part, led to the ongoing development of new catalysts.[908] A metal-free ring-opening metathesis polymerization has been developed.[909] Catalysts have been developed that are compatible with both water and methanol.[910] The reaction is compatible with the presence of other functional groups,[911] such as other alkene units,[912] carbonyl units,[913] allyl alcohols,[914]

[902] Schwab, P.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* ***1996***, *118*, 100.

[903] Scholl, M.; Ding, S.; Lee, C.W.; Grubbs, R.H. *Org. Lett.* ***1999***, *1*, 953; Xi, Z.; Bazzi, H.S.; Gladysz, J.A. *Org. Lett.* ***2011***, *13*, 6188; Kobayashi, Y.; Miyazaki, H.; Inukai, S.; Takagi, C.; Makino, R.; Shimowaki, K.; Igarashi, R.; Sugiyama, Y.; Nakamura, S.; Matsugi, M. *Synlett* ***2016***, *27*, 2352.

[904] Bazan, G.C.; Oskam, J.H.; Cho, H.-N.; Park, L.Y.; Schrock, R.R. *J. Am. Chem. Soc.* ***1991***, *113*, 6899, and references cited therein; Conley, M.P.; Mougel, V.; Peryshkov, D.V.; Forrest Jr., W.P.; Gajan, D.; Lesage, A.; Emsley, L.; Copéret, C.; Schrock, R.R. *J. Am. Chem. Soc.* ***2013***, *135*, 19068; Torker, S.; Khan, R.K.M.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2014***, *136*, 3429.

[905] Louie, J.; Grubbs, R.H. *Angew. Chem. Int. Ed.* ***2001***, *40*, 247.

[906] See Nicolaou, K.C.; Bulger, P.G.; Sarlah, D. *Angew. Chem. Int. Ed.* ***2005***, *44*, 4490; Donohoe, T.J.; Fishlock, L.P.; Procopiou, P.A. *Chem. Eur. J.* ***2008***, *14*, 5716; Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed.* ***2006***, *45*, 6086; Higman, C.S.; Lummiss, J.A.M.; Fogg, D.E. *Angew. Chem. Int. Ed.* ***2016***, *55*, 3552.

[907] Kobayashi, S.; Pitet, L.M.; Hillmyer, M.A. *J. Am. Chem. Soc.* ***2011***, *133*, 5794; Keitz, B.K.; Fedorov, A.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2012***, *134*, 2040; Blencowe, A.; Qiao, G.G. *J. Am. Chem. Soc.* ***2013***, *135*, 5717; Ogawa, K.A.; Goetz, A.E.; Boydston, A.J. *Synlett* ***2016***, *27*, 203.

[908] Rosebrugh, L.E.; Herbert, M.B.; Marx, V.M.; Keitz, B.K.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2013***, *135*, 1276; Occhipinti, G.; Hansen, F.R.; Törnroos, K.W.; Jensen, V.R. *J. Am. Chem. Soc.* ***2013***, *135*, 3331; Miyazaki, H.; Herbert, M.B.; Liu, P.; Dong, X.; Xu, X.; Keitz, B.K.; Ung, T.; Mkrtumyan, G.; Houk, K.N.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2013***, *135*, 5848; Cannon, J.S.; Grubbs, R.H. *Angew. Chem. Int. Ed.* ***2013***, *52*, 9001; Herbert, M.B.; Grubbs, R.H. *Angew. Chem. Int. Ed.* ***2015***, *54*, 5018; Ahmed, T.S.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2017***, *139*, 1532; Sues, P.E.; Bukhryakov, K.V.; Schrock, R.R. *Helv. Chim. Acta* ***2017***, *100*, e1700181. See references cited in these references.

[909] Ogawa, K.A.; Goetz, A.E.; Boydston, A.J. *J. Am. Chem. Soc.* ***2015***, *137*, 1400.

[910] Kirkland, T.A.; Lynn, D.M.; Grubbs, R.H. *J. Org. Chem.* ***1998***, *63*, 9904.

[911] See Deiter, S.A.; Martin, S.F. *Chem. Rev.* ***2004***, *104*, 2199.

[912] See Grotevendt, A.G.D.; Lummiss, J.A.M.; Mastronardi, M.L.; Fogg, D.E. *J. Am. Chem. Soc.* ***2011***, *133*, 15918.

[913] Schneider, M.F.; Junga, H.; Blechert, S. *Tetrahedron* ***1995***, *51*, 13003.

[914] Moulins, J.R.; Burnell, D.J. *Tetrahedron Lett.* ***2011***, *52*, 3992.

carbonyl alkenes,[915] the alkene unit of conjugated esters,[916] butenolides[917] and other lactones,[918] amines,[919] amides,[920] sulfones,[921] phosphine oxides,[922] dienyl phosphonates,[923] alkenyl boronates,[924] sulfonate esters,[925] and sulfonamides.[926] Ether groups,[927] including vinyl ethers,[928] vinyl halides,[929] vinyl silanes,[930] vinyl sulfones,[931] allylic ethers,[932] and thioethers[933] are also compatible.

Molybdenum/tungsten complexes have been explored for (*Z*)-selective metathesis,[934] and W catalysts have been developed.[935] Metal-free metathesis reactions have been developed.[936] A mechanochemical Ru-catalyzed metathesis has been developed.[937] Solid-state metathesis reactions are known.[938] Polyethylene-oligomer-supported *N*-heterocyclic carbene ligands were converted to their Ru complexes and used as metathesis catalysts.[939] Artificial metalloenzymes have been developed as metathesis catalysts,[940] as do artificial metalloproteins.[941] Ring-closing metathesis has been reported in aqueous micellar medium.[942]

Asymmetric ring-closing metathesis reactions have been reported,[943] and chiral metathesis catalysts are continually being developed.[944] Stereoretentive alkene metathesis has been reported.[945] The enantioselective synthesis of bicyclic lactams from dienyl

[915] Ludwig, J.R.; Schindler, C.S. *Synlett* ***2017***, *28*, 1501.
[916] Lee, C.W.; Grubbs, R.H. *J. Org. Chem.* ***2001***, *66*, 7155.
[917] Paquette, L.A.; Méndez-Andino, J. *Tetrahedron Lett.* ***1999***, *40*, 4301.
[918] Brimble, M.A.; Trzoss, M. *Tetrahedron* ***2004***, *60*, 5613.
[919] Dolman, S.J.; Sattely, E.S.; Hoveyda, A.H.; Schrock, R.R. *J. Am. Chem. Soc.* ***2002***, *124*, 6991.
[920] See Ma, S.; Ni, B.; Liang, Z. *J. Org. Chem.* ***2004***, *69*, 6305.
[921] Yao, Q. *Org. Lett.* ***2002***, *4*, 427.
[922] Demchuk, O.M.; Pietrusiewicz, K.M.; Michrowska, A.; Grela, K. *Org. Lett.* ***2003***, *5*, 3217.
[923] Schmidt, B.; Kunz, O. *Org. Lett.* ***2013***, *15*, 4470.
[924] Hemelaere, R.; Carreaux, F.; Carboni, B. *J. Org. Chem.* ***2013***, *78*, 6786.
[925] LeFlohic, A.; Meyer, C.; Cossy, J.; Desmurs, J.-R.; Galland, J.-C. *Synlett* ***2003***, 667.
[926] See Kinderman, S.S.; van Maarseveen, J.H.; Schoemaker, H.E.; Hiemstra, H.; Rutjes, F.P.J.T. *Org. Lett.* ***2001***, *3*, 2045.
[927] Edwards, S.D.; Lewis, T.; Taylor, R.J.K. *Tetrahedron Lett.* ***1999***, *40*, 4267.
[928] See Rainier, J.D.; Cox, J.M.; Allwein, S.P. *Tetrahedron Lett.* ***2001***, *42*, 179.
[929] Chao, W.; Weinreb, S.M. *Org. Lett.* ***2003***, *5*, 2505.
[930] Schuman, M.; Gouverneur, V. *Tetrahedron Lett.* ***2002***, *43*, 3513.
[931] Kim, S.; Lim, C.J. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3265.
[932] Delgado, M.; Martín, J.D. *Tetrahedron Lett.* ***1997***, *38*, 6299; Miller, S.J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R.H. *J. Am. Chem. Soc.* ***1995***, *117*, 2108.
[933] Leconte, M.; Pagano, S.; Mutch, A.; Lefebvre, F.; Basset, J.M. *Bull. Soc. Chim. Fr.* ***1995***, *132*, 1069.
[934] See Kiesewetter, E.T.; O'Brien, R.V.; Yu, E.C.; Meek, S.J.; Schrock, R.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2013***, *135*, 6026; Schrock, R.R. *Chem. Commun.* ***2013***, *49*, 5529.
[935] Schowner, R.; Frey, W.; Buchmeiser, M.R. *J. Am. Chem. Soc.* ***2015***, *137*, 6188.
[936] Grange, R.L.; Evans, P.A. *J. Am. Chem. Soc.* ***2014***, *136*, 11870.
[937] Do, J.-L.; Mottillo, C.; Tan, D.; Štrukil, V.; Friščić, T. *J. Am. Chem. Soc.* ***2015***, *137*, 2476.
[938] Martinolich, A.J.; Kurzman, J.A.; Neilson, J.R. *J. Am. Chem. Soc.* ***2016***, *138*, 11031.
[939] Hobbs, C.; Yang, Y.-C.; Ling, J.; Nicola, S.; Su, H.-L.; Bazzi, H.S.; Bergbreiter, D.E. *Org. Lett.* ***2011***, *13*, 3904.
[940] Lo, C.; Ringenberg, M.R.; Gnandt, D.; Wilson, Y.; Ward, T.R. *Chem. Commun.* ***2011***, *47*, 12065; Mayer, C.; Gilingham, D.G.; Ward, T.R.; Hilvert, D. *Chem. Commun.* ***2011***, *47*, 12068.
[941] For a review, see Sauer, D.F.; Gotzen, S.; Okuda, J. *Org. Biomol. Chem.* ***2016***, *14*, 9174.
[942] Laville, L.; Charnay, C.; Lamaty, F.; Martinez, J.; Colacino, E. *Chem. Eur. J.* ***2012***, *18*, 760.
[943] Cefalo, D.R.; Kiely, A.F.; Wuchrer, M.; Jamieson, J.Y.; Schrock, R.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2001***, *123*, 3139.
[944] See Funk, T.W.; Berlin, J.M.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2006***, *128*, 1840.
[945] Montgomery, T.P.; Ahmed, T.S.; Grubbs, R.H. *Angew. Chem. Int. Ed.* ***2017***, *56*, 11024.

lactams used a chiral Mo catalyst.[946] Asymmetric ring-opening metathesis has also been reported.[947]

Recyclable catalysts have been developed,[948] and the reaction has been done in ionic liquids,[949] supercritical CO_2[950] (Sec. 9.D.ii), and in aqueous media.[951] Microwave-induced ring-closing metathesis[952] and also cross-metathesis reactions[953] are known. Polymer-bound Ru catalysts[954] and Mo catalysts[955] have been used, and catalyst **85** has been immobilized on polyethylene glycol (PEG).[956] Efficient methods have been developed for the removal of Ru by-products from metathesis reactions that include the use of a scavenger resin[957] and removal by aqueous extraction.[958] It is noted that an alkane metathesis reaction is known.[959]

By choice of the proper catalyst, the reaction has been applied to terminal and internal alkenes, straight chain or branched. The effect of substitution on the ease of reaction is $CH_2{=}{>}RCH_2CH{=}{>}R_2CHCH{=}{>}R_2C{=}$.[960] Note that isomerization of the C=C unit can occur after metathesis,[961] but methods have been developed to prevent this, including addition of 2,6-dichlorobenzoquinone.[962] Cross metathesis[963] (or symmetrical homometathesis[964]) of alkenes to give new alkenes can be accomplished. Monosubstituted alkenes react faster than disubstituted alkenes.[965] A double metathesis reaction of a diene (also called *domino metathesis*[966] or *tandem metathesis*[967]) with conjugated aldehydes has been reported,[968] and a triple metathesis was reported for a dihydropyran with two dihydropyran substituents.[969] Cross metathesis of vinylcyclopropanes leads to an alkene with

[946] Sattely, E.S.; Cortez, G.A.; Moebius, D.C.; Schrock, R.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2005***, *127*, 8526.
[947] Gillingham, D.G.; Kataoka, O.; Garber, S.B.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2004***, *126*, 12288.
[948] Kingsbury, J.S.; Harrity, J.P.A.; Bonitatebus Jr., P.J.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1999***, *121*, 791.
[949] Buijsman, R.C.; van Vuuren, E.; Sterrenburg, J.G. *Org. Lett.* ***2001***, *3*, 3785. See Clavier, H.; Audic, N.; Mauduit, M.; Guillemin, J.-C. *Chem. Commun.* ***2004***, 2282.
[950] Fürstner, A.; Ackermann, L.; Beck, K.; Hori, H.; Koch, D.; Langemann, K.; Liebl, M.; Six, C.; Leitner, W. *J. Am. Chem. Soc.* ***2001***, *123*, 9000.
[951] See Burtscher, D.; Grela, K. *Angew. Chem. Int. Ed.* ***2009***, *48*, 442.
[952] See Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* ***2008***, 1125. For a solvent-free microwave-induced reaction, see Thanh, G.V.; Loupy, A. *Tetrahedron Lett.* ***2003***, *44*, 9091.
[953] Bargiggia, F.C.; Murray, W.V. *J. Org. Chem.* ***2005***, *70*, 9636.
[954] Yao, Q. *Angew. Chem. Int. Ed.* ***2000***, *39*, 3896; Schürer, S.C.; Gessler, S.; Buschmann, N.; Blechert, S. *Angew. Chem. Int. Ed.* ***2000***, *39*, 3898.
[955] Hultzsch, K.C.; Jernelius, J.A.; Hoveyda, A.H.; Schrock, R.R. *Angew. Chem. Int. Ed.* ***2002***, *41*, 589.
[956] A recyclable catalyst, see Yao, Q.; Motta, A.R. *Tetrahedron Lett.* ***2004***, *45*, 2447.
[957] Cho, J.H.; Kim, B.M. *Org. Lett.* ***2003***, *5*, 531. See Westhus, M.; Gonthier, E.; Brohm, D.; Breinbauer, R. *Tetrahedron Lett.* ***2004***, *45*, 3141.
[958] Hong, S.H.; Grubbs, R.H. *Org. Lett.* ***2007***, *9*, 1955.
[959] See Basset, J.-M.; Copret, C.; Soulivong, D.; Taoufik, M.; Cazat, J.T. *Acc. Chem. Res.* ***2010***, *43*, 323.
[960] See Chatterjee, A.K.; Choi, T.-L.; Sanders, D.P.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2003***, *125*, 11360.
[961] See Schmidt, B. *J. Org. Chem.* ***2004***, *69*, 7672; Sutton, A.E.; Seigal, B.A.; Finnegan, D.F.; Snapper, M.L. *J. Am. Chem. Soc.* ***2002***, *124*, 13390.
[962] Hong, S.H.; Sanders, D.P.; Lee, C.W.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2005***, *127*, 17160.
[963] See Stewart, I.C.; Douglas, C.J.; Grubbs, R.H. *Org. Lett.* ***2008***, *10*, 441; Lipshutz, B.H.; Aguinaldo, G.T.; Ghorai, S.; Voigtritter, K. *Org. Lett.* ***2008***, *10*, 1325.
[964] Blanco, O.M.; Castedo, L. *Synlett* ***1999***, 557.
[965] See Lautens, M.; Maddess, M.L. *Org. Lett.* ***2004***, *6*, 1883.
[966] Rückert, A.; Eisele, D.; Blechert, S. *Tetrahedron Lett.* ***2001***, *42*, 5245.
[967] Choi, T.-L.; Grubbs, R.H. *Chem. Commun.* ***2001***, 2648.
[968] See van Otterlo, W.A.L.; Ngidi, E.L.; de Koning, C.D.; Fernandes, M.A. *Tetrahedron Lett.* ***2004***, *45*, 659.
[969] Sundararajan, G.; Prabagaran, N.; Varghese, B. *Org. Lett.* ***2001***, *3*, 1973.

two cyclopropyl substituents.[970] Vinylcyclopropane-alkyne metathesis reactions have been reported.[971]

Dienes can react intermolecularly or intramolecularly.[972] Intramolecular reactions generate rings, including small rings,[973] usually alkenes or dienes. Alkene metathesis can be used to form very large rings, including 21-membered lactone rings.[974] Diynes undergo both cross metathesis and ring-closing metathesis.[975] Diynes can also react intramolecularly to give large-ring alkynes.[976] Metathesis with vinyl cyclopropyl alkynes is also known, producing a ring-expanded product.[977] Vinyl halides undergo metathesis reactions.[978] Two cyclic alkenes react to give dimeric dienes in the metathesis reaction of cyclopentene to give cyclodeca-1,6-diene.[979] With many catalysts, the products can then react with additional monomers and with each other, so that polymers are produced, and the cyclic dienes are obtained only in low yield. The reaction between a cyclic and a linear alkene can give a ring-opened diene.[980] The reaction has also been applied to internal alkynes,[981] and some success has been reported for terminal triple bonds.[982] As noted above, molecules with a terminal alkene and a terminal alkyne react quite well (ene-yne metathesis).[983] Intramolecular reactions of a double bond with a triple bond are known[984] and a tetracyclic tetraene has been prepared from a poly-yne-diene.[985] Cross metathesis of terminal alkynes and terminal alkenes (en-ynes)[986] to give a diene has also been reported.[987] En-yne metathesis generates 1,3-dienes.[988]

[970] Verbicky, C.A.; Zercher, C.K. *Tetrahedron Lett.* ***2000***, *41*, 8723.

[971] López, F.; Delgado, A.; Rodríguez, J.R.; Castedo, L.; Mascareñas, J.L. *J. Am. Chem. Soc.* ***2004***, *126*, 10262.

[972] See Grubbs, R.H.; Miller, S.J.; Fu, G.C. *Acc. Chem. Res.* ***1995***, *28*, 446.

[973] Grela, K. *Angew. Chem. Int. Ed.* ***2008***, *47*, 5504.

[974] Fürstner, A.; Langemann, K. *J. Org. Chem.* ***1996***, *61*, 3942. Also see, Goldring, W.P.D.; Hodder, A.S.; Weiler, L. *Tetrahedron Lett.* ***1998***, *39*, 4955; Ghosh, A.K.; Hussain, K.A. *Tetrahedron Lett.* ***1998***, *39*, 1881.

[975] See Kim, M.; Miller, R.L.; Lee, D. *J. Am. Chem. Soc.* ***2005***, *127*, 12818.

[976] Chen, F.-E.; Kuang, Y.-Y.; Dai, H.-F.; Lu, L.; Huo, M. *Synthesis* ***2003***, 2629.

[977] Wender, P.A.; Sperandio, D. *J. Org. Chem.* ***1998***, *63*, 4164.

[978] Macnaughtan, M.L.; Johnson, M.J.A.; Kampf, J.W. *J. Am. Chem. Soc.* ***2007***, *129*, 7708.

[979] Calderon, N.; Ofstead, E.A.; Judy, W.A. *J. Polym. Sci. Part A-1* ***1967***, *5*, 2209; Wasserman, E.; Ben-Efraim, D.A.; Wolovsky, R. *J. Am. Chem. Soc.* ***1968***, *90*, 3286; Wolovsky, R.; Nir, Z. *Synthesis* ***1972***, 134.

[980] Rossi, R.; Diversi, P.; Lucherini, A.; Porri, L. *Tetrahedron Lett.* ***1974***, 879; Lal, J.; Smith, R.R. *J. Org. Chem.* ***1975***, *40*, 775.

[981] See Du, Y.; Yang, H.; Zhu, C.; Ortiz, M.; Okochi, K.D.; Shoemaker, R.; Jin, Y.; Zhang, W. *Chem. Eur. J.* ***2016***, *22*, 7959. For reviews, see Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett* ***1992***, 539; Fürstner, A.; Davies, P.W. *Chem. Commun.* ***2005***, 2307.

[982] Couteliera, O.; Mortreux, A. *Adv. Synth. Catal.* ***2006***, *348*, 2038; Mortreux, A.; Petit, F.; Petit, M.; Szymanska-Buza, T. *J. Mol. Catal. A: Chem.* ***1995***, *96*, 95. However, see McCullough, L.G.; Listemann, M.L.; Schrock, R.R.; Churchill, M.R.; Ziller, J.W. *J. Am. Chem. Soc.* ***1983***, *105*, 6729.

[983] See Kitamura, T.; Mori, M. *Org. Lett.* ***2001***, *3*, 1161.

[984] See Gilbertson, S.R.; Hoge, G.S. *Tetrahedron Lett.* ***1998***, *39*, 2075.

[985] Zuercher, W.J.; Scholl, M.; Grubbs, R.H. *J. Org. Chem.* ***1998***, *63*, 4291.

[986] See Griffiths, J.R.; Keister, J.B.; Diver, S.T. *J. Am. Chem. Soc.* ***2016***, *138*, 5380; Wallace, D.J.; Reamer, R.A. *J. Org. Chem.* ***2014***, *79*, 5644; Laroche, B.; Detraz, M.; Blond, A.; Dubost, L.; Mailliet, P.; Nay, B. *J. Org. Chem.* ***2015***, *80*, 5359.

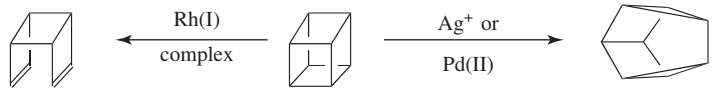
[987] Poulsen, C.S.; Madsen, R. *Synthesis* ***2003***, 1. See Lee, H.-Y.; Kim, B.G.; Snapper, M.L. *Org. Lett.* ***2003***, *5*, 1855; Kim, M.; Park, S.; Maifeld, S.V.; Lee, D. *J. Am. Chem. Soc.* ***2004***, *126*, 10242. See also, Kang, B.; Kim, D.-h.; Do, Y.; Chang, S. *Org. Lett.* ***2003***, *5*, 3041.

[988] Hansen, E.C.; Lee, D. *Acc. Chem. Res.* ***2006***, *39*, 509; Debleds, O.; Campagne, J.-M. *J. Am. Chem. Soc.* ***2008***, *130*, 1562. For a mechanistic study, see Galan, B.R.; Giessert, A.J.; Keister, J.B.; Diver, S.T. *J. Am. Chem. Soc.* ***2005***, *127*, 5762.

Ring-opening metathesis generates dienes from cyclic alkenes.[989] Allenes undergo a metathesis reaction to give symmetrical allenes.[990] An interesting variation reacts an α,ω-diene with a cyclic alkene. The combination of ring-opening metathesis and ring-closing cross metathesis leads to ring expansion to give a macrocyclic nonconjugated diene.[991]

OS **80**, 85; **81**, 1.

18-38 Metal Ion-Catalyzed σ-Bond Rearrangements

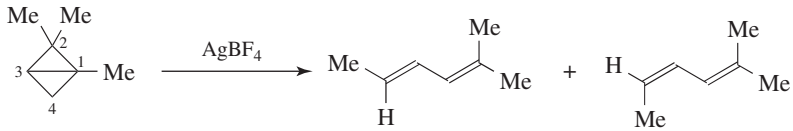


87 Cubane Cuneane

Many highly strained cage molecules undergo rearrangement when treated with metallic ions, such as Ag^+, Rh(I), or Pd(II).[992] The bond rearrangements observed are formally classified into two main types: type 1 are [2 + 2] ring openings of cyclobutanes and type 2 are conversions of a bicyclo[2.2.0] system to a bicyclopropyl system. The molecule cubane supplies an example of each type. Treatment with Rh complexes converts cubane to tricyclo[4.2.0.$0^{2,5}$]octa-3,7-diene (**87**),[993] an example of type 1, while Ag^+ or Pd(II) causes the second type of reaction, producing cuneane.[994]

The mechanisms of these reactions are not completely understood, although relief of strain undoubtedly supplies the driving force. The reactions are thermally forbidden by the orbital symmetry rules, and the role of the catalyst is to provide low-energy pathways so that the reactions can take place. The type 1 reactions are the reverse of the catalyzed [2 + 2] ring closures discussed at **15-59**.

Simple bicyclobutanes can also be converted to dienes, but in this case the products usually result from cleavage of the central bond and one of the edge bonds.[995] For example, treatment of **88** with $AgBF_4$[996] or $[(\pi\text{-allyl})PdCl]_2$[997] gives a mixture of the two dienes shown, resulting from a formal cleavage of the C-1—C-3 and C-1—C-2 bonds (note that a hydride shift has taken place).

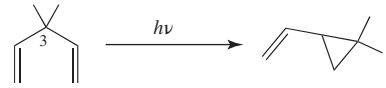


88

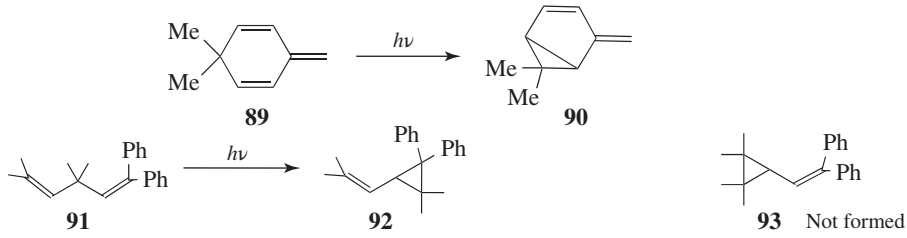
Dienes can also be converted to bicyclobutanes under photochemical conditions.[998]

[989] See Morgan, J.P.; Morrill, C.; Grubbs, R.H. *Org. Lett.* ***2002***, *4*, 67.
[990] Ahmed, M.; Arnauld, T.; Barrett, A.G.M.; Braddock, D.C.; Flack, K.; Procopiou, P.A. *Org. Lett.* ***2000***, *2*, 551.
[991] Lee, C.W.; Choi, T.-L.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2002***, *124*, 3224.
[992] Halpern, J. in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 705–721; Bishop III, K.C. *Chem. Rev.* ***1976***, *76*, 461; Paquette, L.A. *Synthesis* ***1975***, 347; *Acc. Chem. Res.* ***1971***, *4*, 280.
[993] Eaton, P.E.; Chakraborty, U.R. *J. Am. Chem. Soc.* ***1978***, *100*, 3634.
[994] Cassar, L.; Eaton, P.E.; Halpern, J. *J. Am. Chem. Soc.* ***1970***, *92*, 6336.
[995] See Paquette, L.A.; Zon, G. *J. Am. Chem. Soc.* ***1974***, *96*, 203, 224.
[996] Paquette, L.A.; Henzel, R.P.; Wilson, S.E. *J. Am. Chem. Soc.* ***1971***, *93*, 2335.
[997] Gassman, P.G.; Meyer, R.G.; Williams, F.J. *Chem. Commun.* ***1971***, 842.
[998] Garavelli, M.; Frabboni, B.; Fato, M.; Celani, P.; Bernardi, F.; Robb, M.A.; Olivucci, M. *J. Am. Chem. Soc.* ***1999***, *121*, 1537.

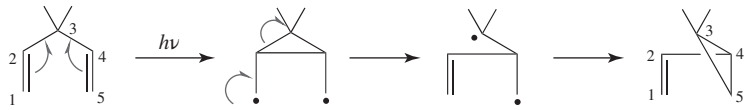
18-39 The Di-π-Methane and Related Rearrangements



1,4-Dienes carrying alkyl or aryl substituents on C-3[999] can be photochemically rearranged to vinylcyclopropanes in a reaction called the *di-π-methane rearrangement*.[1000] An example is conversion of **89** to **90**.[1001] For most 1,4-dienes it is only the singlet excited state that gives the reaction; triplet states generally take other pathways.[1002] For unsymmetrical dienes, the reaction is regioselective. For example, **91** gave **92**, not **93**.[1003]



The mechanism can be described by the diradical pathway given[1004] (the C-3 substituents act to stabilize the radical), although the species shown are not necessarily intermediates, but may represent transition states. It has been shown, for the case of certain substituted substrates, that configuration is retained at C-1 and C-5 and inverted at C-3.[1005]



The reaction has been extended to allylic benzenes, which give cyclopropylbenzenes,[1006] to β,γ-unsaturated ketones, which give cyclopropyl ketones[1007] (this reaction, called the

[999] Zimmerman, H.E.; Pincock, J.A. *J. Am. Chem. Soc.* ***1973***, *95*, 2957.

[1000] Zimmerman, H.E. *Org. Photochem.* ***1991***, *11*, 1; Zimmerman, H.E. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 131–166; Hixson, S.S.; Mariano, P.S.; Zimmerman, H.E. *Chem. Rev.* ***1973***, *73*, 531. See also, Roth, W.R.; Wildt, H.; Schlemenat, A. *Eur. J. Org. Chem.* **2001**, 4081.

[1001] Zimmerman, H.E.; Hackett, P.; Juers, D.F.; McCall, J.M.; Schröder, B. *J. Am. Chem. Soc.* ***1971***, *93*, 3653.

[1002] However, some substrates, generally rigid bicyclic molecules (e.g., barrelene, which is converted to semibullvalene), give the di-π-methane rearrangement only from triplet states.

[1003] Zimmerman, H.E.; Baum, A.A. *J. Am. Chem. Soc.* ***1971***, *93*, 3646. See also, Paquette, L.A.; Bay, E.; Ku, A.Y.; Rondan, N.G.; Houk, K.N. *J. Org. Chem.* ***1982***, *47*, 422.

[1004] See Zimmerman, H.E.; Boettcher, R.J.; Buehler, N.E.; Keck, G.E. *J. Am. Chem. Soc.* ***1975***, *97*, 5635. However, see Adam, W.; De Lucchi, O.; Dörr, M. *J. Am. Chem. Soc.* ***1989***, *111*, 5209.

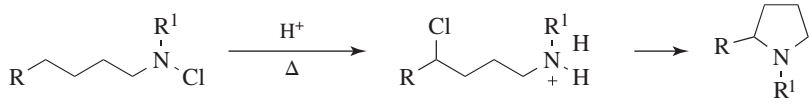
[1005] Zimmerman, H.E.; Robbins, J.D.; McKelvey, R.D.; Samuel, C.J.; Sousa, L.R. *J. Am. Chem. Soc.* ***1989***, *111*, 5209.

[1006] See Paquette, L.A.; Bay, E. *J. Am. Chem. Soc.* ***1984***, *106*, 6693; Zimmerman, H.E.; Swafford, R.L. *J. Org. Chem.* ***1984***, *49*, 3069.

[1007] See Schuster, D.I. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 167–279; Houk, K.N. *Chem. Rev.* ***1976***, *76*, 1; Schaffner, K. *Tetrahedron* ***1976***, *32*, 641; Dauben, W.G.; Lodder, G.; Ipaktschi, J. *Top. Curr. Chem.* ***1975***, *54*, 73.

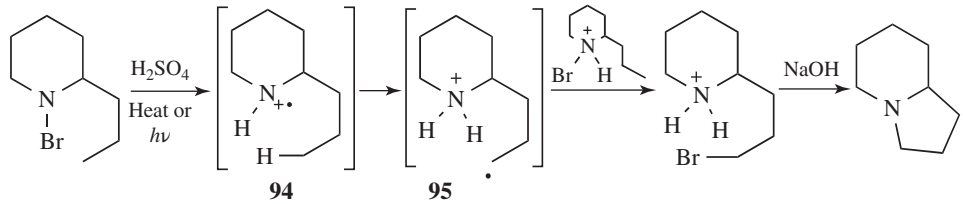
oxa-di-π-methane rearrangement,[1008] generally occurs only from the triplet state), to β,γ-unsaturated imines,[1009] and to triple bond systems.[1010] 2,4-Cyclohexadienones also undergo photochemical rearrangements, but the products are different, generally involving ring opening.[1011]

18-40 The Hofmann-Löffler and Related Reactions



A common feature of the reactions in this section[1012] is that they serve to introduce functionality at a position remote from functional groups already present. As such, they have proved very useful in synthesizing many compounds, especially in the steroid field (see also **19-2** and **19-18**). When *N*-haloamines in which one alkyl group has a hydrogen in the 4 or 5 position are heated with sulfuric acid, then pyrrolidines or piperidines are formed, in a reaction known as the *Hofmann-Löffler reaction* (also called the *Hofmann-Löffler-Freytag reaction*).[1013] The R′ group is normally alkyl, but the reaction has been extended to R′ = H by the use of concentrated sulfuric acid solution and ferrous salts.[1014] An iodine-catalyzed reaction has been reported.[1015]

As illustrated by the reaction of 1-bromo-2-propylpiperidine,[1016] a radical anion is formed (**94**) and hydrogen transfer leads to a distal radical (**95**).



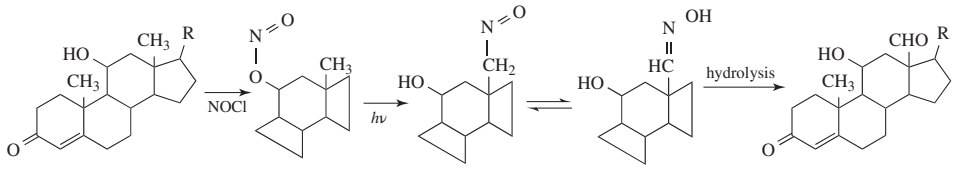
94 **95**

Reaction with protonated 1-bromo-2-propylpiperidine occurs *in situ* to give the distal bromide, which reacts via internal substitution to give octahydroindolizine. The reaction is most often induced by heat, but this is not necessary, and irradiation and chemical initiators (e.g., peroxides) have been used instead. The mechanism is of a free-radical type, with

[1008] For a review, see Demuth, M. *Org. Photochem.* ***1991***, *11*, 37.
[1009] Armesto, D.; Horspool, W.M.; Langa, F.; Ramos, A. *J. Chem. Soc., Perkin Trans. 1* ***1991***, 223.
[1010] See Griffin, G.W.; Chihal, D.M.; Perreten, J.; Bhacca, N.S. *J. Org. Chem.* ***1976***, *41*, 3931.
[1011] Schaffner, K.; Demuth, M. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, p. 281; Quinkert, G. *Angew. Chem. Int. Ed.* ***1972***, *11*, 1072; Kropp, P.J. *Org. Photochem.* ***1967***, *1*, 1.
[1012] See Carruthers, W. *Some Modern Methods of Organic Synthesis*, 3rd ed., Cambridge University Press, Cambridge, ***1986***, pp. 263–279.
[1013] See Stella, L. *Angew. Chem. Int. Ed.* ***1983***, *22*, 337; Sosnovsky, G.; Rawlinson, D.J. *Adv. Free-Radical Chem.* ***1972***, *4*, 203 (see pp. 249–259); Deno, N.C. *Methods Free-Radical Chem.* ***1972***, *3*, 135 (see pp. 136–143).
[1014] Schmitz, E.; Murawski, D. *Chem. Ber.* ***1966***, *99*, 1493.
[1015] Martínez, C.; Muñiz, K. *Angew. Chem. Int. Ed.* ***2015***, *54*, 8287.
[1016] Corey, E.J.; Hertler, W.R. *J. Am. Chem. Soc.* ***1960***, *82*, 1657; Kovacic, P.; Lowery, M.K.; Field, K.W. *Chem. Rev.* ***1970***, *70*, 639.

the main step involving an internal hydrogen abstraction.[1017] A similar reaction has been carried out on *N*-halo amides, which give γ-lactones.[1018]

Another related reaction is the *Barton reaction*,[1019] by which a methyl group in a unique position relative to an OH group can be oxidized to a CHO group. The alcohol is first converted to the nitrite ester. Photolysis of the nitrite results in conversion of the nitrite group to the OH group and nitrosation of the methyl group. Formation of a radical and with the methyl group in the appropriate position, hydrogen atom transfer via a six-center transition state leads to a nitrite. Hydrolysis of the oxime tautomer gives the aldehyde, for example:[1020]

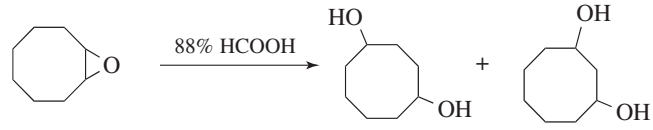


This reaction takes place only when the methyl group is in a favorable steric position.[1021] The mechanism is similar to that of the *Hofmann-Löffler reaction*.[1022] This is one of the few known methods for effecting substitution at an angular methyl group. Not only CH_3 groups but also alkyl groups of the form RCH_2 and R_2CH can give the Barton reaction if the geometry of the system is favorable. An RCH_2 group is converted to the oxime R(C=NOH) (which is hydrolyzable to a ketone) or to a nitroso dimer, while an R_2CH group gives a nitroso compound $R_2C(NO)$. With very few exceptions, the only carbons that become nitrosated are those in the position δ to the original OH group, indicating that a six-membered transition state is necessary for the hydrogen abstraction.[1023]

OS **III**, 159.

D. Noncyclic Rearrangements

18-41 Hydride Shifts



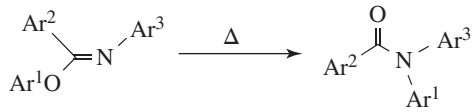
The example shown is typical of a transannular hydride shift. The 1,2-diol is formed by a normal epoxide hydrolysis reaction (**10-7**).[1024] For a discussion of 1,3- and longer hydride

[1017] Wawzonek, S.; Thelan, P.J. *J. Am. Chem. Soc.* ***1950***, *72*, 2118.
[1018] Barton, D.H.R.; Beckwith, A.L.J.; Goosen, A. *J. Chem. Soc.* ***1965***, 181; Neale, R.S.; Marcus, N.L.; Schepers, R.G. *J. Am. Chem. Soc.* ***1966***, *88*, 3051. See Neale, R.S. *Synthesis* ***1971***, 1.
[1019] See Hesse, R.H. *Adv. Free-Radical Chem.* ***1969***, *3*, 83; Barton, D.H.R. *Pure Appl. Chem.* ***1968***, *16*, 1; Saraiva, M.F.; Couri, M.R.C.; Le Hyaric, M.; de Almeida, M.V. *Tetrahedron* ***2009***, *65*, 3563.
[1020] Barton, D.H.R.; Beaton, J.M. *J. Am. Chem. Soc.* ***1961***, *83*, 4083.
[1021] See Burke, S.D.; Silks III, L.A.; Strickland, S.M.S. *Tetrahedron Lett.* ***1988***, *29*, 2761.
[1022] See Green, M.M.; Boyle, B.A.; Vairamani, M.; Mukhopadhyay, T.; Saunders Jr., W.H.; Bowen, P.; Allinger, N.L. *J. Am. Chem. Soc.* ***1986***, *108*, 2381; Grossi, L. *Chem. Eur. J.* ***2005***, *11*, 5419.
[1023] See Nickon, A.; Ferguson, R.; Bosch, A.; Iwadare, T. *J. Am. Chem. Soc.* ***1977***, *99*, 4518.
[1024] Cope, A.C.; Fournier Jr., A.; Simmons Jr., H.E. *J. Am. Chem. Soc.* ***1957***, *79*, 3905.

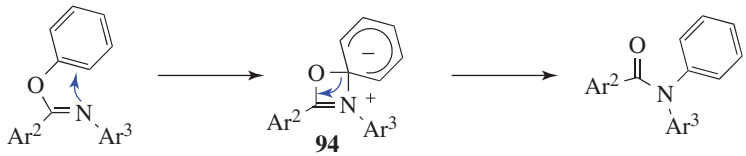
shifts see Sec. 18.B. The gold or Brønsted acid catalysis of allenyl ethers caused them to be converted to fused or spiro tetrahydrofurans and tetrahydropyrans via a hydride shift/cyclization sequence.[1025]

The glycerol-3-phosphate dehydrogenase-catalyzed primary deuterium kinetic isotope effects for the dianion-activated hydride transfer from NADL to glycolaldehyde were determined.[1026]

18-42 The Chapman Rearrangement



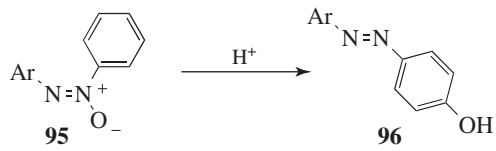
In the *Chapman rearrangement*, *N*,*N*-diaryl amides are formed when aryl imino esters are heated.[1027] Best yields are obtained in refluxing tetraethylene glycol dimethyl ether (tetraglyme),[1028] although the reaction can also be carried out without any solvent at all. Many groups may be present in the rings, for example, alkyl, halo, OR, CN, and CO_2R. Aryl migrates best when it contains electron-withdrawing groups. On the other hand, electron-withdrawing groups in Ar^2 or Ar^3 decrease the reactivity. The products can be hydrolyzed to diarylamines, and this is a method for preparing these compounds. The mechanism probably involves an intramolecular[1029] aromatic nucleophilic substitution, resulting in a 1,3 oxygen-to-nitrogen shift via a species such as **94**.



Aryl imino esters can be prepared from *N*-aryl amides by reaction with PCl_5, followed by treatment of the resulting imino chloride with an aroxide ion.[1030] Imino esters with any or all of the three groups being alkyl also rearrange, but they require catalysis by H_2SO_4 or a trace of methyl iodide or methyl sulfate.[1031] The mechanism is different, involving an intermolecular process.[1032] This is also true for derivatives for formamide ($Ar^2 = H$).

[1025] Bolte, B.; Gagosz, F. *J. Am. Chem. Soc.* ***2011***, *133*, 7696.
[1026] Reyes, A.C.; Amyes, T.L.; Richard, J.P. *J. Am. Chem. Soc.* ***2016***, *138*, 14526.
[1027] Schulenberg, J.W.; Archer, S. *Org. React.* ***1965***, *14*, 1; McCarty, C.G. in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 439–447; McCarty, C.G.; Garner, L.A. in Patai, S. *The Chemistry of Amidines and Imidates*, Wiley, NY, ***1975***, pp. 189–240. For a review of 1,3-migrations of R, in general, see Landis, P.S. *Mech. Mol. Migr.* ***1969***, *2*, 43.
[1028] Wheeler, O.H.; Roman, F.; Santiago, M.V.; Quiles, F. *Can. J. Chem.* ***1969***, *47*, 503.
[1029] See Kimura, M. *J. Chem. Soc., Perkin Trans. 2* ***1987***, 205.
[1030] See Bonnett, R. in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 597–662.
[1031] Landis, P.S. *Mech. Mol. Migr.* ***1969***, *2*, 43.
[1032] See Challis, B.C.; Frenkel, A.D. *J. Chem. Soc., Perkin Trans. 2* ***1978***, 192.

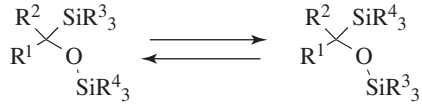
18-43 The Wallach Rearrangement



The conversion of azoxy compounds such as **95**, upon acid treatment, to *p*-hydroxy azo compounds such as **96** (or sometimes the *o*-hydroxy isomers[1033]) is called the *Wallach rearrangement*.[1034] When both *para* positions are occupied, the *o*-hydroxy product may be obtained, but *ipso* substitution at one of the *para* positions is also possible.[1035] The following facts are known for the proposed mechanism.[1036] (i) The *para* rearrangement is intermolecular.[1037] (ii) When the reaction was carried out with an azoxy compound in which the N—O nitrogen was labeled with ^{15}N, *both* nitrogens of the product carried the label equally,[1038] demonstrating that the oxygen did not have a preference for migration to either the near or the far ring. This shows that there is a symmetrical intermediate. (iii) Kinetic studies show that two protons are normally required for the reaction.[1039] The mechanism[1040] involves the symmetrical intermediate, Ar—$^{+}$N≡N^{+}—Ar, which has been proposed to explain the facts.[1041] It has proved possible to obtain intermediates as stable species in superacid solutions.[876] Another mechanism, involving an intermediate with only one positive charge, has been proposed for certain substrates at low acidities.[1042]

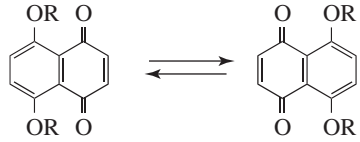
A photochemical Wallach rearrangement[1043] is also known. The product is the *o*-hydroxy azo compound, the OH group is found in the farther ring, and the rearrangement is intramolecular.[1044]

18-44 Dyotropic Rearrangements[1045]



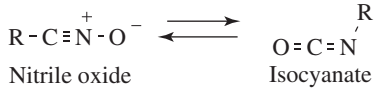
[1033] See Yamamoto, J.; Nishigaki, Y.; Umezu, M.; Matsuura, T. *Tetrahedron* ***1980***, *36*, 3177.
[1034] See Buncel, E. *Mech. Mol. Migr.* ***1968***, *1*, 61; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1969***, pp. 272–284, 357–359; Cox, R.A.; Buncel, E. in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 808–837.
[1035] See Shimao, I.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 643.
[1036] Furin, G.G. *Russ. Chem. Rev.* ***1987***, *56*, 532; Williams, D.L.H.; Buncel, E. *Isot. Org. Chem.* ***1980***, *5*, 184; Buncel, E. *Acc. Chem. Res.* ***1975***, *8*, 132.
[1037] See Oae, S.; Fukumoto, T.; Yamagami, M. *Bull. Chem. Soc. Jpn.* ***1963***, *36*, 601.
[1038] Shemyakin, M.M.; Maimind, V.I.; Vaichunaite, B.K. *Chem. Ind. (London)* ***1958***, 755; *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1960***, 808. Also see, Behr, L.C.; Hendley, E.C. *J. Org. Chem.* ***1966***, *31*, 2715.
[1039] See Cox, R.A. *J. Am. Chem. Soc.* ***1974***, *96*, 1059.
[1040] See Buncel, E.; Keum, S. *J. Chem. Soc., Chem. Commun.* ***1983***, 578.
[1041] Also see Shemyakin, M.M.; Agadzhanyan, Ts.E.; Maimind, V.I.; Kudryavtsev, R.V. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1963***, 1216; Hendley, E.C.; Duffey, D. *J. Org. Chem.* ***1970***, *35*, 3579.
[1042] See Cox, R.A.; Buncel, E. *J. Am. Chem. Soc.* ***1975***, *97*, 1871.
[1043] See Shimao, I.; Hashidzume, H. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 754.
[1044] See Shine, H.J.; Subotkowski, W.; Gruszecka, E. *Can. J. Chem.* ***1986***, *64*, 1108.
[1045] Also see Gutierrez, O.; Tantillo, D.J. *J. Org. Chem.* ***2012***, *77*, 8845.

A *dyotropic rearrangement*[1046] is an uncatalyzed process in which two σ bonds simultaneously migrate intramolecularly.[1047] There are two types. The above is an example of type 1, which consists of reactions in which the two σ bonds interchange positions. In type 2, the two σ bonds do not interchange positions. An example is:



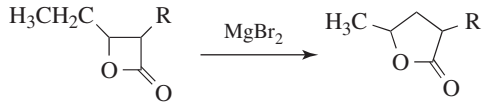
Some other examples are:

Type 1



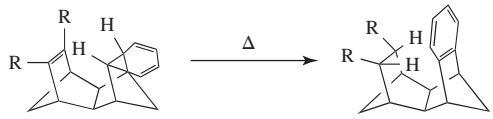
Ref. 1048

Type 1



Ref. 1049

Type 2



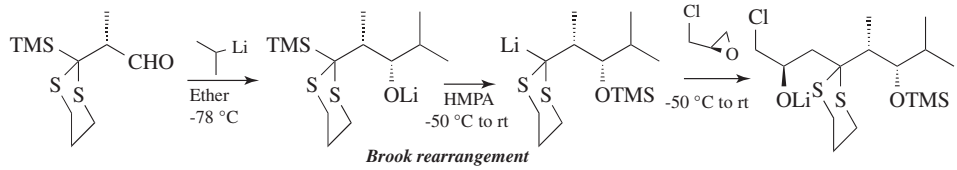
Ref. 1050

A useful type 1 example is the *Brook rearrangement*,[1051] a stereospecific intramolecular migration of silicon from carbon to oxygen that occurs for (α-hydroxybenzyl)trialkylsilanes in the presence of a catalytic amount of base.[1052] Formation of a Si—O bond rather than the Si—C bond drives the rearrangement, which is believed to proceed via formation of a —C—O—S— three-membered ring intermediate, and proceeds with inversion of configuration at carbon and retention of configuration at silicon.[1053] A *reverse Brook rearrangement* is also known.[1054] The reaction has been extended to other systems. A *homo-Brook rearrangement* has also been reported.[1055] Another variation is the *aza-Brook rearrangement* of

[1046] See Davis, R.L.; Tantillo, D.J. *J. Org. Chem.* ***2010***, *75*, 1693.
[1047] Minkin, V.I.; Olekhnovich, L.P.; Zhdanov, Yu.A. *Molecular Design of Tautomeric Compounds*, Reidel, Dordrecht, ***1988***, pp. 221–246. Also see, Mackenzie, K.; Gravaatt, E.C.; Gregory, R.J.; Howard, J.A.K.; Maher, J.P. *Tetrahedron Lett.* ***1992***, *33*, 5629.
[1048] See Taylor, G.A. *J. Chem. Soc., Perkin Trans. 1* ***1985***, 1181.
[1049] See Black, T.H.; Hall, J.A.; Sheu, R.G. *J. Org. Chem.* ***1988***, *53*, 2371.
[1050] See Mackenzie, K.; Proctor, G.; Woodnutt, D.J. *Tetrahedron* ***1987***, *43*, 5981, and cited references.
[1051] For a review, see Moser, W.H. *Tetrahedron* ***2001***, *57*, 2065.
[1052] Brook, A.G. *Acc. Chem. Res.* ***1974***, *7*, 77; Brook, A.G.; Bassendale, A.R. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 2, Academic Press, NY, ***1980***, pp. 149–227.
[1053] Brook, A.G.; Pascoe, J.D. *J. Am. Chem. Soc.* ***1971*** *93*, 6224.
[1054] See Linderman, J.J.; Ghannam, A. *J. Am. Chem. Soc.* ***1990***, *112*, 2392.
[1055] Wilson, S.R.; Georgiadis, G.M. *J. Org. Chem.* ***1983***, *48*, 4143.

α-(silylallyl)amines.[1056] A phospha-Brook rearrangement has been reported.[1057] A retro-Brook rearrangement is known.[1058] The Brook rearrangement has been used in a synthesis involving silyl dithianes[1059] and for the ring opening of strained carbocycles.[1060] A Brook rearrangement-mediated [6 + 2] annulation has been used for the construction of eight-membered carbocycles.[1061]

The Brook rearrangement has been used in two important synthetic applications: (i) a multicomponent coupling protocol initiated by a Brook rearrangement involving silyl dithianes, as mentioned, and (ii) anion relay chemistry[1062] (ARC) that involves a Brook rearrangement. An example of the latter is taken from the convergent total synthesis of (−)-nahuoic acid Ci(Bii).[1063] Addition of isopropyllithium to the aldehyde to give the lithium alkoxide, and addition of HMPA triggered a Brook rearrangement in which the negative charge was relayed from O to C, which then allowed reaction with epichlorohydrin to give the final product.



[1056] Honda, T.; Mori, M. *J. Org. Chem.* ***1996***, *61*, 1196; Lin, C.-Y.; Sun, Z.; Xu, Y.-Z.; Lu, C.-D. *J. Org. Chem.* ***2015***, *80*, 3714.

[1057] Pallikonda, G.; Santosh, R.; Ghosal, S.; Chakravarty, M. *Tetrahedron Lett.* ***2015***, *56*, 3796; Hayashi, M.; Nakamura, S. *Angew. Chem. Int. Ed.* ***2011***, *50*, 2249.

[1058] He, Y.; Hu, H.; Xie, X.; She, X. *Tetrahedron* ***2013***, *69*, 559.

[1059] See Smith III, A.B.; Adams, C.M. *Acc. Chem. Res.* ***2004***, *37*, 365; Smith III, A.B.; Kim, D.-S. *Org. Lett.* ***2005***, *7*, 3247.

[1060] Zhang, F.-G.; Eppe, G.; Marek, I. *Angew. Chem. Int. Ed.* ***2016***, *55*, 714.

[1061] Sawada, Y.; Sasaki, M.; Takeda, K. *Org. Lett.* ***2004***, *6*, 2277.

[1062] Li, M.; Lin, S.; Dong, Z.; Zhang, X.; Liang, F.; Zhang, J. *Org. Lett.* ***2013***, *15*, 3978.

[1063] Liu, Q.; Deng, Y.; Smith III, A.B. *J. Am. Chem. Soc.* ***2017***, *139*, 13668.

CHAPTER 19

Oxidations and Reductions

Before there can be a discussion of oxidation and reduction, the terms "oxidation" and "reduction" must be clarified. Inorganic chemists define oxidation in two ways: (i) loss of electrons and (ii) an increase in oxidation number. In organic chemistry, these definitions, while still correct, are not easy to apply. While electrons are directly transferred in some organic oxidations and reductions, and electrons are certainly transferred by making and breaking bonds, the mechanisms of most of these reactions do not involve a direct electron transfer. As for oxidation number, while this is easy to apply in some cases (e.g., the oxidation number of carbon in CH_4 is -4), in most cases attempts to apply the concept lead to fractional values or to apparent absurdities. The carbon atoms in propane have an oxidation number of -2.67 and those in butane are -2.5, although organic chemists seldom think of these two compounds as having different oxidation states. An improvement could be made by assigning different oxidation states to different carbon atoms in a molecule, depending on what is bonded to them (e.g., the two carbons in acetic acid are obviously in different oxidation states), but for this a whole set of arbitrary assumptions would be required, since the oxidation number of an atom in a molecule is assigned on the basis of the oxidation numbers of the atoms attached to it. There would seem little to be gained by such a procedure.

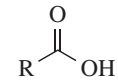
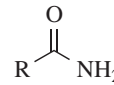
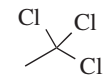
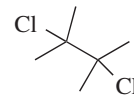
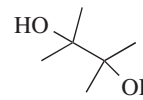
The practice in organic chemistry has been to set up a series of functional groups, in a qualitative way, arranged in order of increasing oxidation state, and then to define oxidation as *the conversion of a functional group in a molecule from one category to a higher one*. Reduction is the opposite. This series is shown in Table 19.1 for the simple functional groups.[1] Note that this classification applies only to a single carbon atom or to two adjacent carbon atoms. Thus 1,3-dichloropropane is in the same oxidation state as chloromethane, but 1,2-dichloropropane is in a higher one. Obviously, such distinctions are somewhat arbitrary; if we attempt to carry them too far we will find ourselves painted into a corner. Nevertheless, the basic idea has served organic chemistry well. Note that conversion of any compound to another in the same category is not an oxidation or a reduction. Most oxidations in organic chemistry involve a gain of oxygen and/or a loss of hydrogen (Lavoisier's original definition of oxidation). The reverse is true for reductions.

Of course, there is no oxidation without a concomitant reduction. However, reactions are classified as oxidations or reductions depending on whether the *organic compound* is

[1] For more extensive tables, see Soloveichik, S.; Krakauer, H. *J. Chem. Educ.* ***1966***, *43*, 532.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

TABLE 19.1 Categories of simple functional groups arranged according to oxidation state[a]

RH		—C≡C—		CO_2
	ROH			CCl_4
	RCl RNH_2			
	…and so on			
			…and so on	
				
		…and so on		

Approximate Oxidation Number				
−4	−2	0	+2	+4

[a]Oxidation is the conversion of a functional group in a molecule to a higher category; reduction is conversion to a lower one. Conversions within a category are neither oxidations nor reductions. The numbers given at the bottom are only approximations.

oxidized or reduced. In some cases both the oxidant and reductant are organic; those reactions are treated separately at the end of the chapter.

19.A. MECHANISMS

Note that the stated definition of oxidation has nothing to do with mechanism. Thus the conversion of bromomethane to methanol with KOH (**10-1**) is a substitution and the reaction methane of bromomethane with $LiAlH_4$ (**19-57**) is a reduction. It is impractical to consider the mechanisms of oxidation and reduction reactions in broad categories in this chapter as has been done for the reactions considered in Chapters 10–18.[2] The main reason is that the mechanisms are too diverse, and this in turn is because the bond changes are too different. Another reason is that the mechanism of a given oxidation or reduction reaction can vary

[2] See Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 16, Elsevier, NY, ***1980***; *Oxidation in Organic Chemistry*, Academic Press, NY, pt. A [Wiberg, K.B.], ***1965***, pts. B, C, and D [Trahanovsky, W.S.], ***1973***, ***1978***, ***1982***; Waters, W.A. *Mechanisms of Oxidation of Organic Compounds*, Wiley, NY, ***1964***; Stewart, R. *Oxidation Mechanisms*, W.A. Benjamin, NY, ***1964***. For a review, see Stewart, R. *Isot. Org. Chem.* ***1976***, *2*, 271.

greatly with the oxidizing or reducing agent employed. Very often the mechanism has been studied intensively for only one or a few of many possible agents. Although oxidation and reduction mechanisms are not covered in the same way as other mechanisms, it is still possible to list a few broad mechanistic categories. The scheme of Wiberg is followed.[3]

1. *Direct electron transfer*.[4] Several reactions have been encountered in which the reduction is a direct gain of electrons or the oxidation a direct loss of them. An example is the *Birch reduction* (**19-36**), where sodium directly transfers an electron to an aromatic ring. An example from this chapter is found in the bimolecular reduction of ketones with a metal (**19-80**), where again it is a metal that supplies the electrons. This kind of mechanism is found largely in three types of reaction:[5]
   a. the oxidation or reduction of a free radical (oxidation to a positive ion or reduction to a negative ion)
   b. the oxidation of a negative ion or the reduction of a positive ion to a comparatively stable free radical
   c. electrolytic oxidations or reductions (an example is the Kolbe reaction, **14-23**).

   An important example of point b is oxidation of phenolate ions to phenoxide radicals. These reactions occur easily because of the relative stability of the radicals involved.[6] The single electron-transfer mechanism (SET), which has been seen several times (Sec. 10.B) is an important case.
2. *Hydride transfer*.[7] In some reactions, a hydride ion is transferred to or from the substrate.[8] The reduction of epoxides with $LiAlH_4$ is an example (**19-39**). Another is the *Cannizzaro reaction* (**19-85**). Reactions in which a hydride ion is transferred to a carbocation belong in this category.
3. *Hydrogen-atom transfer*. Many oxidation and reduction reactions are free-radical substitutions and involve the transfer of a hydrogen atom. For example, one of the two main propagation steps of **14-1** involves abstraction of hydrogen:

$$RH + Cl\bullet \rightarrow R\bullet + HCl$$

   This is the case for many of the reactions of Chapter 14.
4. *Displacement mechanisms*. In these reactions, the organic substrate uses its electrons to cause displacement on an electrophilic oxidizing agent. One example is the addition of bromine to an alkene (**15-35**), which gives a bromonium ion as an intermediate. An example from this chapter is found in **19-28**.
5. *Addition-elimination mechanisms*. In the reaction between α,β-unsaturated ketones and alkaline peroxide (**15-46**), the oxidizing agent adds to the substrate and then part of it is lost. In this case, the oxygen of the oxidizing agent is in oxidation state −1 and the hydroxide ion departs with its oxygen in the −2 state; the oxidizing agent is

[3] Wiberg, K.B. *Surv. Prog. Chem.* ***1963***, *1*, 211.
[4] See Eberson, L. *Electron Transfer Reactions in Organic Chemistry*, Springer, NY, ***1987***; Eberson, L. *Adv. Phys. Org. Chem.* ***1982***, *18*, 79; Deuchert, K.; Hünig, S. *Angew. Chem. Int. Ed.* ***1978***, *17*, 875.
[5] Littler, J.S.; Sayce, I.G. *J. Chem. Soc.* ***1964***, 2545.
[6] See Mihailovic, M.Lj.; Cekovic, Z. in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 505–592.
[7] For a review, see Watt, C.I.F. *Adv. Phys. Org. Chem.* ***1988***, *24*, 57.
[8] See Nenitzescu, C.D. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 463–520.

reduced and so the substrate is oxidized. There are several reactions that follow this pattern of addition of an oxidizing agent and the loss of part of the agent, usually in a different oxidation state. Another example is the oxidation of ketones with SeO_2 (**19-15**). This reaction is also an example of category 4, since it involves formation and E2 cleavage of an ester. This example shows that these five categories are not mutually exclusive.

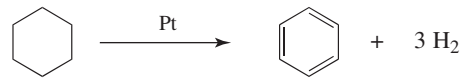
19.B. REACTIONS

In this chapter, the reactions are classified by the type of bond change occurring to the organic substrate, in conformity with other chapters.[9] This classification means that there is no discussion in any one place of the use of a particular oxidizing or reducing agent, for example, acid dichromate or $LiAlH_4$ (except for a discussion of selectivity of reducing agents, for which see 19.B.ii, part A). Some oxidizing or reducing agents are fairly specific in their action, attacking only one or a few types of substrate. Others, like acid dichromate, permanganate, $LiAlH_4$, and catalytic hydrogenation, are much more versatile.[10]

19.B.i. Oxidations[11]

A. Eliminations Of Hydrogen

19-1 Aromatization of Six-Membered Rings



Six-membered alicyclic rings can be aromatized in a number of ways.[12] Aromatization is accomplished most easily if there are already one or two double bonds in the ring or if the ring is fused to an aromatic ring. The reaction can also be applied to heterocyclic five- and six-membered rings. Many groups may be present on the ring without interference, and even *gem*-dialkyl substitution does not always prevent the reaction. In such cases one alkyl group often migrates or is eliminated, but more drastic conditions are usually required for this. In some cases OH and COOH groups are lost from the ring. Cyclic ketones are converted to phenols. Seven-membered and larger rings are often isomerized to six-membered aromatic

[9] See Hudlicky, M. *J. Chem. Educ.* ***1977***, *54*, 100.

[10] See Mijs, W.J.; de Jonge, C.R.J.I. *Organic Synthesis by Oxidation with Metal Compounds*, Plenum, NY, ***1986***; Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Springer, NY, ***1984***; Arndt, D. *Manganese Compounds as Oxidizing Agents in Organic Chemistry*, Open Court Publishing Company, La Salle, IL, ***1981***.

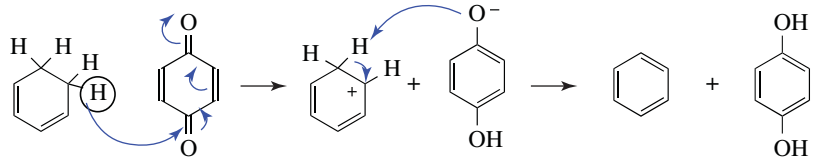
[11] For books on oxidation reactions, see Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, ***1990***; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, 2 Vols., Academic Press, NY, ***1985***, ***1988*** [The first volume pertains to hydrocarbon substrates; the second mostly to oxygen- and nitrogen-containing substrates]; Chinn, L.J. *Selection of Oxidants in Synthesis*, Marcel Dekker, NY, ***1971***; Augustine, R.L.; Trecker, D.J. *Oxidation*, 2 Vols., Marcel Dekker, NY, ***1969***, ***1971***.

[12] See Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1985***, pp. 16–22, 217–222; Fu, P.P.; Harvey, R.G. *Chem. Rev.* ***1978***, *78*, 317; Valenta, Z. in Bentley, K.W.; Kirby, G.W. *Elucidation of Chemical Structures by Physical and Chemical Methods* (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), 2nd ed., pt. 2, Wiley, NY, ***1973***, pp. 1–76; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 34–44. See Peterson, P.W.; Mohamed, R.K.; Alabugin, I.V. *Eur. J. Org. Chem.* ***2013***, 2505.

rings, although this is not the case for partially hydrogenated azulene systems (which are frequently found in nature); these are converted to azulenes.

There are three types of reagents most frequently used to effect aromatization.

1. Hydrogenation catalysts,[13] such as Pt, Pd,[14] and Ni.[15] Palladium trifluoroacetate also facilitates oxidative aromatization of cyclohexene.[16] In this case, the reaction is the *reverse* of double-bond hydrogenation (**19-34** and **19-38**), and presumably the mechanism is also the reverse, although not much is known.[17] Cyclohexene has been detected as an intermediate in the conversion of cyclohexane to benzene, using Pt.[18] The substrate is heated with the catalyst at ~300–350 °C. The reactions can often be carried out under milder conditions if a hydrogen acceptor, such as maleic acid, cyclohexene, or benzene, is present to remove hydrogen as it is formed. The acceptor is reduced to the saturated compound. Other transition metals can be used.[19] It has been reported that dehydrogenation of 1-methylcyclohexene-1-^{13}C over an alumina catalyst gave toluene with the label partially scrambled throughout the aromatic ring.[20] For polycyclic systems, heating with oxygen on activated carbon generates the aromatic compound, as in the conversion of dihydroanthracene to anthracene.[21]
2. The elements sulfur and selenium, which combine with the hydrogen evolved to give, respectively, H_2S and H_2Se. Little is known about this mechanism either.[22]
3. Quinones[23] become reduced to the corresponding hydroquinones. Two important quinones often used for aromatizations are chloranil (2,3,5,6-tetrachloro-1,4-benzoquinone) and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone).[24] The latter is more reactive and can be used in cases where the substrate is difficult to dehydrogenate. It is likely that the mechanism involves a transfer of hydride to the quinone oxygen, followed by the transfer of a proton to the phenolate ion.[25]



[13] See Rylander, P.N. *Organic Synthesis with Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 1–59.
[14] See Cossy, J.; Belotti, D. *Org. Lett.* ***2002***, *4*, 2557. See Cho, C.S.; Patel, D.B.; Shim, S.C. *Tetrahedron* ***2005***, *61*, 9490.
[15] See *Transition-Metal-Mediated Aromatic Ring Construction*, Tanaka, K. (Ed.), Wiley, Hoboken, ***2013***.
[16] Bercaw, J.E.; Hazari, N.; Labinger, J.A. *J. Org. Chem.* ***2008***, *73*, 8654.
[17] See Tsai, M.; Friend, C.M.; Muetterties, E.L. *J. Am. Chem. Soc.* ***1982***, *104*, 2539. See also, Augustine, R.L.; Thompson, M.M. *J. Org. Chem.* ***1987***, *52*, 1911.
[18] Land, D.P.; Pettiette-Hall, C.L.; McIver Jr., R.T.; Hemminger, J.C. *J. Am. Chem. Soc.* ***1989***, *111*, 5970.
[19] Srinivas, G.; Periasamy, M. *Tetrahedron Lett.* ***2002***, *43*, 2785.
[20] Marshall, J.L.; Miiller, D.E.; Ihrig, A.M. *Tetrahedron Lett.* ***1973***, 3491.
[21] Nakamichi, N.; Kawabata, H.; Hiyashi, M. *J. Org. Chem.* ***2003***, *68*, 8272.
[22] Silverwood, H.A.; Orchin, M. *J. Org. Chem.* ***1962***, *27*, 3401.
[23] Becker, H.; Turner, A.B. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 2, Wiley, NY, ***1988***, pp. 1351–1384; Becker, H. in Patai, S. *The Chemistry of the Quinonoid Compounds*, Vol. 1, pt. 1, Wiley, NY, ***1974***, pp. 335–423.
[24] See Turner, A.B. in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, ***1977***, pp. 193–225; Walker, D.; Hiebert, J.D. *Chem. Rev.* ***1967***, *67*, 153.
[25] Trost, B.M. *J. Am. Chem. Soc.* ***1967***, *89*, 1847. See also, Höfler, C.; Rüchardt, C. *Liebigs Ann. Chem.* ***1996***, 183.

Other reagents[26] have been used for aromatization of six-membered rings, including atmospheric oxygen, MnO_2,[27] SeO_2, H_2SO_4, and a Ru catalyst.[28] The last-mentioned reagent also dehydrogenates cyclopentanes to cyclopentadienes. In some instances, the hydrogen is not released as H_2 or transferred to an external oxidizing agent, but instead serves to reduce another molecule of substrate. This is a disproportionation reaction, as illustrated by the conversion of cyclohexene to cyclohexane and benzene.

A Pd-catalyzed aerobic dehydrogenation of substituted cyclohexenes gave the corresponding arene derivatives using sodium anthraquinone-2-sulfonate as a co-catalyst.[29] The cycloaromatization of dienyl propargylic ethers used Triton B in DMSO to give highly substituted phenol derivatives via an electrocyclization followed by 1,3-proton transfer.[30] The Pd-catalyzed aerobic bimolecular carbocyclization of (*Z*)-hexa-1,5-diyn-3-ene derivatives, in the presence of a Cu salt, gave 2,6-diacylnaphthalenes.[31] A Pd-catalyzed tandem Sonogashira coupling (**13-13**)/cyclization/aromatization sequence of β-halo vinyl sulfones/ketones with terminal alkynes gave benzene derivatives.[32]

The Pd-catalyzed aerobic dehydrogenative aromatization of cyclohexanone imines, generated by *in situ* reaction of cyclohexanone derivatives and amines, gave arylamines.[33] Heating benzoin and deoxybenzoin with acetic acid and ammonium acetate led to tetraaryl-substituted pyrroles via cross-dehydrative aromatization.[34] Heating the Nd-catalyzed reaction of 2-alkynylbiphenyl derivatives gave phenanthrene derivatives.[35] Phenols were prepared from cyclohexenones via the reaction with a copper acetate catalyst, in the presence of LiBr and CF_3COOH under oxygen.[36] Note that hydrogenolysis of cyclohexane leads to *n*-hexane with hydrogen and an Ir catalyst.[37] It is noted that hydrogenolysis of alkanes in general has been examined.[38]

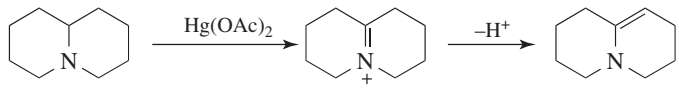
Heteroatom rings, as found in quinoline derivatives, for example, can be generated from amino ketones with [hydroxy(tosyloxy)iodo]benzene and perchloric acid[39] or with $NaHSO_4/Na_2Cr_2O_7$ on wet silica.[40] Dihydropyridines are converted to pyridines with $NaNO_2$/oxalic acid and wet silica,[41] $BaMnO_4$,[42] $FeCl_3$/acetic acid,[43] or SeO_2.[44] *Hantzsch*

[26] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 187–191.
[27] See Leffingwell, J.C.; Bluhm, H.J. *Chem. Commun.* ***1969***, 1151.
[28] Tanaka, H.; Ikeno, T.; Yamada, T. *Synlett* ***2003***, 576.
[29] Iosub, A.V.; Stahl, S.S. *J. Am. Chem. Soc.* ***2015***, *137*, 3454.
[30] Spencer III, W.T.; Frontier, A.J. *J. Org. Chem.* ***2012***, *77*, 7730.
[31] Ling, F.; Wan, Y.; Wang, D.; Ma, C. *J. Org. Chem.* ***2016***, *81*, 2770.
[32] Xie, M.; Wang, S.; Wang, J.; Fang, K.; Liu, C.; Zha, C.; Jia, J. *J. Org. Chem.* ***2016***, *81*, 3329.
[33] Hajra, A.; Wei, Y.; Yoshikai, N. *Org. Lett.* ***2012***, *14*, 5488. Also see Girard, S.A.; Hu, X.; Knauber, T.; Zhou, F.; Simon, M.-O.; Deng, G.-J.; Li, C.-J. *Org. Lett.* ***2012***, *14*, 5606.
[34] Wu, X.; Li, K.; Wang, S.; Liu, C.; Lei, A. *Org. Lett.* ***2016***, *18*, 56.
[35] Xu, D.; Jin, R.; Liu, W.; Ba, F.; Li, Y.; Ding, A.; Guo, H. *Tetrahedron Lett.* ***2016***, *57*, 3235.
[36] Tong, H.-C.; Reddy, K.R.; Liu, S.-T. *Eur. J. Org. Chem.* ***2014***, 3256.
[37] Locatelli, F.; Candy, J.-P.; Didillon, B.; Niccolai, G.P.; Uzio, D.; Basset, J.-M. *J. Am. Chem. Soc.* ***2001***, *123*, 1658.
[38] Flaherty, D.W.; Iglesia, E. *J. Am. Chem. Soc.* ***2013***, *135*, 18586.
[39] Varma, R.S.; Kumar, D. *Tetrahedron Lett.* ***1998***, *39*, 9113.
[40] Damavandi, J.A.; Zolfigol, M.A.; Karami, B. *Synth. Commun.* ***2001***, *31*, 3183.
[41] Zolfigol, M.A.; Kiany-Borazjani, M.; Sadeghi, M.M.; Mohammadpoor-Baltork, I.; Memarian, H.R. *Synth. Commun.* ***2000***, *30*, 551.
[42] Memarian, H.R.; Sadeghi, M.M.; Momeni, A.R. *Synth. Commun.* ***2001***, *31*, 2241.
[43] Lu, J.; Bai, Y.; Wang, Z.; Yang, B.Q.; Li, W. *Synth. Commun.* ***2001***, *31*, 2625.
[44] Cai, X.-h.; Yang, H.-j.; Zhang, G.-l. *Can. J. Chem.* ***2005***, *83*, 273.

1,4-dihydropyridines (see **19-37**, **16-15**) are aromatized by treatment with ferric perchlorate in acetic acid.[45] Cyclic imines are converted to pyridine derivatives with NCS and then excess sodium methoxide.[46] Enamines are aromatized by reaction with Sn or Sb compounds.[47] The *Rauhut-Currier reaction* is the trialkylphosphine-mediated dimerization or isomerization of electron-deficient alkenes such as an enone, to give a 2-substituted acrylate derivative.[48] This reaction has also been referred to as a vinylogous Morita-Baylis-Hillman reaction (**16-26**).[49] An aza-Rauhut-Currier/cyclization/desulfonation cascade of allenoates with *N*-sulfonyl-1-aza-1,3-dienes, catalyzed by TMEDA, gave pyridine derivatives.[50] The Pd/Brønsted acid-catalyzed aerobic oxidative aromatization of simple aliphatic alcohols by reaction with anilines gave substituted quinoline derivatives.[51] *N*-Substituted anilines were prepared via an aromatization reaction of 3-phenyl-2,4-dioxa-3-borabicyclo[3.3.1]nonan-7-one derivatives and primary or secondary amines.[52] Hantzch 1,4-dihydropyridines were converted to pyridine derivatives with tris(4-bromophenyl)aminium hexachloroantimonate ($TBPA^{+\bullet}$), which is a radical cation salt, under aerobic conditions.[53]

OS **II**, 214, 423; **III**, 310, 358, 729, 807; **IV**, 536; **VI**, 731. Also see, OS **III**, 329.

19-2 Dehydrogenations Yielding Carbon-Carbon Double Bonds



1

Dehydrogenation of an aliphatic compound to give a double bond in a specific location is not usually a feasible process, although industrially mixtures of alkenes are obtained in this way from mixtures of alkanes (generally by heating with chromia/alumina catalysts). There are, however, some notable exceptions. Heating cyclooctane with an Ir catalyst leads to cyclooctene.[54] Treating alkenes that have an allylic hydrogen with $CrCl_2$ converts them to allenes.[55] It is not surprising, however, that most of the exceptions generally involve cases where the new double bond can be in conjugation with a double bond or with an unshared pair of electrons already present.[56] One example is the synthesis developed by Leonard and co-workers,[57] in which tertiary amines give enamines (**10-69**) when treated with mercuric

[45] Heravi, M.M.; Behbahani, F.K.; Oskooie, H.A.; Shoar, R.H. *Tetrahedron Lett.* ***2005***, *46*, 2775.
[46] DeKimpe, N.; Keppens, M.; Fonck, G. *Chem. Commun.* ***1996***, 635.
[47] Bigdeli, M.A.; Rahmati, A.; Abbasi-Ghadim, H.; Mahdavinia, G.H. *Tetrahedron Lett.* ***2007***, *48*, 4575.
[48] Rauhut, M.M.; Currier, H. *U.S. Patent* 3 074 999 ***1963***, *U.S. Patent* 3 074 999.
[49] Frank, S.A.; Mergott, D.J.; Roush, W.R. *J. Am. Chem. Soc.* ***2002***, *124*, 2404.
[50] Shi, Z.; Loh, T.-P. *Angew. Chem. Int. Ed.* ***2013***, *52*, 8584.
[51] Li, J.; Zhang, J.; Yang, H.; Jiang, G. *J. Org. Chem.* ***2017***, *82*, 3284.
[52] Luo, J.; Ji, E.; Ye, J.; Wu, R.; Qiu, L. *Tetrahedron Lett.* ***2013***, *54*, 4505.
[53] Jia, X.; Yu, L.; Huo, C.; Wang, Y.; Liu, J.; Wang, X. *Tetrahedron Lett.* ***2014***, *55*, 264.
[54] Göttker-Schnetmann, I.; White, P.; Brookhart, M. *J. Am. Chem. Soc.* ***2004***, *126*, 1804.
[55] Takai, K.; Kokumai, R.; Toshikawa, S. *Synlett* ***2002***, 1164.
[56] See Haines, A.J. *Methods for the Oxidation of Organic Compounds*, Vol. 1, Academic Press, NY, ***1985***, pp. 6–16, 206–216. For lists of examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 251–256.
[57] See Leonard, N.J.; Musker, W.K. *J. Am. Chem. Soc.* ***1959***, *81*, 5631; ***1960***, *82*, 5148.

acetate.[58] In one example, the initial product is the iminium ion **1**, which loses a proton to give the enamine. Other transition metal catalysts convert amines to enamines, including Co compounds.[59]

The oxidizing agent SeO_2 can in certain cases convert a carbonyl compound to an α,β-unsaturated carbonyl compound by removing H_2[60] (note that this reagent more often gives **19-18**). Similarly, SeO_2 has been used to dehydrogenate 1,4-diketones[61] and 1,2-diarylalkanes. These conversions can also be carried out by certain quinones, most notably DDQ (see **19-1**).[25]

Simple aldehydes and ketones have been dehydrogenated (e.g., cyclopentanone → cyclopentenone) by $PdCl_2$[62] and by $FeCl_3$,[63] among other reagents. In an indirect method of achieving this conversion, the silyl enol ether of a simple ketone is treated with DDQ[64] or with triphenylmethyl cation.[65] For another indirect method, see **17-10**.

The Ru-catalyzed reaction with a cobalt(salophen) co-catalyst lead to oxidative dehydrogenation of tetrahydroquinolines to give the corresponding quinoline.[66] The Pd-catalyzed dehydrogenation of cyclic ketones to the corresponding enones used O_2 as the oxidant.[67] Formation of a zinc enolate followed by the addition of allyl pivalate and a Pd catalyst gave the α,β-unsaturated ester, lactone, or nitrile.[68] Using a Au nanoparticle catalyst, the dehydrogenative oxidation reaction of 2-substituted indoline and dihydropyridine under molecular oxygen was accomplished in aqueous solution.[69] The DMF-promoted dehydrogenation of 1-substituted 1,2,3,4-tetrahydroisoquinolines gave cyclic imines.[70] 2-Arylpyrroles were prepared from 1-aryl-1-pyrrolines using a Pd catalyst on alumina.[71]

Simple linear alkanes have been converted to alkenes by treatment with certain transition metal compounds.[72] A transient Ti alkylidyne facilitated the dehydrogenation conversion of ethane to ethene.[73] The Ru-catalyzed dehydrogenation of alkanes to alkenes[74] was

[58] See Haynes, L.W.; Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, pp. 103–163; Lee, D.G. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 102–107.

[59] Bolig, A.D.; Brookhart, M. *J. Am. Chem. Soc.* ***2007***, *129*, 14544.

[60] See Back, T.G. in Patai, S. *The Chemistry of Organic Selenium and Tellurium Compounds*, pt. 2, Wiley, NY, ***1987***, pp. 91–213, 110–114; Jerussi, R.A. *Sel. Org. Transform.* ***1970***, *1*, 301 (see pp. 315–321).

[61] See Barnes, C.S.; Barton, D.H.R. *J. Chem. Soc.* ***1953***, 1419.

[62] See Mukaiyama, T.; Ohshima, M.; Nakatsuka, T. *Chem. Lett.* ***1983***, 1207. See also, Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 103–110.

[63] Cardinale, G.; Laan, J.A.M.; Russell, S.W.; Ward, J.P. *Recl. Trav. Chim. Pays-Bas* ***1982***, *101*, 199.

[64] Jung, M.E.; Pan, Y.; Rathke, M.W.; Sullivan, D.F.; Woodbury, R.P. *J. Org. Chem.* ***1977***, *42*, 3961.

[65] Ryu, I.; Murai, S.; Hatayama, Y.; Sonoda, N. *Tetrahedron Lett.* ***1978***, 3455. Also see Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* ***1983***, *24*, 5635, 5639.

[66] Wendlandt, A.E.; Stahl, S.S. *J. Am. Chem. Soc.* ***2014***, *136*, 11910.

[67] Diao, T.; Stahl, S.S. *J. Am. Chem. Soc.* ***2011***, *133*, 14566. See Turlik, A.; Chen, Y.; Newhouse, T.R. *Synlett* ***2016***, *27*, 331; Yoshii, D.; Jin, X.; Yatabe, T.; Hasegawa, J.-y.; Yamaguchi, K.; Mizuno, N. *Chem. Commun.* ***2016***, *52*, 14314.

[68] Chen, Y.; Romaire, J.P.; Newhouse, T.R. *J. Am. Chem. Soc.* ***2015***, *137*, 5875.

[69] Amaya, T.; Ito, T.; Inada, Y.; Saio, D.; Hirao, T. *Tetrahedron Lett.* ***2012***, *53*, 6144.

[70] Feng, G.-S.; Ji, Y.; Liu, H.-F.; Shi, L.; Zhou, Y.-G. *Tetrahedron Lett.* ***2016***, *57*, 747.

[71] Figueira, C.A.; Lopes, P.S.; Gomes, P.T. *Tetrahedron* ***2015***, *71*, 4362.

[72] See Maguire, J.A.; Boese, W.T.; Goldman, A.S. *J. Am. Chem. Soc.* ***1989***, *111*, 7088; Sakakura, T.; Ishida, K.; Tanaka, M. *Chem. Lett.* ***1990***, 585, and references cited therein.

[73] Cavaliere, V.N.; Crestani, M.G.; Pinter, B.; Pink, M.; Chen, C.-H.; Baik, M.-H.; Mindiola, D.J. *J. Am. Chem. Soc.* ***2011***, *133*, 10700.

[74] Sattler, J.J.H.B.; Ruiz-Martinez, J.; Santillan-Jimenez, E.; Weckhuysen, B.M. *Chem. Rev.* ***2014***, *114*, 10613.

accomplished using photoirradiation.[75] An entirely different approach (remote functionalization) allows specific dehydrogenation, as reported by R. Breslow[76] and by J.E. Baldwin.[77] 3α-Cholestanol was converted to 5α-cholest-14-en-3α-ol, for example, thus introducing a double bond at a specific site remote from any functional group.[78] A different kind of dehydrogenation was used in the final step of Paquette's synthesis of dodecahedrane.[79]

OS **V**, 428, **VII**, 4, 473.

19-3 Oxidation of Alcohols to Aldehydes and Ketones[80]

$$RCH_2OH \xrightarrow[\text{dichromate}]{\text{Pyridinium}} RCHO \qquad RCHOHR' \xrightarrow[H_2SO_4]{K_2Cr_2O_7} RCOR'$$

Primary alcohols can be converted to aldehydes and secondary alcohols converted to ketones via a dehydrogenation reaction that constitutes an oxidation.[81] There are myriad oxidizing agents, categorized by reagent type where possible.

1. *With chromium reagents*.[82] Secondary alcohols are easily oxidized to ketones by dichromate in acidic media[83] at room temperature or slightly above. A solution of chromic acid and sulfuric acid in water is known as the *Jones reagent*.[84] Secondary alcohols are oxidized to ketones rapidly and in high yield without disturbing any double or triple bonds that may be present (see **19-10**) and without epimerizing an adjacent stereogenic center.[85] Mixing sodium dichromate with an alcohol, without solvent, provides a method for oxidation when the mixture is shaken.[86] CrO_3[87]

[75] Chowdhury, A.D.; Weding, N.; Julis, J.; Franke, R.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed.* ***2014***, *53*, 6477.

[76] See Breslow, R. *Chemtracts: Org. Chem.* ***1988***, *1*, 333; *Acc. Chem. Res.* ***1980***, *13*, 170; *Isr. J. Chem.* ***1979***, *18*, 187; *Chem. Soc. Rev.* ***1972***, *1*, 553.

[77] Baldwin, J.E.; Bhatnagar, A.K.; Harper, R.W. *Chem. Commun.* ***1970***, 659.

[78] See Czekay, G.; Drewello, T.; Schwarz, H. *J. Am. Chem. Soc.* ***1989***, *111*, 4561. See also, Nagata, R.; Saito, I. *Synlett* ***1990***, 291. See Batr, R.; Breslow, R. *Tetrahedron Lett.* ***1989***, *30*, 535; Orito, K.; Ohto, M.; Suginome, H. *J. Chem. Soc., Chem. Commun.* ***1990***, 1076.

[79] Paquette, L.A.; Doherty, A.M. *Polyquinane Chemistry*, Springer, NY, ***1987***. See in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, ***1990***, the reviews by Paquette, L.A. pp. 313–352, and by Fessner, W.; Prinzbach, H. pp. 353–405; Paquette, L.A. *Chem. Rev.* ***1989***, *89*, 1051; Lindberg, T. in *Strategies and Tactics in Organic Synthesis*, Academic Press, NY, ***1984***, pp. 175–200.

[80] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 216–244.

[81] Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 114–126, 132–149; Haines, A.M. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, pp. 5–148, 326–390; Müller, P. in Patai, S. *The Chemistry of Functional Groups*, Supplement E, Wiley, NY, ***1980***, pp. 469–538. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1234–1250.

[82] See Lee, D.G. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***, pp. 56–81; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 257–273.

[83] See Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Open Court Pub. Co., La Salle, IL, ***1981***, pp. 118–216; Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 1, Wiley, NY, ***1967***, pp. 142–147, 1059–1064, and subsequent volumes in this series.

[84] Bowers, A.; Halsall, T.G.; Jones, E.R.H.; Lemin, A.J. *J. Chem. Soc.* ***1953***, 2548. Also see Ali, M.H.; Wiggin, C.J. *Synth. Commun.* ***2001***, *31*, 3383.

[85] See Djerassi, C.; Hart, P.A.; Warawa, E.J. *J. Am. Chem. Soc.* ***1964***, *86*, 78.

[86] Lou, J.-D.; Gao, C.-L.; Ma, Y.-C.; Huang, L.-H.; Li, L. *Tetrahedron Lett.* ***2006***, *47*, 311.

[87] Lou, J.-D.; Xu, Z.-N. *Tetrahedron Lett.* ***2002***, *43*, 6095.

has been used to oxidize primary alcohols under solvent-free conditions. Chromium trioxide on silica gel, in supercritical CO_2, oxidizes alcohols to the corresponding carbonyl.[88] For acid-sensitive compounds, trimethylsilyl chromates[89] can be used. Phase-transfer catalysis is particularly useful,[90] especially when the substrates are generally insoluble in water (Sec. 10.G.v).

The Jones reagent can also oxidize primary allylic alcohols to the corresponding aldehydes,[91] although over-oxidation to the carboxylic acid is a problem.[92] Oxidative cleavage of primary alcohols has been observed in the presence of molecular sieves 3 Å.[93] One way to mitigate over-oxidation is to distil the aldehyde as it is formed, but this is not always possible. Due to these problems, other oxidizing conditions or modified chromium reagents have been used to convert at least some primary alcohols to aldehydes.[94] Perhaps the three most commonly used Cr(VI) reagents used for the oxidation of allylic alcohols include[95] dipyridine Cr(VI) oxide (*Collins' reagent*),[96] pyridinium chlorochromate (PCC),[97] and pyridinium dichromate (PDC).[98] PCC is somewhat acidic, and acid-catalyzed rearrangements have been observed.[99] For allylic alcohols and alkenyl alcohols, (*Z*)/(*E*) isomerization has been observed.[100] The Ru-catalyzed, asymmetric isomerization of allylic alcohols to chiral aliphatic ketones has been reviewed.[101] Platinum metals have also been used.[102] An Ir-catalyzed isomerization is selective for primary alcohols.[103]

Analogous to the use of pyridine for PCC and PDC, a variety of amines and diamines have been converted to tetraalkylammonium halochromates or dichromates, including *N*-benzyl 1,4-diazabicyclo[2.2.2]octane ammonium dichromate

[88] González-Núñez, M.E.; Mello, R.; Olmos, A.; Acerete, R.; Asensio, G. *J. Org. Chem.* ***2006***, *71*, 1039.

[89] Moiseenkov, A.M.; Cheskis, B.A.; Veselovskii, A.B.; Veselovskii, V.V.; Romanovich, A.Ya.; Chizhov, B.A. *J. Org. Chem. USSR* ***1987***, *23*, 1646.

[90] For a review, see Patel, S.; Mishra, B.K. *Tetrahedron* ***2007***, *63*, 4367.

[91] Harding, K.E.; May, L.M.; Dick, K.F. *J. Org. Chem.* ***1975***, *40*, 1664.

[92] Though ketones are much less susceptible to further oxidation than aldehydes, such oxidation is possible (**19-8**), and care must be taken to avoid it, usually by controlling the temperature and/or the oxidizing agent.

[93] Fernandes, R.A.; Kumar, P. *Tetrahedron Lett.* ***2003***, *44*, 1275.

[94] Also see Nishiguchi, T.; Asano, F. *J. Org. Chem.* ***1989***, *54*, 1531; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1234–1250.

[95] See Warrener, R.N.; Lee, T.S.; Russell, R.A.; Paddon-Row, M.N. *Aust. J. Chem.* ***1978***, *31*, 1113.

[96] Collins, J.C.; Hess, W.W. *Org. Synth.* ***VI***, 644; Sharpless, K.B.; Akashi, K. *J. Am. Chem. Soc.* ***1975***, *97*, 5927.

[97] Corey, E.J.; Suggs, J.W. *Tetrahedron Lett.* ***1975***, 2647. See Luzzio, F.A.; Guziec Jr., F.S. *Org. Prep. Proced. Int.* ***1988***, *20*, 533; Agarwal, S.; Tiwari, H.P.; Sharma, J.P. *Tetrahedron* ***1990***, *46*, 4417; Salehi, P.; Firouzabadi, H.; Farrokhi, A.; Gholizadeh, M. *Synthesis* ***2001***, 2273.

[98] See Czernecki, S.; Georgoulis, C.; Stevens, C.L.; Vijayakumaran, K. *Tetrahedron Lett.* ***1985***, *26*, 1699.

[99] See Ren, S.-K.; Wang, F.; Dou, H.-N.; Fan, C.-A.; He, L.; Song, Z.-L.; Xia, W.-J.; Li, D.-R.; Jia, Y.-X.; Li, X.; Tu, Y.-Q. *Synthesis* ***2001***, 2384.

[100] For examples with chromium oxidant, see Martinez, Y.; de las Heras, M.A.; Vaquero, J.J.; Garcia-Navio, J.L.; Alvarez-Builla, J. *Tetrahedron Lett.* ***1995***, *36*, 8513; Schneider, R.; Gerardin, P.; Loubinoux, B.; Rihs, G. *Tetrahedron* ***1995***, *51*, 4997. For examples with MnO_2, see: Domínguez, M.; Álvarez, R.; Borràs, E.; Farrés, J.; Parés, X.; de Lera, A.R. *Org. Biomol. Chem.* ***2006***, *4*, 155; Valla, A.; Cartier, D.; Laurent, A.; Valla, B.; Labia, R.; Potier, P. *Synth. Commun.* ***2003***, *33*, 1195. For examples with hypervalent iodine compounds, see: Xue, H.; Gopal, P.; Yang, J. *J. Org. Chem.* ***2012***, *77*, 8933; Martínez-Bescos, P.; Cagide-Fagín, F.; Roa, L.F.; Ortiz-Lara, J.C.; Kierus, K.; Ozores-Viturro, L.; Fernández-González, M.; Alonso, R. *J. Org. Chem.* ***2008***, *73*, 3745. For an example using a biocatalyst, see Gargiulo, S.; Opperman, D.J.; Hanaefeld, U.; Arends, I.W.C.E.; Hollmann, F. *Chem. Commun.* ***2012***, *48*, 6630.

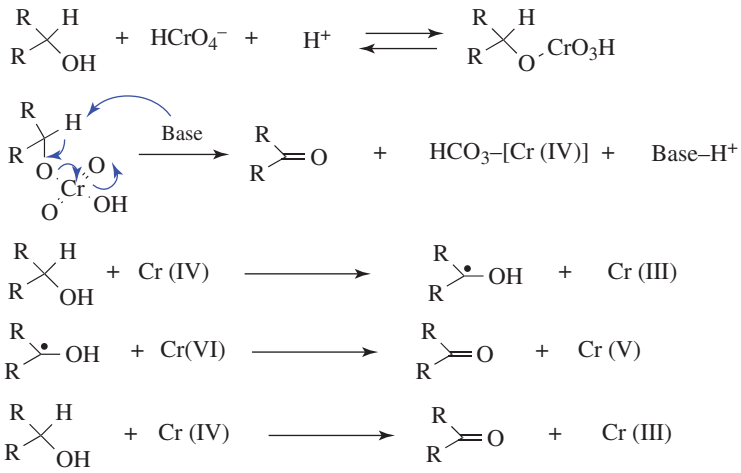
[101] Cahard, D.; Gaillard, S.; Renaud, J.-L. *Tetrahedron Lett.* ***2015***, *56*, 6159.

[102] Mantilli, L.; Mazet, C. *Chem. Lett.* ***2011***, *40*, 341; Nagamine, T.; Kon, Y.; Sato, K. *Chem. Lett.* ***2012***, *41*, 744.

[103] Li, H.; Mazet, C. *Acc. Chem. Res.* ***2016***, *49*, 1232.

with microwave irradiation,[104] guanidinium chlorochromate,[105] γ-picolinium chlorochromate,[106] and quinolinium fluorochromate.[107] Benzyltriphenylphosphonium chlorochromate has been used in a similar manner.[108] Triphenylmethylphosphonium dichromate is effective for selective oxidation of benzylic alcohols.[109]

Studies on the mechanism of oxidation with acid dichromate[110] led to the currently accepted mechanism as proposed by Westheimer.[111] The base in the second step may be water, although it is also possible[112] that in some cases no external base is involved and that the proton is transferred directly to one of the CrO_3H oxygen atoms, in which case the Cr(IV) species produced would be H_2CrO_3. Part of the evidence for this mechanism was the isotope effect of ~6 found on use of MeCDOHMe, showing that the α hydrogen is removed in the rate-determining step.[113] Note that the substrate is oxidized by three different oxidation states of chromium.[114]



Mechanisms are less clear for the other oxidizing agents discussed below.[115] A summary of many proposed mechanisms is given by Littler.[116]

[104] Hajipour, A.R.; Mallakpour, S.E.; Khoee, S. *Synlett* ***2000***, 740.
[105] Goswami, S.; Kar, A. *Synth. Commun.* ***2010–2011***, *41*, 2500.
[106] Khodaei, M.M.; Salehi, P.; Goodarzi, M. *Synth. Commun.* ***2001***, *31*, 1253.
[107] Rajkumar, G.A.; Arabindoo, B.; Murugesan, V. *Synth. Commun.* ***1999***, *29*, 2105.
[108] Hajipour, A.R.; Mallakpour, S.E.; Backnejad, H. *Synth. Commun.* ***2000***, *30*, 3855.
[109] Hajipour, A.R.; Safaei, S.; Ruoho, A.E. *Synth. Commun.* ***2009***, *39*, 3687.
[110] See Müller, P. *Chimia* ***1977***, *31*, 209; Wiberg, K.B. in Wiberg, K.B. *Oxidation in Organic Chemistry*, pt. A, Academic Press, NY, ***1965***, pp. 142–170; Waters, W.A. *Mechanisms of Oxidation of Organic Compounds*, Wiley, NY, ***1964***, pp. 49–71; Stewart, R. *Oxidation Mechanisms*, W.A. Benjamin, NY, ***1964***, pp. 37–48; Sengupta, K.K.; Samanta, T.; Basu, S.N. *Tetrahedron* ***1985***, *41*, 205.
[111] Westheimer, F.H. *Chem. Rev.* ***1949***, *45*, 419 (see p. 434); Holloway, F.; Cohen, M.; Westheimer, F.H. *J. Am. Chem. Soc.* ***1951***, *73*, 65.
[112] Kwart, H.; Nickle, J.H. *J. Am. Chem. Soc.* ***1979***, *98*, 2881 and cited references. See also, Agarwal, S.; Tiwari, H.P.; Sharma, J.P. *Tetrahedron* ***1990***, *46*, 1963.
[113] Westheimer, F.H.; Nicolaides, N. *J. Am. Chem. Soc.* ***1949***, *71*, 25. Also see Lee, D.G.; Raptis, M. *Tetrahedron* ***1973***, *29*, 1481.
[114] See Wiberg, K.B.; Mukherjee, S.K. *J. Am. Chem. Soc.* ***1974***, *96*, 1884, 6647.
[115] See Cockerill, A.F.; Harrison, R.G. in Patai, S. *The Chemistry of Functional Groups*, Supplement A, pt. 1, Wiley, NY, ***1977***, pp. 264–277.
[116] Littler, J.S. *J. Chem. Soc.* ***1962***, 2190.

2. *With manganese oxidizing agents.* Potassium permanganate ($KMnO_4$) has been used for the oxidation of alcohols.[117] Benzylic and allylic alcohols have been selectively oxidized to the aldehyde in the presence of saturated alcohols by the use of potassium manganate(VI) (K_2MnO_4) under phase-transfer conditions.[118] Phase-transfer catalysis has also been used with chromic acid,[119] ruthenium tetroxide,[120] and Lewis acid-activated potassium permanganate.[121] Ultrasound has been used for $KMnO_4$ oxidations.[122] Potassium permanganate has been supported on Kieselgühr,[123] and manganese dioxide supported on aluminum silica has been used.[124]

   The oxidizing reagent MnO_2[125] is an important reagent for the selective oxidation of benzylic alcohols, in preference to aliphatic substrates.[126] Benzylic and allylic alcohols were oxidized using $Mn(OAc)_3$ and a 2,3-dichloro-5,6-dicyano-1,4-benzoquinone catalyst.[127] Manganese(VI) oxidizing agents that are soluble in organic solvents have been developed.[128] Manganese complexes of N_4 ligands have been used for the oxidation of secondary alcohols to ketones.[129]
3. *The Oppenauer oxidation*. When a ketone in the presence of an aluminum alkoxide is used as the oxidizing agent (it is reduced to a secondary alcohol), the reaction is known as the *Oppenauer oxidation*.[130] Triorganoaluminum reagents have been used.[131] This oxidation is the reverse of the *Meerwein-Ponndorf-Verley reduction* (**19-40**) and the mechanism is also the reverse. The ketones most commonly used are acetone, butanone, and cyclohexanone. A common base is aluminum *tert*-butoxide. The chief advantage of the method is its high selectivity. Although the method is most often used for the preparation of ketones, it has also been used for aldehydes. An In catalyst[132] and an Ir catalyst[133] have been developed for the Oppenauer oxidation, as has a water-soluble Ir catalyst.[134] Homogeneous water-soluble complexes

[117] See Takemoto, T.; Yasuda, K.; Ley, S.V. *Synlett* ***2001***, 1555. For oxidation in an ionic liquid, see Kumar, A.; Jain, N.; Chauhan, S.M.S. *Synth. Commun.* ***2004***, *34*, 2835.

[118] Kim, K.S.; Chung, S.; Cho, I.H.; Hahn, C.S. *Tetrahedron Lett.* ***1989***, *30*, 2559. See Lee, D.G. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. D, Academic Press, NY, ***1982***, pp. 147–206.

[119] See Landini, D.; Montanari, F.; Rolla, F. *Synthesis* ***1979***, 134; Pletcher, D.; Tait, S.J.D. *J. Chem. Soc., Perkin Trans. 2* ***1979***, 788.

[120] Morris Jr., P.E.; Kiely, D.E. *J. Org. Chem.* ***1987***, *52*, 1149.

[121] Du, H.; Lo, P.K.; Hu, Z.; Liang, H.; Lau, K.-C.; Wang, Y.-N.; Lam, W.W.Y.; Lau, T.-C. *Chem. Commun.* ***2011***, *47*, 7143.

[122] Yamawaki, J.; Sumi, S.; Ando, T.; Hanfusa, T. *Chem. Lett.* ***1983***, 379.

[123] Hunag, L.-H.; Wang, Q.; Ma, Y.-C.; Lou, J.-D.; Zhang, C. *Synth. Commun.* ***2010–2011***, *41*, 1682.

[124] Huang, L.-H.; Ma, Y.-C.; Zhang, C.; Wang, Q.; Zou, X.-N.; Lou, J.-D. *Synth. Commun.* ***2012***, *42*, 3377.

[125] Lou, J.D.; Xu, Z.-N. *Tetrahedron Lett.* ***2002***, *43*, 6149; Kamimura, A.; Komatsu, H.; Moriyama, T.; Nozaki, Y. *Tetrahedron* ***2013***, *69*, 5968.

[126] Taylor, R.J.K.; Reid, M.; Foot, J.; Raw, S.A. *Acc. Chem. Res.* ***2005***, *38* 851. See Varma, R.S.; Saini, R.K.; Dahiya, R. *Tetrahedron Lett.* ***1997***, *38*, 7823.

[127] Cosner, C.C.; Cabrera, P.J.; Byrd, K.M.; Thomas, A.M.A.; Helquist, P. *Org. Lett.* ***2011***, *13*, 2071.

[128] Ellis, R.; Lee, K.-H.; Ainsworth, M.; Kerr, A.; Viseux, E.M.E. *Synlett* ***2012***, *23*, 1371.

[129] Shen, D.; Miao, C.; Xu, D.; Xia, C.; Sun, W. *Org. Lett.* ***2015***, *17*, 54.

[130] See Djerassi, C. *Org. React.* ***1951***, *6*, 207. See Graves, C.R.; Zeng, B.-S.; Nguyen, S.T. *J. Am. Chem. Soc.* ***2006***, *128*, 12596.

[131] Fu, Y.; Yang, Y.; Hügel, H.M.; Du, Z.; Wang, K.; Huang, D.; Hu, Y. *Org. Biomol. Chem.* ***2013***, *11*, 4429.

[132] Ogiwara, Y.; Ono, Y.; Sakai, N. *Synthesis* ***2016***, *48*, 4043.

[133] Suzuki, T.; Morita, K.; Tsuchida, M.; Hiroi, K. *J. Org. Chem.* ***2003***, *68*, 1601.

[134] Ajjou, A.N. *Tetrahedron Lett.* ***2001***, *42*, 13.

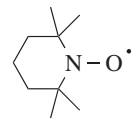
catalyze the reaction.[135] An uncatalyzed reaction under supercritical conditions was reported.[136] A heterogeneous zirconia catalyst was used in a flow system (Sec. 7.D).[137] A Ru-NNN complex was used to catalyze Oppenauer oxidation of secondary alcohols.[138]

4. *DMSO-based reagents*. The use of oxalyl chloride and DMSO at low temperature is called the *Swern oxidation*[139] and is widely used. A sulfonium salt is produced *in situ*, which reacts with the alcohol to generate the key intermediate required for oxidation.[140] Maintaining the low reaction temperature is essential in this reaction, however, since the reagent generated *in situ* decomposes at temperatures significantly below ambient. Note that Swern oxidation of molecules having alcohol moieties, as well as a disulfide, leads to the carbonyl compound without oxidation of the sulfur.[141] Sulfoxides other than DMSO can be used in conjunction with oxalyl chloride for the oxidation of alcohols,[142] including fluorinated sulfoxides[143] and a polymer-bound sulfoxide.[144]

   Similar oxidation of alcohols has been carried out with DMSO and other reagents[145] in place of DCC: acetic anhydride,[146] SO_3/pyridine/triethylamine,[147] trifluoroacetic anhydride,[148] trimethylamine *N*-oxide,[149] and a Mo catalyst and O_2.[150] Iodine has been used in conjunction with DMSO and hydrazine.[151] DMSO and polymer bromide has been used for the oxidation of alcohols.[152] An alcohol is treated with DMSO, DCC, and anhydrous phosphoric acid[153] in what is called *Moffatt oxidation*. In this way a primary alcohol can be converted to the aldehyde with no carboxylic acid being produced. The strong acid conditions are sometimes a problem, and complete removal of the dicyclohexylurea by-product can be difficult.[154] Oxidation of alcohols was reported using [methoxycarbonylsulfamoyl]triethylammonium hydroxide (*Burgess reagent*) in DMSO.[155]

[135] Ajjou, A.N.; Pinet, J.-L. *Can. J. Chem.* ***2005***, *83*, 702.
[136] Sominsky, L.; Rozental, E.; Gottlieb, H.; Gedanken, A.; Hoz, S. *J. Org. Chem.* ***2004***, *69*, 1492.
[137] Chorghade, R.; Battilocchio, C.; Hawkins, J.M.; Ley, S.V. *Org. Lett.* ***2013***, *15*, 5698.
[138] Wang, Q.; Du, W.; Liu, T.; Chai, H.; Yu, Z. *Tetrahedron Lett.* ***2014***, *55*, 1585.
[139] Omura, K.; Swern, D. *Tetrahedron* ***1978***, *34*, 1651. See Wang, Y.; Wang, C.; Sun, J. *Synth. Commun.* ***2014***, *44*, 2961; Ye, X.; Fu, H.; Ma, J.; Zhong, W. *Synth. Commun.* ***2016***, *46*, 885; Nguyen, T.V.; Hall, M. *Tetrahedron Lett.* ***2014***, *55*, 6895; Tsuchiya, D.; Moriyama, K.; Togo, H. *Synlett* ***2011***, *22*, 2701.
[140] For a mechanism study, see Giagou, T.; Meyer, M.P. *J. Org. Chem.* ***2010***, *75*, 8088.
[141] Fang, X.; Bandarage, U.K.; Wang, T.; Schroeder, J.D.; Garvey, D.S. *J. Org. Chem.* ***2001***, *66*, 4019.
[142] Nishida, K.; Ohsugi, S.-i.; Fudesaka, M.; Kodama, S.; Node, M. *Tetrahedron Lett.* ***2002***, *43*, 5177.
[143] Crich, D.; Neelamkavil, S. *Tetrahedron* ***2002***, *58*, 3865.
[144] Choi, M.K.W.C.; Toy, P.H. *Tetrahedron* ***2003***, *59*, 7171.
[145] For a review, see Mancuso, A.J.; Swern, D. *Synthesis* ***1981***, 165.
[146] Albright, J.D.; Goldman, L. *J. Am. Chem. Soc.* ***1967***, *89*, 2416.
[147] Parikh, J.R.; Doering, W. von E. *J. Am. Chem. Soc.* ***1967***, *89*, 5507.
[148] Huang, S.L.; Omura, K.; Swern, D. *Synthesis* ***1978***, 297.
[149] Godfrey, A.G.; Ganem, B. *Tetrahedron Lett.* ***1990***, *31*, 4825.
[150] Khenkin, A.M.; Neumann, R. *J. Org. Chem.* ***2002***, *67*, 7075.
[151] Gogoi, P.; Sarmah, G.K.; Konwar, D. *J. Org. Chem.* ***2004***, *69*, 5153.
[152] Prasanna, T.S.R.; Mohanaraju, K. *Tetrahedron Lett.* ***2011***, *52*, 6971.
[153] Fenselau, A.H.; Moffatt, J.G. *J. Am. Chem. Soc.* ***1966***, *88*, 1762; Albright, J.D.; Goldman, L. *J. Org. Chem.* ***1965***, *30*, 1107.
[154] One way to avoid this problem is to use a carbodiimide linked to an insoluble polymer: Weinshenker, N.M.; Shen, C. *Tetrahedron Lett.* ***1972***, 3285.
[155] Sultane, P.R.; Bielawski, C.W. *J. Org. Chem.* ***2017***, *82*, 1046.

5. *TEMPO and related reagents*. The nitroxyl radical TEMPO (**2**) has been used in conjunction with co-reagents, including mcpba,[156] O_2 with transition metal catalysts,[157] Cu/air,[158] CuBr•SMe_2 in perfluorous solvents,[159] enzymes,[160] carbenes,[161] NaOCl,[162] Fe,[163] $NaIO_4$,[164] periodic acid,[165] and H_5IO_6.[166]



2

Silica-supported TEMPO,[167] polymer-bound TEMPO,[168] and PEG-TEMPO[169] (where PEG is polyethylene glycol) have been used. TEMPO-derived ionic liquids,[170] or ionic liquid-supported TEMPO,[171] have been used for the oxidation of alcohols. An ionic liquid immobilized TEMPO reagent was developed for oxidation under solvent-free conditions[172] and a TEMPO-based ionic liquid has been developed.[173] A Cu/TEMPO catalyst system has been used for the aerobic oxidation of primary alcohols.[174] A catalytic reaction using 5% TEMPO and 5% CuCl with O_2 in an ionic liquid oxidizes benzylic alcohols to the corresponding aldehyde.[175] The Fe/9-azabicyclo[3.3.1]nonan-*N*-oxyl (ABNO)-catalyzed aerobic oxidation of alcohols gave aldehydes or ketones.[176]

Other nitroxyl radical oxidizing agents are known.[177] A related oxidizing agent is oxoammonium salt **3** (*Bobbitt's reagent)*, a stable and nonhygroscopic salt that

[156] Rychnovsky, S.D.; Vaidyanathan, R. *J. Org. Chem.* ***1999***, *64*, 310.

[157] **Mn/Co**: Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F. *Tetrahedron Lett.* ***2001***, *42*, 6651. **Mo**: Ben-Daniel, R.; Alsteers, P.; Neumann, R. *J. Org. Chem.* ***2001***, *66*, 8650. **Ru**: Dijksman, A.; Marino-González, A.; Payeras, A.M.; Arends, I.W.C.E.; Sheldon, R.A. *J. Am. Chem. Soc.* ***2001***, *123*, 6826. Also see Seki, Y.; Oisaki, K.; Kanai, M. *Tetrahedron Lett.* ***2014***, *55*, 3738.

[158] See Chen, C.; Liu, B.; Chen, W. *Synthesis* ***2013***, *45*, 3387.

[159] Betzemeier, B.; Cavazzini, M.; Quici, S.; Knochel, P. *Tetrahedron Lett.* ***2000***, *41*, 4343.

[160] Fabbrini, M.; Galli, C.; Gentili, P.; Macchitella, D. *Tetrahedron Lett.* ***2001***, *42*, 7551.

[161] Guin, J.; Sarkar, S.D.; Grimme, S.; Studer, A. *Angew. Chem. Int. Ed.* ***2008***, *47*, 8727.

[162] Fukuda, N.; Izumi, M.; Ikemoto, T. *Tetrahedron Lett.* ***2015***, *56*, 3905; Okada, T.; Asawa, T.; Sugiyama, Y.; Kirihara, M.; Iwai, T.; Kimura, Y. *Synlett* ***2014***, *25*, 596.

[163] Liu, J.; Ma, S. *Tetrahedron* ***2013***, *69*, 10161. See Wang, N.; Liu, R.; Chen, J.; Liang, X. *Chem. Commun.* ***2005***, 5322.

[164] Lei, M.; Hu, R.-J.; Wang, Y.-G. *Tetrahedron* ***2006***, *62*, 8928.

[165] Attoui, M.; Vatèle, J.-M. *Synlett* ***2014***, *25*, 2923.

[166] Kim, S.S.; Nehru, K. *Synlett* ***2002***, 616.

[167] See Wang, L.; Li, J.; Zhao, X.; Lv, Y.; Zhang, H.; Gao, S. *Tetrahedron* ***2013***, *69*, 6041.

[168] Fey, T.; Fischer, H.; Bachmann, S.; Albert, K.; Bolm, C. *J. Org. Chem.* ***2002***, *66*, 8154.

[169] See Miao, C.-X.; He, L.-N.; Wang, J.-Q.; Gao, J. *Synlett* ***2009***, 3291.

[170] Wu, X.-E.; Ma, L.; Ding, M.-X.; Gao, L.-X. *Synlett* ***2005***, 607.

[171] Fall, A.; Sene, M.; Gaye, M.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* ***2010***, *51*, 4501.

[172] Wang, Z.-g.; Xu, K.; Shen, M.-n.; Lu, M. *Synlett* ***2014***, *25*, 2459.

[173] Zhu, J.; Wang, P.-c.; Ming, L. *Synth. Commun.* ***2013***, *43*, 1871.

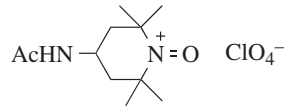
[174] Liu, X.; Xia, Q.; Zhang, Y.; Chen, C.; Chen, W. *J. Org. Chem.* ***2013***, *78*, 8531. See Steves, J.E.; Stahl, S.S. *J. Am. Chem. Soc.* ***2013***, *135*, 15742.

[175] Ansar, I.A.; Gree, R. *Org. Lett.* ***2002***, *4*, 1507.

[176] Wang, L.; Shang, S.S.; Li, G.; Ren, L.; Lv, Y.; Gao, S. *J. Org. Chem.* ***2016***, *81*, 2189.

[177] See Gilhespy, M.; Lok, M.; Baucherel, X. *Chem. Commun.* ***2005***, 1085. See Ryland, B.L.; McCann, S.D.; Brunold, T.C.; Stahl, S.S. *J. Am. Chem. Soc.* ***2014***, *136*, 12166.

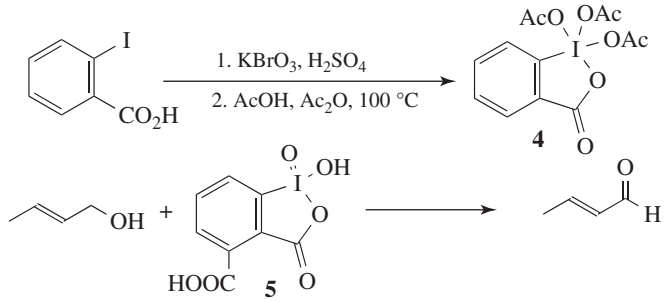
oxidizes primary and secondary alcohols in dichloromethane.[178] The mechanism of oxidation for **3** has been examined.[179]



3

The chemoselective oxidation of benzylic alcohols was reported in the presence of aliphatic alcohols by reaction with a nitroxyl radical, and proceeded via an oxoammonium species.[180] The oxidative cleavage of allylic ethers by an oxoammonium salt was reported.[181] The oxidation of primary and secondary benzyl and alkyl alcohols to the carbonyl compound by the metal-free reaction with air, catalytic amounts of NH_4NO_3, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), and HCl or H_2SO_4 has been reported.[182]

6. *With hypervalent iodine reagents*.[183] Treatment of 2-iodobenzoic acid with $KBrO_3$ in sulfuric acid and heating the resulting product to 100 °C with acetic anhydride and acetic acid[184] gives hypervalent iodine reagent **4**, the so-called *Dess-Martin periodinane*.[185] This reagent reacts with alcohols at ambient temperature to give the corresponding aldehyde or ketone.[186] The reaction is accelerated by water[187] and a water-soluble periodinane (*o*-iodoxybenzoic acid, **5**, IBX)[188] has been prepared that oxidized allylic alcohols to conjugated aldehydes.[189]



[178] See Merbouh, N.; Bobbitt, J.M.; Brückner, C. *Org. Prep. Proceed. Int.* ***2004***, *36*, 1; Bobbitt, J.M.; Bartelson, A.L.; Bailey, W.F.; Hamlin, T.A.; Kelly, C.B. *J. Org. Chem.* ***2014***, *79*, 1055.

[179] Bailey, W.F.; Bobbitt, J.M.; Wiberg, K.B. *J. Org. Chem.* ***2007***, *72*, 4504.

[180] Hamada, S.; Furuta, T.; Wada, Y.; Kawabata, T. *Angew. Chem. Int. Ed.* ***2013***, *52*, 8093.

[181] Kelly, C.B.; Ovian, J.M.; Cywar, R.M.; Grossein, T.R.; Wiles, R.J.; Leadbeater, N.E. *Org. Biomol. Chem.* ***2015***, *13*, 4255.

[182] Prebil, R.; Stavber, G.; Stavber, S. *Eur. J. Org. Chem.* ***2014***, 395.

[183] For a review, see Berthiol, F. *Synthesis* ***2015***, *47*, 587. Lex, T.R.; Swasy, M.I.; Whitehead, D.C. *J. Org. Chem.* ***2015***, *80*, 12234. See Moorthy, J.N.; Senapati, K.; Parida, K.N.; Jhulki, S.; Sooraj, K.; Nair, N.N. *J. Org. Chem.* ***2011***, *76*, 9593.

[184] See Lin, C.-K.; Lu, T.-J. *Tetrahedron* ***2010***, *66*, 9688.

[185] Dess, D.B.; Martin, J.C. *J. Am. Chem. Soc.* ***1991***, *113*, 7277. See Salvo, A.M.P.; Campisciano, V.; Beejapur, H.A.; Giacalone, F.; Gruttadauria, M. *Synlett* ***2015***, *26*, 1179.

[186] See Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* ***1994***, *35*, 8019.

[187] Meyer, S.D.; Schreiber, S.L. *J. Org. Chem.* ***1994***, *59*, 7549. In aqueous β-cyclodextrin-acetone solution, see Surendra, K.; Krishnaveni, N.S.; Reddy, M.A.; Nageswar, Y.V.D.; Rao, K.R. *J. Org. Chem.* ***2003***, *68*, 2058.

[188] Gallen, M.J.; Goumont, R.; Clark, T.; Terrier, F.; Williams, C.M. *Angew. Chem. Int. Ed.* ***2006***, *45*, 2929; Duschek, A.; Kirsch, S.F. *Angew. Chem. Int. Ed.* ***2011***, *50*, 1524.

[189] Thottumkara, A.P.; Vinod, T.K. *Tetrahedron Lett* ***2001***, *43*, 569.

An ionic liquid-supported IBX reagent has been used,[190] as has a graphene oxide-supported reagent.[191] 2-Methylpropan-2-ol has been used as a solvent.[192] The reagent has an indefinite shelf life in a sealed container but hydrolysis occurs upon long-term exposure to atmospheric moisture. A note of CAUTION! The Dess-Martin reagent can be shock sensitive under some conditions and can explode at temperatures above 200 °C.[193]

Iodine has been used as a co-catalyst.[194] Other hypervalent iodine oxidizing reagents are known,[195] including $PhI(OAc)_2$/TEMPO,[196] and $PhI(OAc)_2$-chromium salen.[197] Microwave irradiation of benzylic alcohols with PhI(OH)OTs gave the corresponding aldehyde.[198] Hypervalent iodine compounds have been used in ionic liquids.[199] A recyclable, soluble polyisobutylene-bound oxidizing agent has been reported.[200] Heating benzylic alcohols with *o*-iodoxybenzoic acid under solvent-free conditions gave the aldehyde.[201] 2-Iodobenzenesulfonic acid is a very active catalyst for oxidation of alcohols using Oxone.[202]

7. *Tetrapropylammonium perruthenate* (Pr_4N^+ RuO_4^-; also called TPAP; the *Ley reagent*).[203] This is an important oxidizing agent that is compatible with the presence of other functionality in the molecule.[204] In the presence of molecular oxygen, oxidation of alcohols is catalytic in TPAP.[205] This reagent has been bound to a polymer.[206] Methods have been developed for recovery of the catalyst and reuse of TPAP.[207]
8. *By catalytic dehydrogenation*. For the conversion of primary alcohols to aldehydes, dehydrogenation catalysts have the advantage over strong oxidizing agents that further oxidation to the carboxylic acid is prevented. Copper chromite is often used, but other catalysts (e.g., Ag and Cu) have also been employed. Many ketones were prepared in this manner. Catalytic dehydrogenation is more often used industrially than as a laboratory method. However, procedures using Cu,[208] Rh,[209]

[190] Koguchi, S.; Mihoya, A.; Mimura, M. *Tetrahedron* ***2016***, *72*, 7633.
[191] Kim, Y.-H.; Jang, H.-S.; Kim, Y.-O.; Ahn, S.-D.; Yeo, S.; Lee, S.-M.; Lee, Y.-S. *Synlett* ***2013***, *24*, 2282.
[192] Van Arman, S.A. *Tetrahedron Lett.* ***2009***, *50*, 4693.
[193] Plumb, J.B.; Harper, D.J. *Chem. Eng. News* ***1990***, July 16, p. 3. For an improved procedure, see Ireland, R.E.; Liu, L. *J. Org. Chem.* ***1993***, *58*, 2899.
[194] Karade, N.N.; Tiwari, G.B.; Huple, D.B. *Synlett* ***2005***, 2039.
[195] Moriarty, R.M.; Prakash, O. *Accts. Chem. Res.* ***1986***, *19*, 244; Dohi, T.; Takenaga, N.; Fukushima, K.-i.; Uchiyama, T.; Kato, D.; Motoo, S.; Fujioka, H.; Kita, Y. *Chem. Commun.* ***2010***, 7697.
[196] DeMico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* ***1997***, *62*, 6974.
[197] Adam, W.; Hajra, S.; Herderich, M.; Saha-Möller, C.R. *Org. Lett.* ***2000***, *2*, 2773.
[198] Lee, J.C.; Lee, J.Y.; Lee, S.J. *Tetrahedron Lett.* ***2004***, *45*, 4939.
[199] Liu, Z.; Chen, Z.-C.; Zheng, Q.-C. *Org. Lett.* ***2003***, *5*, 3321; Karthikeyan, G.; Perumal, P.T. *Synlett* ***2003***, 2249.
[200] Samunual, P.; Bergbreiter, D.E. *Tetrahedron Lett.* ***2016***, *57*, 3272.
[201] Moorthy, J.N.; Singhal, N.; Venkatakrishnan, P. *Tetrahedron Lett.* ***2004***, *45*, 5419.
[202] Uyanik, M.; Akakura, M.; Ishihara, K. *J. Am. Chem. Soc.* ***2009***, *131*, 251.
[203] Griffith, W.P.; Ley, S.V. *Aldrichimica Acta* ***1990***, *23*, 13; Chandler, W.D.; Wang, Z.; Lee, D.G. *Can. J. Chem.* ***2005***, *83*, 1212.
[204] With organotrifluoroborates: Molander, G.A.; Petrillo, D.E. *J. Am. Chem. Soc.* ***2006***, *128*, 9634.
[205] Lenz, R.; Ley, S.V. *J. Chem. Soc., Perkin Trans. 1* ***1997***, 3291.
[206] Hinzen, B.; Lenz, R.; Ley, S.V. *Synthesis* ***1998***, 977. Also see Brown, D.S.; Kerr, W.J.; Lindsay, D.M.; Pike, K.G.; Ratcliffe, P.D. *Synlett* ***2001***, 1257.
[207] Ley, S.V.; Ramarao, C.; Smith, M.D. *Chem. Commun.* ***2001***, 2278.
[208] Muldoon, J.; Brown, S.N. *Org. Lett.* ***2002***, *4*, 1043.
[209] Takahashi, M.; Oshima, K.; Matsubara, S. *Tetrahedron Lett.* ***2003***, *44*, 9201.

Ru,[210] Raney nickel,[211] and Pd complexes[212] (under phase-transfer conditions)[213] have been reported. Allylic alcohols[214] are oxidized to the corresponding saturated aldehyde or ketone by heating with a Rh catalyst, and benzylic alcohols are converted to the aldehyde with a Rh catalyst.[215] Propargylic alcohols are oxidized by heating with a V catalyst.[216] Secondary alcohols are oxidized with $Bi(NO_3)_3$ on Montmorillonite.[217] Biooxidation is possible as well via hydrogen transfer.[218]

9. *Miscellaneous reagents*.[219] Enzymatic oxidations have been reported.[220] Dimethyl dioxirane[221] oxidizes benzylic alcohols to the corresponding aldehyde,[222] and dioxirane reagents are sufficiently mild that an α,β-epoxy alcohol was oxidized to the corresponding ketone, without disturbing the epoxide, using methyl trifluoromethyl dioxirane.[223]

   The oxidation of benzylic alcohols to aldehydes or ketones used H_2O_2 with a catalytic amount of Br^- and acid in a continuous-flow system (Sec. 7.D).[224] Nitric acid in dichloromethane oxidizes benzylic alcohols to the corresponding ketone.[225] Bromine is an effective oxidant, and iodine under photochemical conditions has been used.[226] Heating a 1,2-diol with NBS in CCl_4 gave the 1,2-diketone,[227] as did an iron nitrite oxidant with microwave irradiation.[228] The Pd/Cu-catalyzed oxidation of alkynes to 1,2-diketones used DMSO as a solvent.[229] A V/air catalyst was used for the oxidation of benzyl alcohols.[230] Oxidation of alcohols in water is

[210] Meijer, R.H.; Ligthart, G.B.W.L.; Meuldijk, J.; Vekemans, J.A.J.M.; Hulshof, L.A.; Mills, A.M.; Kooijman, H.; Spek, A.L. *Tetrahedron* ***2004***, *60*, 1065.
[211] Krafft, M.E.; Zorc, B. *J. Org. Chem.* ***1986***, *51*, 5482.
[212] See Mandal, S.K.; Jensen, D.R.; Pugsley, J.S.; Sigman, M.S. *J. Org. Chem.* ***2003***, *68*, 4600. See also, Mandal, S.K.; Sigman, M.S. *J. Org. Chem.* ***2003***, *68*, 7535; Guram, A.S.; Bei, X.; Turner, H.W. *Org. Lett.* ***2003***, *5*, 2485. For a review, see Muzart, J. *Tetrahedron* ***2003***, *59*, 5789.
[213] Choudary, B.M.; Reddy, N.P.; Kantam, M.L.; Jamil, Z. *Tetrahedron Lett.* ***1985***, *26*, 6257.
[214] Tanaka, K.; Fu, G.C. *J. Org. Chem.* ***2001***, *66*, 8177.
[215] Miyata, A.; Murakami, M.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* ***2001***, *42*, 7067; Csjernyik, G.; Ell, A.H.; Fadini, L.; Pugin, B.; Bäckvall, J.-E. *J. Org. Chem.* ***2002***, *67*, 1657.
[216] Maeda, Y.; Kakiuchi, N.; Matsumura, S.; Nishimura, T.; Uemura, S. *Tetrahedron Lett.* ***2001***, *42*, 8877.
[217] Samajdar, S.; Becker, F.F.; Banik, B.K. *Synth. Commun.* ***2001***, *31*, 2691.
[218] See Orbegozo, T.; de Vries, J.G.; Kroutil, W. *Eur. J. Org. Chem.* ***2010***, 3445; Orbegozo, T.; Lavandera, I.; Fabian, W.M.F.; Mautner, B.; de Vries, J.G.; Kroutil, W. *Tetrahedron* ***2009***, *65*, 6805.
[219] See Sheldon, R.A.; Arends, I.W.C.E.; ten Brink, G.-J.; Dijksman, A. *Acc. Chem. Res.* ***2002***, *35*, 774. See *Liquid Phase Oxidation via Heterogeneous Catalysis. Organic Synthesis and Industrial Applications*, Clerici, M.G.; Kholdeeva, O.A. (Eds.), Wiley, Hoboken, ***2013***.
[220] *Bacilus stearothermophilus*: Fantin, G.; Fogagnolo, M.; Giovannini, P.P.; Medici, A.; Pedrini, P.; Poli, S. *Tetrahedron Lett.* ***1995***, *36*, 441. *Chloroperoxidase*: Hu, S.; Dordick, J.S. *J. Org. Chem.* ***2002***, *67*, 314. *Gluconobaccter oxydans* DSM 2343: Villa, R.; Romano, A.; Gandolfi, R.; Gargo, J.V.S.; Molinari, F. *Tetrahedron Lett.* ***2002***, *43*, 6059.
[221] See Deubel, D.V. *J. Org. Chem.* ***2001***, *66*, 3790.
[222] Baumstark, A.L.; Kovac, F.; Vasquez, P.C. *Can. J. Chem.* ***1999***, *77*, 308. See Angelis, Y.S.; Hatzakis, N.S.; Smonou, I.; Orfanopoulos, M. *Tetrahedron Lett.* ***2001***, *42*, 3753.
[223] D'Accolti, L.; Fusco, C.; Annese, C.; Rella, M.R.; Turteltaub, J.S.; Williard, P.G.; Curci, R. *J. Org. Chem.* ***2004***, *69*, 8510.
[224] Liu, C.; Fang, Z.; Yang, Z.; Li, Q.; Guo, S.; Zhang, K.; Ouyang, P.; Guo, K. *Tetrahedron Lett.* ***2015***, *56*, 5973.
[225] Strazzolini, P.; Runcio, A. *Eur. J. Org. Chem.* ***2003***, 526.
[226] See Shimada, Y.; Hattori, K.; Tada, N.; Miura, T.; Itoh, A. *Synthesis* ***2013***, *45*, 2684.
[227] Khurana, J.M.; Kandpal, B.M. *Tetrahedron Lett.* ***2003***, *44*, 4909.
[228] Soni, P.A.; Gupta, P.K.; Maurya, C.K.; Halve, A.K.; Ganesan, K. *Tetrahedron Lett.* ***2015***, *56*, 2817.
[229] Gao, A.; Yang, F.; Li, J.; Wu, Y. *Tetrahedron* ***2012***, *68*, 4950.
[230] Kodama, S.; Hashidate, S.; Nomoto, A.; Yano, S.; Ueshima, M.; Ogawa, A. *Chem. Lett.* ***2011***, *40*, 495.

possible using I_2O_5.[231] Potassium monoperoxysulfate oxidizes secondary alcohols in the presence of O_2.[232] The oxidation of alcohols to carbonyl compounds used KBr and Oxone or used a Brønsted acid, KBr, and aqueous H_2O_2.[233] The combination of H_2O_2, acetic acid, and NaBr has been used for the selective oxidation of activated alcohols.[234]

Reagents that can be used specifically to oxidize a secondary OH group in the presence of a primary OH group[235] are H_2O_2/ammonium molybdate[236] or urea/H_2O_2 with $MgBr_2$,[237] while osmium tetroxide[238] and Br_2/Ni$(OBz)_2$[239] oxidize primary OH groups in the presence of a secondary OH group.[240] Secondary alcohols have been chemoselectively and regioselectively oxidized in vicinal diols.[241] The selective oxidation of unsaturated alcohols was catalyzed by sodium nitrite and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone with molecular oxygen.[242] Alcohols ere oxidized using diisopropyl azodicarboxylate and catalyzed by nitroxyl radicals.[243] Alkoxyamine organocatalysts have been developed for the oxidation of alcohols.[244] Sodium hypochlorite in acetic acid[245] or in water with β-cyclodextrin[246] is a useful oxidizing agent. Calcium hypochlorite on moist alumina with microwave irradiation has been used to oxidize benzylic alcohols.[247] With ultrasound, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) selectively oxidizes a benzylic or allylic hydroxyl group of 1,2-diols.[248] Photooxidation of alcohols is possible in the presence of a catalytic amount of NBS.[249] The selective electrochemical oxidation of aromatic alcohols using sodium nitrite has been reported.[250] *tert*-Butyl nitrite has been used for the oxidation of benzylic alcohols.[251] Aromatic aldehydes were prepared by the action of laccase of *Pleurotus ostreatus* MTCC-1801.[252]

[231] Liu, Z.-Q.; Zhao, Y.; Luo, H.; Chai, L.; Sheng, Q. *Tetrahedron Lett.* ***2007***, *48*, 3017.
[232] Döbler, C.; Mehltretter, G.M.; Sundermeier, U.; Eckert, M.; Militzer, H.-C.; Beller, M. *Tetrahedron Lett.* ***2001***, *42*, 8447.
[233] Moriyama, K.; Takemura, M.; Togo, H. *J. Org. Chem.* ***2014***, *79*, 6094.
[234] Qi, X.; Wang, J.; Zheng, L.; Qi, L. *Synlett* ***2011***, *22*, 555.
[235] For a review, see Arterburn, J.B. *Tetrahedron* ***2001***, *57*, 9765.
[236] See Sakata, Y.; Ishii, Y. *J. Org. Chem.* ***1991***, *56*, 6233.
[237] Park, H.J.; Lee, J.C. *Synlett* ***2009***, 79.
[238] Maione, A.M.; Romeo, A. *Synthesis* ***1984***, 955.
[239] Doyle, M.P.; Dow, R.L.; Bagheri, V.; Patrie, W.J. *J. Org. Chem.* ***1983***, *48*, 476.
[240] For a list of references, see Kulkarni, M.G.; Mathew, T.S. *Tetrahedron Lett.* ***1990***, *31*, 4497.
[241] Eisink, N.N.H.M.; Minnaard, A.J.; Witte, M.D. *Synthesis* ***2017***, *49*, 822. Also see Mecozzi, F.; Dong, J.J.; Saisaha, P.; Browne, W.R. *Eur. J. Org. Chem.* ***2017***, *23*, 6919.
[242] Wang, L.; Li, J.; Yang, H.; Lv, Y.; Gao, S. *J. Org. Chem.* ***2012***, *77*, 790.
[243] Hayashi, M.; Shibuya, M.; Iwabuchi, Y. *J. Org. Chem.* ***2012***, *77*, 3005.
[244] Sasano, Y.; Murakami, K.; Nishiyama, T.; Kwon, E.; Iwabuchi, Y. *Angew. Chem. Int. Ed.* ***2013***, *52*, 12624.
[245] Stevens, R.V.; Chapman, K.T.; Weller, H.N. *J. Org. Chem.* ***1980***, *45*, 2030. See also, Xie, H.; Zhang, S.; Duan, H. *Tetrahedron Lett.* ***2004***, *45*, 2013.
[246] Ji, H.-B.; Shi, D.-P.; Shao, M.; Li, Z.; Wang, L.-F. *Tetrahedron Lett.* ***2005***, *46*, 2517.
[247] Mojtahedi, M.M.; Saidi, M.R.; Bolourtchian, M.; Shirzi, J.S. *Monat. Chem.* ***2001***, *132*, 655.
[248] Peng, K.; Chen, F.; She, X.; Yang, C.; Cui, Y.; Pan, X. *Tetrahedron Lett.* ***2005***, *46*, 1217.
[249] Kuwabara, K.; Itoh, A. *Synthesis* ***2006***, 1949.
[250] Christopher, C.; Lawrence, S.; Kulandainathan, M.A.; Kulangiappar, K.; Raja, M.E.; Xavier, N.; Raja, S. *Tetrahedron Lett.* ***2012***, *53*, 2802.
[251] Hamasaki, A.; Kuwada, H.; Tokunaga, M. *Tetrahedron Lett.* ***2012***, *53*, 811.
[252] Chaurasia, P.K.; Yadava, S.; Bharati, S.L.; Singh, S.K. *Synth. Commun.* ***2014***, *44*, 2535.

Many other oxidizing agents have been employed. Examples of catalytic systems include Ru,[253] Re,[254] Yb/HNO_3,[255] Fe/H_2O_2,[256] Bi catalyst,[257] Bi/H_2O_2,[258] NaBr/H_2O_2,[259] ceric ammonium nitrate in an ionic liquid,[260] O_2 with transition metal catalysts,[261] and RuO_2 and a zeolite catalyst.[262] Hydrogen peroxide with urea oxidizes aryl aldehydes in formic acid.[263] *tert*-Butylhydroperoxide with a Cu catalyst gives oxidation in an ionic liquid.[264] A Cu/diamine complex catalyzed the aerobic oxidation[265] of primary and secondary alcohols without an external *N*-oxide co-oxidant.[266] A Pd-catalyzed aerobic oxidation of alcohols has been reported.[267] Certain zirconocene complexes can selectively oxidize only one OH group of a diol, even if both are primary.[268] 1,2-Diols are oxidized to chiral α-hydroxy ketones using NBS with a chiral Cu catalyst.[269] An Ir catalyst[270] in aqueous media has been used.[271] A Ru catalyst has been used for the oxidation of benzylic alcohols.[272]

A cobalt oxide catalyst supported on activated carbon has been used.[273] The Ru-catalyzed oxidation of alcohols used molecular oxygen as an oxidant.[274] The Cu/chloride/carboxylate anion complex catalyzed reaction of alcohols to aldehydes was accomplished in water at 250 °C and 40 bar.[275] The V complex catalyst and NEt_3 oxidized benzylic, allylic, and propargylic alcohols with air.[276] A Cu-catalyzed oxidation of alcohols to the corresponding carbonyl used di-*tert*-butyldiaziridinone as the oxidant.[277]

[253] See Lee, D.G.; van den Engh, M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 197–222.
[254] Divalentin, C.; Gandolfi, R.; Gisdakis, P.; Rösch, N. *J. Am. Chem. Soc.* ***2001***, *123*, 2365; Jain, S.L.; Sharma, V.B.; Sain, B. *Tetrahedron Lett.* ***2004***, *45*, 1233.
[255] Barrett, A.G.M.; Braddock, D.C.; McKinnell, R.M.; Waller, F.J. *Synlett* ***1999***, 1489.
[256] Martín, S.E.; Garrone, A. *Tetrahedron Lett.* ***2003***, *44*, 549.
[257] Matano, Y.; Nomura, H. *J. Am. Chem. Soc.* ***2001***, *123*, 6443. With *tert*-butylhydroperoxide, see Malik, P.; Chakraborty, D. *Synthesis* ***2010***, 3736.
[258] Han, M.-k.; Kim, S.; Kim, S.T.; Lee, J.C. *Synlett* ***2015***, *26*, 2434.
[259] Komagawa, H.; Maejima, Y.; Nagano, T. *Synlett* ***2016***, *27*, 789.
[260] Mehdi, H.; Bodor, A.; Lantos, D.; Horváth, I.T.; De Vos, D.E.; Binnemans, K. *J. Org. Chem.* ***2007***, *72*, 517.
[261] See Schultz, M.J.; Sigman, M.S. *Tetrahedron* ***2006***, *62*, 8227; Lenoir, D. *Angew. Chem. Int. Ed.* ***2006***, *45*, 3206; Mallat, T.; Baiker, A. *Chem. Rev.* ***2004***, *104*, 3037; Uma, R.; Crévisy, C.; Grée, R. *Chem. Rev.* ***2003***, *103*, 27.
[262] Zhan, B.-Z.; White, M.A.; Sham, T.-K.; Pincock, J.A.; Doucet, R.J.; Rao, K.V.R.; Robertson, K.N.; Cameron, T.S. *J. Am. Chem. Soc.* ***2003***, *125*, 2195.
[263] Balicki, R. *Synth. Commun.* ***2001***, *31*, 2195.
[264] Liu, C.; Han, J.; Wang, J. *Synlett* ***2007***, 643.
[265] For a discussion of selective aerobic oxidation of primary alcohols, see Shibuya, M.; Furukawa, K.; Yamamoto, Y. *Synlett.* ***2017***, *28*, 1554.
[266] Xu, B.; Lumb, J.-P.; Arndtsen, B.A. *Angew. Chem. Int. Ed.* ***2015***, *54*, 4208.
[267] Zhu, J.; Faria, J.L.; Figueiredo, J.L.; Thomas, A. *Chem. Eur. J.* ***2011***, *17*, 7112.
[268] Nakano, T.; Terada, T.; Ishii, Y.; Ogawa, M. *Synthesis* ***1986***, 774.
[269] Onomura, O.; Arimoto, H.; Matsumura, Y.; Demizu, Y. *Tetrahedron Lett.* ***2007***, *48*, 8668.
[270] For a review, see Suzuki, T. *Chem. Rev.* ***2011***, *111*, 1825.
[271] Kawahara, R.; Fujita, K.-i.; Yamaguchi, R. *J. Am. Chem. Soc.* ***2012***, *134*, 3643.
[272] Vannucci, A.K.; Hull, J.F.; Chen, Z.; Binstead, R.A.; Concepcion, J.J.; Meyer, T.J. *J. Am. Chem. Soc.* ***2012***, *134*, 3972.
[273] Zhu, J.; Faria, J.L.; Figueiredo, J.L.; Thomas, A. *Chem. Eur. J.* ***2011***, *17*, 7112.
[274] Ray, R.; Chandra, S.; Maiti, D.; Lahiri, G.K. *Chem. Eur. J.* ***2016***, *22*, 8814.
[275] Yang, Z.; Hartnett, H.E.; Shock, E.L.; Gould, I.R. *J. Org. Chem.* ***2015***, *80*, 12159.
[276] Hanson, S.K.; Wu, R.; Silks, L.A. *Org. Lett.* ***2011***, *13*, 1908.
[277] Zhu, Y.; Zhao, B.; Shi, Y. *Org. Lett.* ***2013***, *15*, 992.

A V-based catalytic system has been used as a reusable catalyst for the oxidation of alcohols.[278] Nanoporous Au catalysts have been used for the liquid-phase aerobic oxidation of alcohols.[279] A cyclometalated Ru catalyst has been used for the oxidation of benzyl alcohols.[280] Graphite oxide with sonication has been used for the oxidation of alcohols.[281] The Os-catalyzed chemoselective oxidation of allylic and benzylic alcohols was reported.[282] A Ru catalyst immobilized on silica was used for the oxidation of alcohols in water.[283] Magtrieve (CrO_2) has been used as a catalyst for the oxidation of alcohols.[284] A magnetically recoverable, bimetallic Co/Pd nanoparticle catalyst was used for the oxidation of alcohols.[285] Chloramine-T (*N*-chloro tosylamide, sodium salt) with a Zn catalyst was used to oxidize alcohols.[286] The oxidation of allylic and benzylic alcohols occurs with $NaBrO_3$ in aqueous MeCN[287] or K_2FeO_4 on clay.[288] The reaction of AuCl with an anionic ligand leads to oxidation of primary alcohols to aldehydes.[289] The *Grubbs' catalyst,* $PhCH{=}Ru(PCy_3)_2Cl_2$ (**18-37**), in the presence of KOH, oxidized alcohols.[290] Copper nanoparticles on cellulose in water under microwave irradiation is a green system for the oxidation of alcohols to aldehydes.[291] A mixture of $I_2/KI/K_2CO_3/H_2O$ oxidizes alcohols to aldehydes or ketones under anaerobic conditions.[292] Oxone[293] oxidizes alcohols, catalyzed by $AlCl_3$.[294] Electrocatalytic oxidation of alcohols is possible in the presence of a Au catalyst and a base.[295]

In a related reaction it is possible to oxidize ethers to aldehydes. Oxidation of trimethylsilyl ethers with O_2, a catalytic amount of *N*-hydroxyphthalimide, and a Co catalyst gave an aldehyde.[296] Microwave irradiation with $BiCl_2$ oxidizes benzylic TMS ethers to the aldehyde.[297] Microwave irradiation on zeolite-supported ferric nitrate has been used.[298] *O*-Tetrahydropyran ethers (*O*-THP) have been oxidized to the aldehyde with ferric nitrate

[278] Sarmah, G.; Bharadwaj, S.K.; Dewan, A.; Gogoi, A.; Bora, U. *Tetrahedron Lett.* ***2014***, *55*, 5029. See Marui, K.; Higashiura, Y.; Kodama, S.; Hashidate, S.; Nomoto, A.; Yano, S.; Ueshima, M.; Ogawa, A. *Tetrahedron* ***2014***, *70*, 2431.

[279] Asao, N.; Hatakeyama, N.; Menggenateer, Minato, T.; Ito, E.; Hara, M.; Kim, Y.; Yamamoto, Y.; Chen, M.; Zhnang, W.; Inoue, A. *Chem. Commun.* ***2012***, *48*, 4540.

[280] Taketoshi, A.; Beh, X.N.; Kuwabara, J.; Koizumi, T.-a.; Kanbara, T. *Tetrahedron Lett.* ***2012***, *53*, 3573.

[281] Mirza-Aghayan, M.; Kashef-Azar, E.; Boukherroub, R. *Tetrahedron Lett.* ***2012***, *53*, 4962.

[282] Devari, S.; Deshidi, R.; Kumar, M.; Kumar, A.; Sharma, S.; Rizvi, M.; Kushwaha, M.; Gupta, A.P.; Shah, B.A. *Tetrahedron Lett.* ***2013***, *54*, 6407.

[283] Ganesamoorthy, S.; Tamizh, M.M.; Shanmugasundaram, K.; Karvembu, R. *Tetrahedron Lett.* ***2013***, *54*, 7035.

[284] Few, C.S.; Williams, K.R.; Wagener, K.B. *Tetrahedron Lett.* ***2014***, *55*, 4452.

[285] Ito, Y.; Ohta, H.; Yamada, Y.M.A.; Enoki, T.; Uozumi, Y. *Tetrahedron* ***2014***, *70*, 6146.

[286] Wang, P.; Cai, J.; Yang, J.; Sun, C.; Li, L.; Hu, H.; Ji, M. *Tetrahedron Lett.* ***2013***, *54*, 533.

[287] Shaabani, A.; Karimi, A.-R. *Synth. Commun.* ***2001***, *31*, 759.

[288] Tajbakhsh, M.; Heravi, M.M.; Habibzadeh, S.; Ghassemzadeh, M. *J. Chem. Res. (S)* ***2001***, 39.

[289] Guan, B.; Xing, D.; Cai, G.; Wan, X.; Yu, N.; Fang, Z.; Yang, L.; Shi, Z. *J. Am. Chem. Soc.* ***2005***, *127*, 18004.

[290] Adair, G.R.A.; Williams, J.M.J. *Tetrahedron Lett.* ***2005***, *46*, 8233.

[291] Baruah, D.; Saikia, U.P.; Pahari, P.; Konwar, D. *Tetrahedron Lett.* ***2015***, *56*, 2543.

[292] Gogoi, P.; Konwar, D. *Org. Biomol. Chem.* ***2005***, *3*, 3473.

[293] Parida, S.K.N.; Jhulki, S.; Mandal, S.; Moorthy, J.N. *Tetrahedron* ***2012***, *68*, 9763.

[294] Wu, S.; Ma, H.; Le, Z. *Tetrahedron* ***2010***, *66*, 8641.

[295] Kwon, Y.; Lai, S.C.S.; Rodriguez, P.; Koper, M.T.M. *J. Am. Chem. Soc.* ***2011***, *133*, 6914. For a reaction that used a ruthenium catalyst, see Brownell, K.R.; McCrory, C.C.L.; Chidsey, C.E.D.; Perry, R.H.; Zare, R.N.; Waymouth, R.M. *J. Am. Chem. Soc.* ***2013***, *135*, 14299.

[296] Karimi, B.; Rajabi, J. *Org. Lett.* ***2004***, *6*, 2841.

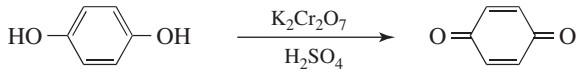
[297] Hajipour, A.R.; Mallakpour, S.E.; Baltork, I.M.; Adibi, H. *Synth. Commun.* ***2001***, *31*, 1625.

[298] Heravi, M.M.; Ajami, D.; Ghassemzadeh, M.; Tabar-Hydar, K. *Synth. Commun.* ***2001***, *31*, 2097.

on zeolites,[299] and the Pd-catalyzed oxidation of allylic esters to conjugated ketones is known.[300] *N*-Bromosuccinimide with β-cyclodextrin oxidizes tetrahydropyranyl ethers in water.[301]

OS **I**, 87, 211, 241, 340; **II**, 139, 541; **III**, 37, 207; **IV**, 189, 192, 195, 467, 813, 838; **V**, 242, 310, 324, 692, 852, 866; **VI**, 218, 220, 373, 644, 1033; **VII**, 102, 112, 114, 177, 258, 297; **VIII**, 43, 367, 386; **IX**, 132, 432. Also see, OS **IV**, 283; **VIII**, 363, 501.

19-4 Oxidation of Phenols and Aromatic Amines to Quinones



Ortho and para diols are easily oxidized to ortho- and para-quinones, respectively.[302] Either or both OH groups can be replaced by NH_2 groups to give the same products, although for the preparation of ortho-quinones, the presence of only OH groups is usually satisfactory. The reaction has been successfully carried out with other groups para to OH or NH_2: halogen, OR, Me, *t*-Bu, and even H, although yields are poor with the latter. Many oxidizing agents have been used: acid dichromate,[303] silver oxide, silver carbonate, lead tetraacetate, HIO_4, $NBS/H_2O/H_2SO_4$,[304] dimethyl dioxirane,[305] and atmospheric oxygen.[306] Oxidation has been done photochemically with O_2 and tetraphenylporphine.[307] The oxidation of hydroquinones to quinones has been reported via reaction with a silica gel-supported $Ce(NH_4)_2(NO_3)_6/NaBrO_3$ reagent.[308] Chlorine dioxide has been used for the oxidation of phenols.[309]

A particularly effective reagent for rings with only one OH or NH_2 group is $(KSO_3)_2N{-}O\bullet$ (dipotassium nitrosodisulfonate; *Fremy's salt*), which is a stable free radical.[310] A mixture of 4-iodophenoxyacetic acid and Oxone is an effective catalyst for the oxidation of *p*-alkoxyphenols to *p*-quinones.[311] A supported iron phthalocyanine facilitates the aromatic oxidation of phenols.[312]

[299] Mohajerani, B.; Heravi, M.M.; Ajami, D. *Monat. Chem.* ***2001***, *132*, 871.
[300] Trost, B.M.; Richardson, J.; Yong, K. *J. Am. Chem. Soc.* ***2006***, *128*, 2540.
[301] Narender, M.; Reddy, M.S.; Rao, K.R. *Synthesis* ***2004***, 1741. See Reddy, M.S.; Narender, M.; Nageswar, Y.V.D.; Rao, K.R. *Synthesis* ***2005***, 714.
[302] See Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, pp. 305–323, 438–447; Naruta, Y.; Maruyama, K. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinoid Compounds*, Vol. 2, pt. 1, Wiley, NY, ***1988***, pp. 247–276; Thomson, R.H. in Patai, S. *The Chemistry of the Quinoiid Compounds*, Vol. 1, pt. 1, Wiley, NY, ***1974***, pp. 112–132. For a discussion of quinoid versus benzenoid for *para*-nitro pyridine *N*-oxides, see Kleinpeter, E.; Michaelis, M.; Koch, A. *Tetrahedron* ***2015***, *71*, 2273.
[303] See Cainelli, G.; Cardillo, G. *Chromium Oxiations in Organic Chemistry*, Open Court Pub. Co., La Salle, IL, ***1981***, pp. 92–117.
[304] Kim, D.W.; Choi, H.Y.; Lee, K.Y.; Chi, D.Y. *Org. Lett.* ***2001***, *3*, 445.
[305] Adam, W.; Schönberger, A. *Tetrahedron Lett.* ***1992***, *33*, 53.
[306] See Hashemi, M.M.; Beni, Y.A. *J. Chem. Res. (S)* ***1998***, 138.
[307] Cossy, J.; Belotti, S. *Tetrahedron Lett.* ***2001***, *42*, 4329.
[308] Ali, M.H.; Welker, A.; York, C. *Synthesis* ***2015***, *47*, 3207.
[309] Loginovas, I.V.; Chukicheva, I.Yu.; Kuchin, A.V. *Russ. J. Org. Chem.* ***2011***, *47*, 1501.
[310] See Zimmer, H.; Lankin, D.C.; Horgan, S.W. *Chem. Rev.* ***1971***, *71*, 229.
[311] Yakura, T.; Konishi, T. *Synlett* ***2007***, 765.
[312] Zalomaeva, O.V.; Sorokin, A.B. *New J. Chem.* ***2006***, *30*, 1768.

Less is known about the mechanism than is the case for oxidizing simple alcohols in **19-3**, and it seems to vary with the oxidizing agent. For oxidation of catechol with $NaIO_4$, it was found that the reaction conducted in $H_2{}^{18}O$ gave unlabeled quinone,[313] possibly via an IO_3 coordination complex with one OH group of the catechol (category 4, Sec. 19.A). When catechol was oxidized with MnO_4^- under aprotic conditions, a semiquinone radical ion intermediate was involved.[314] For autoxidations[315] (i.e., with atmospheric O_2) a free-radical mechanism is known to operate.[316]

OS **I**, 383, 482, 511; **II**, 175, 254, 430, 553; **III**, 663, 753; **IV**, 148; **VI**, 412, 480, 1010.

19-5 Dehydrogenation of Amines or Amides to Nitriles or Imines

$$RCH_2NH_2 \longrightarrow RCN$$

Primary amines on a primary carbon can be dehydrogenated to nitriles. The reaction has been carried out with a variety of reagents, among others, I_2 in aqueous NH_3,[317] iodoxybenzoic acid (IBX, see **19-3**),[318] NaOCl,[319] $TiCl_4$,[320] Co_3O_4,[321] nicotinium dichromate,[322] and $Ru/Al_2O_3/O_2$.[323] Iodine and 1,3-diiodo-5,5-dimethylhydantoin in aqueous ammonia converted both amines and alcohols to nitriles.[324] Dehydrogenation of amines has been done in aqueous micelles.[325]

The NNN/Ru(II) hydride-catalyzed dehydrogenation of primary and secondary amines to give the corresponding nitriles and imines liberates dihydrogen.[326] An oxoammonium salt was used to oxidize primary amines to nitriles.[327] The reaction of DL-threonine with salicylaldehyde to give corresponding Schiff base and subsequent complexation with Fe provided an ionic liquid that functioned as a green catalyst for solvent-free aerobic oxidation of amines to nitriles.[328] The use of a V complex catalyst in an ionic liquid converted an amine to a nitrile, as did a Cu catalyst with hydrogen peroxide in water, or a photoinduced oxidation using oxygen in the presence of a zinc/chlorine complex catalyst.[329] Methyl arenes were converted to aryl nitriles by reaction with a Pd/*N*-hydroxyphthalimide catalyst and *tert*-butyl nitrite.[330] The U-[331] or Zn[332]-catalyzed dehydration of primary

[313] Adler, E.; Falkehag, I.; Smith, B. *Acta Chem. Scand.* ***1962***, *16*, 529.
[314] Bock, H.; Jaculi, D. *Angew. Chem. Int. Ed.* ***1984***, *23*, 305.
[315] For an example, see Rathore, R.; Bosch, E.; Kochi, J.K. *Tetrahedron Lett.* ***1994***, *35*, 1335.
[316] Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, NY, ***1981***, pp. 368–381; Walling, C. *Free Radicals in Solution*, Wiley, NY, ***1957***, pp. 457–461.
[317] Iida, S.; Togo, H. *Synlett* ***2006***, 2633.
[318] Chiampanichayakul, S.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Kuhakarn, C. *Synthesis* ***2008***, 2045.
[319] Yamazaki, S. *Synth. Commun.* ***1997***, *27*, 3559; Jursic, B. *J. Chem. Res. (S)* ***1988***, 168.
[320] Leggio, A.; Belsito, E.L.; Gallo, S.; Liguori, A. *Tetrahedron Lett.* ***2017***, *58*, 1512.
[321] Natte, K.; Jagadeesh, R.V.; Sharif, M.; Neumann, H.; Beller, M. *Org. Biomol. Chem.* ***2016***, *14*, 3356.
[322] Sobhani, S.; Aryanejad, S.; Maleki, M.F. *Helv. Chim. Acta* ***2012***, *95*, 613.
[323] Yamaguchi, K.; Mizuno, N. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1480.
[324] Iida, S.; Togo, H. *Tetrahedron* ***2007***, *63*, 8274.
[325] Biondini, D.; Brinchi, L.; Germani, R.; Goracci, L.; Savelli, G. *Eur. J. Org. Chem.* ***2005***, 3060.
[326] See Tseng, K.-N.T.; Szymczak, N.K. *Synlett* ***2014***, *25*, 2385. Also see Biafora, A.; Patureau, F.W. *Synlett* ***2014***, *25*, 2525.
[327] Lambert, K.M.; Bobbitt, J.M.; Eldirany, S.A.; Wiberg, K.B.; Bailey, W.F. *Org. Lett.* ***2014***, *16*, 6484.
[328] Varyani, M.; Khatri, P.K.; Jain, S.L. *Tetrahedron Lett.* ***2016***, *57*, 723.
[329] Marui, K.; Nomoto, A.; Akashi, H.; Ogawa, A. *Synthesis* ***2016***, *48*, 31.
[330] Shu, Z.; Ye, Y.; Deng, Y.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* ***2013***, *52*, 10573.
[331] Enthaler, S. *Chem. Eur. J.* ***2011***, *17*, 9316.
[332] Enthaler, S.; Inoue, S. *Chem. Asian J.* ***2012***, *7*, 169.

amides gave nitriles. Aldoximes and primary amides were converted to nitriles by reaction with oxalyl chloride, using cyclopropenone as an organocatalyst.[333] The *in situ*-generated Burgess-type reagent was used to convert amides or oximes to the nitrile.[334] Oximes were converted to nitriles by reaction with a phosphonium salt catalyst.[335] A Lewis acid ionic liquid was also used to convert aldoximes to nitriles.[336] An Fe-catalyzed dehydration has also been reported,[337] and PCC has been used to prepare nitriles.[338] A $Ru(OH)_3/Al_2O_3$ catalyst converted primary azides, including benzylic, allylic, and aliphatic, to the corresponding nitriles.[339] Primary azides were oxidized to nitriles and secondary azides were oxidized to ketones with bis(*tert*-butylperoxy)iodobenzene, generated *in situ* by the reaction of diacetoxyl iodobenzene (DIB) with *tert*-butyl hydroperoxide.[340] Aldoximes and primary amides were converted to nitriles by reaction with XtalFluor-E.[341] Oximes of aromatic aldehydes are converted to aryl nitriles with $InCl_3$.[342] Note that ketoximes give a *Beckmann rearrangement*, **18-17**.

Several methods have been reported for the dehydrogenation of secondary amines to imines.[343] Among them[344] are (i) treatment with iodosylbenzene (PhIO) alone or in the presence of a Ru complex,[345] (ii) treatment with DMSO and oxalyl chloride,[346] and (iii) treatment with *t*-BuOOH and a Rh catalyst.[347] *N*-Tosyl aziridines are converted to *N*-tosyl imines when heated with a Pd catalyst.[348] Benzyl amines were oxidized to the imine by heating with H_2O_2.[349] A Cu-catalyzed oxidation of amines to imines used H_2O_2 in water,[350] and a Cu/TEMPO aerobic oxidation was reported.[351] The reaction of 4-*tert*-butyl-2-hydroxybenzoquinone and O_2 selectively oxidized primary benzylic amines to the corresponding imine.[352] The aerobic photocatalytic reaction of amines on TiO_2 gives the corresponding imine.[353]

19-6 Oxidation of Hydrazines, Hydrazones, and Hydroxylamines

$$\text{Ar—NH—NH—Ar} \xrightarrow{\text{NaOBr}} \text{Ar—N=N—Ar}$$

[333] Rai, A.; Yadav, L.D.S. *Eur. J. Org. Chem.* ***2013***, 1889.
[334] Rappai, J.P.; Karthikeyan, J.; Prathapan, S.; Unnikrishnan, P.A. *Synth. Commun.* ***2010–2011***, *41*, 2601.
[335] Denton, R.M.; An, J.; Lindovska, P.; Lewis, W. *Tetrahedron* ***2012***, *68*, 2899.
[336] Nakajima, M.; Qiao, K.; Kobayashi, N.; Bao, Q.; Tomida, D.; Yokoyama, C. *Chem. Lett.* ***2011***, *40*, 396. See Song, Y.; Shen, D.; Zhang, Q.; Chen, B.; Xu, G. *Tetrahedron Lett.* ***2014***, *55*, 639.
[337] Hyodo, K.; Kitagawa, S.; Yamazaki, M.; Uchida, K. *Chem. Asian J.* ***2016***, *11*, 1348.
[338] Chandrappa, S.; Prasanna, T.S.R.; Vinaya, K.; Prasanna, D.S.; Rangappa, K.S. *Synth. Commun.* ***2013***, *43*, 2756.
[339] He, J.; Yamaguchi, K.; Mizuno, N. *J. Org. Chem.* ***2011***, *76*, 4606.
[340] Zhao, Y.; Chew, X.; Leung, G.Y.C.; Yeung, Y.-Y. *Tetrahedron Lett.* ***2012***, *53*, 4766.
[341] Keita, M.; Vandamme, M.; Paquin, J.-F. *Synthesis* ***2015***, *47*, 3758.
[342] Barman, D.C.; Thakur, A.J.; Prajapati, D.; Sandhu, J.S. *Chem. Lett.* ***2000***, 1196.
[343] See Dayagi, S.; Degani, Y. in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 117–124.
[344] See Nishinaga, A.; Yamazaki, S.; Matsuura, T. *Tetrahedron Lett.* ***1988***, *29*, 4115.
[345] Müller, P.; Gilabert, D.M. *Tetrahedron* ***1988***, *44*, 7171.
[346] Keirs, D.; Overton, K. *J. Chem. Soc., Chem. Commun.* ***1987***, 1660.
[347] Murahashi, S.; Naota, T.; Taki, H. *J. Chem. Soc., Chem. Commun.* ***1985***, 613.
[348] Wolfe, J.P.; Ney, J.E. *Org. Lett.* ***2003***, *5*, 4607.
[349] Wu, X.-F.; Petrosyan, A.; Ghochikyan, T.V.; Saghyan, A.S.; Langer, P. *Tetrahedron Lett.* ***2013***, *54*, 3158.
[350] Marui, K.; Nomoto, A.; Ueshima, M.; Ogawa, A. *Tetrahedron Lett.* ***2015***, *56*, 1200.
[351] Huang, B.; Tian, H.; Lin, S.; Xie, M.; Yu, X.; Xu, Q. *Tetrahedron Lett.* ***2013***, *54*, 2861.
[352] Wendlandt, A.E.; Stahl, S.S. *Org. Lett.* ***2012***, *14*, 2850.
[353] Lang, X.; Ji, H.; Chen, C.; Ma, W.; Zhao, J. *Angew. Chem. Int. Ed.* ***2011***, *50*, 3934; Lang, X.; Ma, W.; Zhao, Y.; Chen, C.; Ji, H.; Zhao, J. *Chem. Eur. J.* ***2012***, *18*, 2624.

N,*N*′-Diarylhydrazines (hydrazo compounds) are oxidized to azo compounds by several oxidizing agents, including NaOBr, $K_3Fe(CN)_6$ under phase-transfer conditions,[354] $FeCl_3$,[355] MnO_2 (this reagent yields *cis*-azobenzenes),[356] $CuCl_2$, and air and NaOH.[357] The reaction is also applicable to *N*,*N*′-dialkyl- and *N*,*N*′-diacylhydrazines. Hydrazines (both alkyl and aryl) substituted on only one side also give azo compounds, Ar—N=NH,[358] but these are unstable and decompose to nitrogen and the hydrocarbon, ArH. Aniline derivatives are converted to azo compounds by heating with cetyltrimethylammonium dichromate in chloroform.[359] When hydrazones are oxidized with HgO, Ag_2O, MnO_2, PbO_4, or certain other oxidizing agents, diazo compounds are obtained ($R_2C{=}N{-}NH_2 \rightarrow R_2C{=}N^+{=}N^-$).[360]

Hydrazones of the form $ArCH{=}NNH_2$ react with HgO in solvents, such as diglyme or ethanol, to give nitriles ArCN.[361] It is possible to oxidize dimethylhydrazones ($R{-}C{=}N{-}NMe_2$) to the corresponding nitrile ($R{-}C{\equiv}N$) with magnesium monoperoxyphthalate (MMPP),[362] or with dimethyl dioxirane.[363] Oxone on wet alumina also converts hydrazones to nitriles with microwave irradiation.[364]

The reaction of α,β-unsaturated oximes and diaryliodonium salts with KOH gave α,β-unsaturated *N*-aryl ketonitrones.[365] A nanoporous Au catalyst was used for the aerobic oxidation of hydroxylamines to nitrones.[366] Hypervalent iodine compounds oxidized *N*,*N*-disubstituted hydroxylamines to the corresponding nitrone.[367]

In a related reaction, primary aromatic amines have been oxidized to azo compounds by a variety of oxidizing agents, among them $BaMnO_4$,[368] MnO_2, lead tetraacetate, O_2 and a base, and sodium perborate in acetic acid. *tert*-Butyl hydroperoxide has been used to oxidize certain primary amines to azoxy compounds.[369]

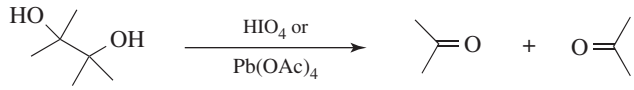
Nitrones, $C{=}N^+(R){-}O^-$, are generated by the oxidation of *N*-hydroxyl secondary amines with 5% aqueous NaOCl.[370] Secondary amines, such as dibenzylamine, can be converted to the corresponding nitrone by heating with cumyl hydroperoxide in the presence of a titanium catalyst.[371]

OS **II**, 496; **III**, 351, 356, 375, 668; **IV**, 66, 411; **V**, 96, 160, 897; **VI**, 78, 161, 334, 392, 803, 936; **VII**, 56. Also see, OS **V**, 258. For oxidation of primary amines, see OS **V**, 341.

[354] Dimroth, K.; Tüncher, W. *Synthesis* ***1977***, 339.
[355] Wang, C.-L.; Wang, X.-X.; Wang, X.-Y.; Xiao, J.-P.; Wang, Y.-L. *Synth. Commun.* ***1999***, *29*, 3435.
[356] Hyatt, J.A. *Tetrahedron Lett.* ***1977***, 141.
[357] See Newbold, B.T. in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 1, Wiley, NY, ***1975***, pp. 543–557, 564–573.
[358] See Mannen, S.; Itano, H.A. *Tetrahedron* ***1973***, *29*, 3497.
[359] Patel, S.; Mishra, B.K. *Tetrahedron Lett.* ***2004***, *45*, 1371.
[360] See Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 233–256.
[361] Mobbs, D.B.; Suschitzky, H. *Tetrahedron Lett.* ***1971***, 361.
[362] Fernández, R.; Gasch, C.; Lassaletta, J.-M.; Llera, J.-M.; Vázquez, J. *Tetrahedron Lett.* ***1993***, *34*, 141.
[363] Altamura, A.; D'Accolti, L.; Detomaso, A.; Dinoi, A.; Fiorentino, M.; Fusco, C.; Curci, R. *Tetrahedron Lett.* ***1998***, *39*, 2009.
[364] Ramalingam, T.; Reddy, B.V.S.; Srinivas, R.; Yadav, J.S. *Synth. Commun.* ***2000***, *30*, 4507.
[365] Ma, X.-P.; Shi, W.-M.; Mo, X.-L.; Li, X.-H.; Li, L.-G.; Pan, C.-X.; Chen, B.; Su, G.-F.; Mo, D.-L. *J. Org. Chem.* ***2015***, *80*, 10098.
[366] Yudha, S.S.; Kusuma, I.; Asao, N. *Tetrahedron* ***2015***, *71*, 6459.
[367] Matassini, C.; Parmeggiani, C.; Cardona, F.; Goti, A. *Org. Lett.* ***2015***, *17*, 4082.
[368] Firouzabadi, H.; Mostafavipoor, Z. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 914.
[369] Kosswig, K. *Liebigs Ann. Chem.* ***1971***, *749*, 206.
[370] Cicchi, S.; Corsi, M.; Goti, A. *J. Org. Chem.* ***1999***, *64*, 7243.
[371] Forcato, M.; Nugent, W.A.; Licini, G. *Tetrahedron Lett.* ***2003***, *44*, 49.

B. Oxidations Involving Cleavage of Carbon-Carbon Bonds[372]

19-7 Oxidative Cleavage of Glycols and Related Compounds



1,2-Diols (glycols) are easily cleaved under mild conditions and in good yield with periodic acid or lead tetraacetate.[373] The reaction generates 2 molar equivalents of aldehyde, or 2 molar equivalents of ketone, or 1 molar equivalent of each, depending on the groups attached to the two carbons. The yields are so good that alkenes are often converted to diols (**15-44**) and then cleaved with HIO_4 or $Pb(OAc)_4$, rather than being cleaved directly with ozone (**19-9**), dichromate, or permanganate (**19-10**). The diol can be generated from an alkene and cleaved *in situ* to give the carbonyl compounds.[374] A number of other oxidizing agents also give the same products, among them[375] aqueous sodium hypochlorite (NaOCl),[376] activated MnO_2,[377] O_2 and a Ru catalyst,[378] and pyridinium chlorochromate (PCC).[379] Permanganate, dichromate, and several other oxidizing agents[380] also cleave glycols, giving carboxylic acids rather than aldehydes, but these reagents are seldom used synthetically. The two reagents (periodic acid and lead tetraacetate) are complementary, since periodic acid is best used in water and lead tetraacetate in organic solvents.

The use of a catalytic amount of 1-Me-nitroxyl radical 2-azaadamantane *N*-oxyls with NaOCl and $NaClO_2$ gave the oxidative cleavage of terminal 1,2-diols to carboxylic acids that are one carbon unit shorter.[381] Nitroxyl radical and $PhI(OAc)_2$ has also been used for the cleavage of vicinal diols to give carboxylic acids.[382] The NaO-*t*-Bu/O_2 oxidative cleavage of 1,2-diols to carboxylic acids has been reported.[383] The aerobic cleavage of vicinal diols to carboxylic acids used photoirradiation with a high-pressure mercury lamp and 2-chloroanthraquinone as an additive.[384]

Other compounds that contain oxygen atoms or nitrogen atoms on adjacent carbons undergo similar cleavage, including β-amino alcohols, 1,2-diamines, α-hydroxy aldehydes,

[372] See Bentley, K.W. in Bentley, K.W.; Kirby, G.W. *Elucidation of Chemical Structures by Physical and Chemical Methods* (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), 2nd ed., pt. 2, Wiley, NY, ***1973***, pp. 137–254.

[373] See Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, pp. 277–301, 432–437; Perlin, A.S. in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 189–212; Bunton, C.A. in Wiberg, K.B. *Oxidation in Organic Chemistry*, pt. A, Academic Press, NY, ***1965***, pp. 367–407. Also see Rubottom, G.M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. D, Academic Press, NY, ***1982***, p. 1; Fatiadi, A.J. *Synthesis* ***1976***, 65, 133; Schmidt, A.-K.C.; Stark, C.B.W. *Synthesis* ***2014***, *46*, 3283.

[374] Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* ***2004***, *6*, 3217.

[375] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1250–1255.

[376] Khurana, J.M.; Sharma, P.; Gogia, A.; Kandpal, B.M. *Org. Prep. Proceed. Int.* ***2007***, *39*, 185.

[377] See Ohloff, G.; Giersch, W. *Angew. Chem. Int. Ed.* ***1973***, *12*, 401.

[378] Takezawa, E.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* ***1999***, *1*, 713.

[379] Cisneros, A.; Fernández, S.; Hernández, J.E. *Synth. Commun.* ***1982***, *12*, 833.

[380] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1650–1652.

[381] Shibuya, M.; Doi, R.; Shibuta, T.; Uesugi, S.-i.; Iwabuchi, Y. *Org. Lett.* ***2012***, *14*, 5006.

[382] Shibuya, M.; Shibuta, T.; Fukuda, H.; Iwabuchi, Y. *Org. Lett.* ***2012***, *14*, 5010.

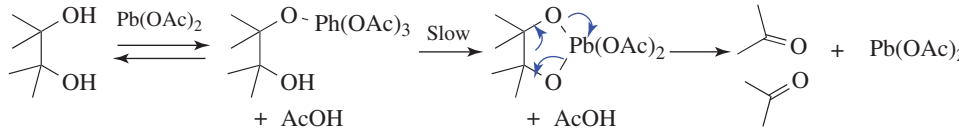
[383] Kim, S.M.; Kim, D.W.; Yang, J.W. *Org. Lett.* ***2014***, *16*, 2876.

[384] Matsusaki, Y.; Yamaguchi, T.; Tada, N.; Miura, T.; Itoh, A. *Synlett* ***2012***, *23*, 2059.

α-hydroxy ketones, α-diketones, α -keto aldehydes, and glyoxals. Cyclic 1,2-diamines are cleaved to diketones with dimethyl dioxirane.[385] α-Diketones and α-hydroxy ketones are also cleaved by alkaline H_2O_2.[386] HIO_4 has been used to cleave epoxides to aldehydes.[387]

α-Hydroxy acids and α-keto acids are not cleaved by HIO_4 but are cleaved by $NaIO_4$ in methanol in the presence of a crown ether,[388] $Pb(OAc)_4$, alkaline H_2O_2, and other reagents. These are oxidative decarboxylations. α-Hydroxy acids give aldehydes or ketones, and α-keto acids give carboxylic acids. Also see, **19-12** and **19-13**.

The mechanism of glycol oxidation with $Pb(OAc)_4$ was proposed by Criegee:[389]

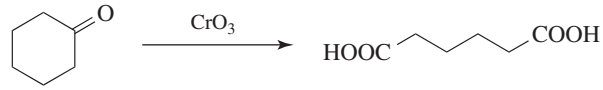


This mechanism is supported by: (i) the kinetics are second order (first order in each reactant); (ii) added acetic acid retards the reaction (drives the equilibrium to the left); and (iii) *cis*-glycols react much more rapidly than *trans*-glycols.[390] The mechanism is similar for periodic acid, with a 1,1-dioxo-1λ^7,2,5-iodadioxolan-1-ol intermediate.[391] However, the cyclic-intermediate mechanism cannot account for all glycol oxidations, since some glycols such as (4a*r*,8a*r*)-octahydronaphthalene-4a,8a-diol, with *trans*-OH units, cannot form such an ester but are nevertheless cleaved by lead tetraacetate to give cyclodecane-1,6-dione (although other glycols that cannot form cyclic esters are *not* cleaved, by either reagent[392]). To account for such cases, a cyclic transition state has been proposed.[390]

Chiral lead carboxylates have been prepared for the oxidative cleavage of 1,2-diols.[393] When three or more OH groups are located on adjacent carbons, the middle one (or ones) is converted to formic acid.

OS **IV**, 124; **VII**, 185; **VIII**, 396.

19-8 Oxidative Cleavage of Ketones, Aldehydes, and Alcohols



[385] Gagnon, J.L.; Zajac Jr., W.W. *Tetrahedron Lett.* ***1995***, *36*, 1803.
[386] See Ogata, Y.; Sawaki, Y.; Shiroyama, M. *J. Org. Chem.* ***1977***, *42*, 4061.
[387] Nagarkatti, J.P.; Ashley, K.R. *Tetrahedron Lett.* ***1973***, 4599.
[388] Kore, A.R.; Sagar, A.D.; Salunkhe, M.M. *Org. Prep. Proceed. Int.* ***1995***, *27*, 373.
[389] Criegee, R.; Kraft, L.; Rank, B. *Liebigs Ann. Chem.* ***1933***, *507*, 159. For reviews, see Waters, W.A. *Mechanisms of Oxidation of Organic Compounds*, Wiley, NY, ***1964***, pp. 72–81; Stewart, R. *Oxidation Mechanisms*, W.A. Benjamin, NY, ***1964***, pp. 97–106.
[390] See Criegee, R.; Höger, E.; Huber, G.; Kruck, P.; Marktscheffel, F.; Schellenberger, H. *Liebigs Ann. Chem.* ***1956***, *599*, 81.
[391] Buist, G.J.; Bunton, C.A.; Hipperson, W.C.P. *J. Chem. Soc. B* ***1971***, 2128.
[392] Angyal, S.J.; Young, R.J. *J. Am. Chem. Soc.* ***1959***, *81*, 5251.
[393] Lena, J.I.C.; Sesenoglu, Ö.; Birlirakis, N.; Arseniyadis, S. *Tetrahedron Lett.* ***2001***, *42*, 21.

Oxidative cleavage of open-chain ketones or alcohols[394] is seldom useful, not because these compounds do not undergo oxidation (they do, except for diaryl ketones), but because the result is generally a hopeless mixture. Aryl methyl ketones, such as acetophenone, however, are readily oxidized to aryl carboxylic acids with Re_2O_7 and 70% aqueous *tert*-butyl hydroperoxide.[395] Oxygen with a mixture of Mn and Co catalysts give similar oxidative cleavage,[396] as do hypervalent iodine compounds.[397] Aldehydes, such as $PhCH_2CHO$, are cleaved to benzaldehyde with phosphonium dichromate in refluxing acetonitrile.[398] 1,3-Diketones, such as 1,3-diphenyl-1,3-propanedione, are oxidatively cleaved with aqueous Oxone to give benzoic acid.[399] Cyclic α-chloro ketones are cleaved to give an α,ω-functionalized compound (acetal ester) when treated with cerium(IV) sulfate tetrahydrate and O_2,[400] and the corresponding secondary alcohols to the dicarboxylic acid in good yield. The formation of adipic acid from cyclohexanone (shown above) is an important industrial procedure. Dichromate in acidic media and permanganate are the most common oxidizing agents, although autoxidation (oxidation with atmospheric oxygen) in alkaline solution[401] and potassium superoxide under phase-transfer conditions[402] have also been used. *O* Silyl ketones have been cleaved to esters using electrolysis in alcohol solvents.[403]

Ynones were prepared by O═C─C cleavage of an aldehyde by reaction with hypervalent alkynyl iodides, a Au catalyst, and pyrrolidine.[404] The reaction of PCC with 4-keto-2-hydroxy esters gave 1,2-diketones via C─C bond cleavage.[405] α-Keto esters and 1,2-diketones were prepared by oxidative cleavage of β-keto esters and 1,3-diketones, mediated by Oxone/aluminum trichloride.[406] Benzoins were oxidatively cleaved to benzoic acids using sodium hydride under an oxygen atmosphere.[407] Heating aromatic and heteroaromatic methyl ketones with S_2Cl_2, SO_2Cl_2, and catalytic amounts of pyridine gave acyl chlorides.[408] The reaction of iodosylbenzene complexes with HBF_4 led to oxidative cleavage of α-aryl aldehydes to give chain-shortened carbonyl compounds and formaldehyde.[409] The oxidative C─C bond cleavage of aldehydes to give ketones used a ruthenium photoredox catalyst.[410]

Cyclic 1,3-diketones, which exist mainly in the mono-enolic form, can be cleaved with sodium periodate with loss of one carbon as CO_2, as in the oxidative cleavage of

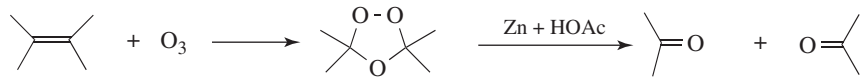
[394] See Trahanovsky, W.S. *Methods Free-Radical Chem.* ***1973***, *4*, 133–169; Verter, H.S. in Zabicky, J. *The Chemistry of the Carbonyl Group*, pt. 2, Wiley, NY, ***1970***, pp. 71–156.
[395] Gurunath, S.; Sudalai, A. *Synlett* ***1999***, 559.
[396] Minisci, F.; Recupero, F.; Fontana, F.; Bjørsvik, H.-R.; Liguori, L. *Synlett* ***2002***, 610.
[397] Lee, J.C.; Choi, J.-H.; Lee, Y.C. *Synlett* ***2001***, 1563.
[398] Hajipour, A.R.; Mohammadpoor-Baltork, I.; Niknam, K. *Org. Prep. Proceed. Int.* ***1999***, *31*, 335.
[399] Ashford, S.W.; Grega, K.C. *J. Org. Chem.* ***2001***, *66*, 1523.
[400] He, L.; Horiuchi, C.A. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 2515.
[401] Bjørsvik, H.-R.; Liguori, L.; González, R.R.; Merinero, J.A.V. *Tetrahedron Lett.* ***2002***, *43*, 4985. See also, Osowska-Pacewicka, K.; Alper, H. *J. Org. Chem.* ***1988***, *53*, 808.
[402] Sotiriou, C.; Lee, W.; Giese, R.W. *J. Org. Chem.* ***1990***, *55*, 2159.
[403] Yoshida, J.; Itoh, M.; Matsunaga, S.; Isoe, S. *J. Org. Chem.* ***1992***, *57*, 4877.
[404] Wang, Z.; Li, L.; Huang, Y. *J. Am. Chem. Soc.* ***2014***, *136*, 12233.
[405] Bhosale, S.M.; Momin, A.A.; Gawade, R.L.; Puranik, V.G.; Kusurkar, R.S. *Tetrahedron Lett.* ***2012***, *53*, 5327.
[406] Stergiou, A.; Bariotaki, A.; Kalaitzakis, D.; Smonou, I. *J. Org. Chem.* ***2013***, *78*, 7268.
[407] Kang, S.; Joo, C.; Kim, S.M.; Han, H.; Yang, J.W. *Tetrahedron Lett.* ***2011***, *52*, 502.
[408] Zaragoza, F. *J. Org. Chem.* ***2015***, *80*, 10370.
[409] Havare, N.; Plattner, D.A. *Org. Lett.* ***2012***, *14*, 5078.
[410] Sun, H.; Yang, C.; Gao, F.; Li, Z.; Xia, W. *Org. Lett.* ***2013***, *15*, 624.

cyclohexan-1,3-dione to 1,5-pentanedioic acid.[411] The species actually undergoing the cleavage is the triketone. Cyclic 1,3-diketones are converted to α,ω-diesters with an excess of $KHSO_5$ in methanol.[412]

In a related reaction, cyclobutanol derivatives were oxidatively cleaved to γ-hydroxyl ketones using phenyliodine diacetate.[413]

OS **I**, 18; **IV**, 19; **VI**, 690. See also, OS **VI**, 1024.

19-9 Ozonolysis



6

When compounds containing double bonds are treated with ozone, usually at low temperatures, initial formation of a 1,2,3-trioxolane is followed by formation of compounds called 1,2,4-trioxolanes (*ozonides*, **6**). Ozonodies can be isolated but, because some of them are explosive, they are decomposed with Zn and acetic acid or catalytic hydrogenation, but more commonly with dimethyl sulfide,[414] to give 2 molar equivalents of aldehyde, or 2 molar equivalents of ketone, or 1 molar equivalent of each, depending on the groups attached to the original alkene.[415] The decomposition of **6** has also been carried out with triethylamine[416] and with reducing agents such as trimethyl phosphite[417] or thiourea.[418] However, ozonides can also be *oxidized* with oxygen, peroxyacids, or H_2O_2 to give ketones and/or carboxylic acids. Note that the presence of a hydrogen atom on the C═C unit (C═C─H) leads to differences in oxidation or reduction of **6**. In such a system, oxidation leads to the acid whereas reduction leads to the aldehyde. It is also possible to reduce **6** with $LiAlH_4$, $NaBH_4$, BH_3, or catalytic hydrogenation with excess H_2 to give 2 molar equivalents of alcohol.[419] Ozonides can be treated with ammonia, hydrogen, and a catalyst to give the corresponding amines,[420] or with an alcohol and anhydrous HCl to give the corresponding carboxylic esters.[421] Ozonolysis is therefore an important synthetic reaction.[422]

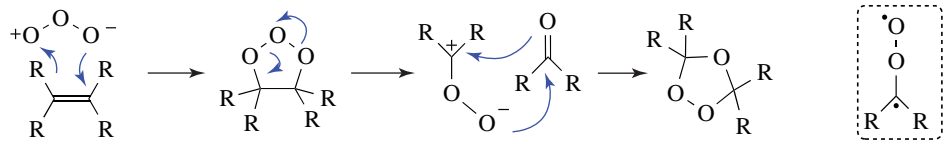
[411] Wolfrom, M.L.; Bobbitt, J.M. *J. Am. Chem. Soc.* ***1956***, *78*, 2489.
[412] Yan, J.; Travis, B.R.; Borhan, B. *J. Org. Chem.* ***2004***, *69*, 9299.
[413] Fujioka, H.; Komatsu, H.; Miyoshi, A.; Murai, K.; Kita, Y. *Tetrahedron Lett.* ***2011***, *52*, 973.
[414] Pappas, J.J.; Keaveney, W.P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* ***1966***, 4273.
[415] See Razumovskii, S.D.; Zaikov, G.E. *Ozone and its Reactions with Organic Compounds*, Elsevier, NY, ***1984***; Bailey, P.S. *Ozonation in Organic Chemistry*, 2 Vols., Academic Press, NY, ***1978***, ***1982***. For reviews, see Odinokov, V.N.; Tolstikov, G.A. *Russ. Chem. Rev.* ***1981***, *50*, 636; Belew, J.S. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 259–335; Menyailo, A.T.; Pospelov, M.V. *Russ. Chem. Rev.* ***1967***, *36*, 284. Also see Cochran, B.M. *Synlett* ***2016***, *27*, 245.
[416] Hon, Y.-S.; Lin, S.-W.; Chen, Y.-J. *Synth. Commun.* ***1993***, *23*, 1543.
[417] Knowles, W.S.; Thompson, Q.E. *J. Org. Chem.* ***1960***, *25*, 1031.
[418] Gupta, D.; Soman, R.; Dev, S. *Tetrahedron* ***1982***, *38*, 3013.
[419] See Flippin, L.A.; Gallagher, D.W.; Jalali-Araghi, K. *J. Org. Chem.* ***1989***, *54*, 1430.
[420] See White, R.W.; King, S.W.; O'Brien, J.L. *Tetrahedron Lett.* ***1971***, 3591.
[421] Neumeister, J.; Keul, H.; Saxena, M.P.; Griesbaum, K. *Angew. Chem. Int. Ed.* ***1978***, *17*, 939. See also, Cardinale, G.; Grimmelikhuysen, J.C.; Laan, J.A.M.; Ward, J.P. *Tetrahedron* ***1984***, *40*, 1881.
[422] Drug synthesis: see van Ornum, S.G.; Champeau, R.M.; Pariza, R. *Chem. Rev.* ***2006***, *106*, 2990.

Ozonolysis can be done in solvent/water mixtures.[423] A biphasic ozonolysis of alkenes has been reported using film shear flow reactor technology (Sec. 7.D).[424]

Many alkenes undergo ozonolysis, including cyclic alkenes. Alkenes in which the double bond is connected to electron-donating groups react many times faster than those in which the double bond is connected to electron-withdrawing groups.[425] Ozonolysis of compounds containing more than one double bond generally leads to cleavage of all the bonds. In some cases, especially when bulky groups are present, conversion of the substrate to an epoxide (**15-46**) becomes an important side reaction and can be the main reaction.[426] Rearrangement is possible in some cases.[427] Ozonolysis of triple bonds[428] is less common and the reaction proceeds less easily, since ozone is an electrophilic agent[429] and prefers double to triple bonds (Sec. 15.B.i). Compounds that contain triple bonds generally give carboxylic acids, although sometimes ozone oxidizes them to α-diketones (**19-26**).

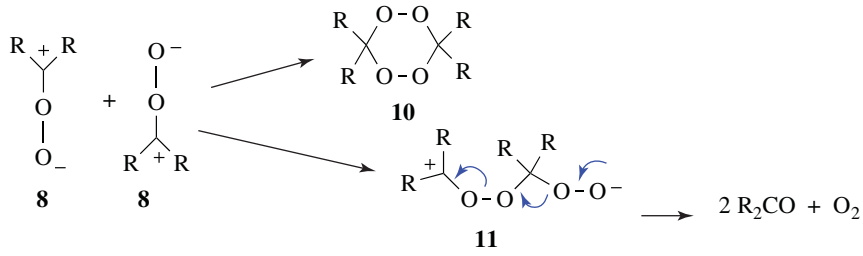
Aromatic compounds are attacked less readily than alkenes, but cleavage is known. Ozonolysis of benzene gives 3 molar equivalents of glyoxal (HCOCHO), and *o*-xylene gives a glyoxal/MeCOCHO/MeCOCOMe ratio of 3:2:1, which shows that in this case cleavage is statistical. With polycyclic aromatic compounds the site of attack depends on the structure of the molecule and on the solvent.[430]

Although a large amount of work has been done on the mechanism of ozonolysis (formation of **6**), not all the details are known. Note that a primary ozonide has been trapped.[431] Criegee formulated the basic mechanism.[432] The first step of the *Criegee mechanism*[433] is a 1,3-dipolar addition (**15-54**) of ozone to the substrate to give a 1,2,3-trioxolane **7**, identified by microwave and other spectral methods.[434] However, **7** is highly unstable and cleaves to an aldehyde or ketone and an intermediate[435] that Criegee showed as a zwitterion (**8**)[436] but which may be a diradical (**9**).[437]



[423] Schiaffo, C.E.; Dussault, P.H. *J. Org. Chem.* ***2008***, *73*, 4688.
[424] Kendall, A.J.; Barry, J.T.; Seidenkranz, D.T.; Ryerson, A.; Hiatt, C.; Salazar, C.A.; Bryant, D.J.; Tyler, D.R. *Tetrahedron Lett.* ***2016***, *57*, 1342.
[425] Pryor, W.A.; Giamalva, D.; Church, D.F. *J. Am. Chem. Soc.* ***1985***, *107*, 2793. See Kuczkowski, R.L. *Adv. Oxygenated Processes* ***1991***, *3*, 1.
[426] See Bailey, P.S.; Hwang, H.H.; Chiang, C. *J. Org. Chem.* ***1985***, *50*, 231.
[427] Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R.; Cuerva, J.M.; Segovia, A. *Synlett.* ***2000***, *1*269.
[428] See Pryor, W.A.; Govindan, C.K.; Church, D.F. *J. Am. Chem. Soc.* ***1982***, *104*, 7563.
[429] See Klutsch, G.; Fliszár, S. *Can. J. Chem.* ***1972***, *50*, 2841.
[430] See O'Murchu, C. *Synthesis* ***1989***, 880.
[431] Jung, M.E.; Davidov, P. *Org. Lett.* ***2001***, *3*, 627.
[432] See Kuczkowski, R.L. *Acc. Chem. Res.* ***1983***, *16*, 42; Criegee, R. *Angew. Chem. Int. Ed.* ***1975***, *14*, 745; Murray, R.W. *Acc. Chem. Res.* ***1968***, *1*, 313.
[433] Also see Ponec, R.; Yuzhakov, G.; Haas, Y.; Samuni, U. *J. Org. Chem.* ***1997***, *62*, 2757.
[434] Gillies, J.Z.; Gillies, C.W.; Suenram, R.D.; Lovas, F.J. *J. Am. Chem. Soc.* ***1988***, *110*, 7991. See also, McGarrity, J.F.; Prodolliet, J. *J. Org. Chem.* ***1984***, *49*, 4465.
[435] See Fajgar, R.; Vítek, J.; Haas, Y.; Pola, J. *Tetrahedron Lett.* ***1996***, *37*, 3391.
[436] Dawes, R.; Jiang, B.; Guo, H. *J. Am. Chem. Soc.* ***2015***, *137*, 50.
[437] See Willand-Charnley, R.; Fisher, T.J.; Johnson, B.M.; Dussault, P.H. *Org. Lett.* ***2012***, *14*, 2242.

This intermediate is usually referred to as a carbonyl oxide.[438] The carbonyl oxide (**8**) can then undergo various reactions, three of which lead to normal products. One is a recombination with the aldehyde or ketone, which leads to the ozonide. The second is a dimerization to the bis(peroxide) **10**, and the third a kind of dimerization to **11**.[439]



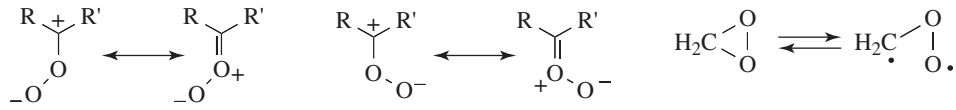
If the first path is taken (this is normally possible only if an aldehyde is formed; most ketones do not do this)[440] the product is an ozonide (see 1,2,4-trioxolane **6**),[441] and hydrolysis of the ozonide gives the normal products. If **10** is formed, hydrolysis of it gives one of the products, and, of course, the carbonyl compound (which then does not undergo further reaction), is the other. If intermediate **11** is formed, direct decomposition is possible, as shown, to give the normal products and oxygen. In protic solvents, **8** is converted to a hydroperoxide, and these have been isolated; for example, $Me_2C(OMe)OOH$ from $Me_2C{=}CMe_2$ in methanol. Further evidence for the mechanism is that **10** can be isolated in some cases; for example, from $Me_2C{=}CMe_2$. But perhaps the most impressive evidence comes from the detection of cross products. In the Criegee mechanism, the two parts of the original alkene break apart and then recombine to form the ozonide. In the case of an unsymmetrical alkene RCH=CHR′ there should be three ozonides since there are two different aldehydes and two different species **8**, and these can recombine in three ways: R—R, R—R′, and R′—R. Actually *six* ozonides, corresponding to the *cis* and *trans* forms, were isolated and characterized for methyl oleate.[442] Similar results have been reported for smaller alkenes, for example, pent-2-ene, non-4-ene, and even 2-methylpent-2-ene.[443] The last-mentioned case is especially interesting, since it is quite plausible that this compound would cleave in only one way, so that only one ozonide (in *cis* and *trans* versions) would be found; but this is not so, and three were found for this case too. However, terminal alkenes give little or no cross ozonide formation.[444] In general, the less alkylated end of the alkene tends to go to the carbonyl and the other to **8**. Still other evidence[445] for the Criegee mechanism is: (i) when $Me_2C{=}CMe_2$ was ozonized in the presence of HCHO,

[438] See Sander, W. *Angew. Chem. Int. Ed.* ***1990***, *29*, 344; Brunelle, W.H. *Chem. Rev.* ***1991***, *91*, 335.
[439] Fliszár, S.; Chylinska, J.B. *Can. J. Chem.* ***1967***, *45*, 29; ***1968***, *46*, 783.
[440] See Griesbaum, K.; Volpp, W.; Greinert, R.; Greunig, H.; Schmid, J.; Henke, H. *J. Org. Chem.* ***1989***, *54*, 383.
[441] Kamata, M.; Komatsu, K.i.; Akaba, R. *Tetrahedron Lett.* ***2001***, *42*, 9203. For a report of an isolable ozonide, see dos Santos, C.; de Rosso, C.R.S.; Imamura, P.M. *Synth. Commun.* ***1999***, *29*, 1903.
[442] Riezebos, G.; Grimmelikhuysen, J.C.; van Dorp, D.A. *Recl. Trav. Chim. Pays-Bas* ***1963***, *82*, 1234; Privett, O.S.; Nickell, E.C. *J. Am. Oil Chem. Soc.* ***1964***, *41*, 72.
[443] Loan, L.D.; Murray, R.W.; Story, P.R. *J. Am. Chem. Soc.* ***1965***, *87*, 737; Lorenz, O.; Parks, C.R. *J. Org. Chem.* ***1965***, *30*, 1976.
[444] Murray, R.W.; Williams, G.J. *J. Org. Chem.* ***1969***, *34*, 1891.
[445] See Wojciechowski, B.J.; Chiang, C.; Kuczkowski, R.L. *J. Org. Chem.* ***1990***, *55*, 1120; Murray, R.W.; Morgan, M.M. *J. Org. Chem.* ***1991***, *56*, 684, 6123.

the ozonide could be isolated;[446] (ii) **8** prepared in an entirely different manner (photooxidation of diazo compounds), reacted with aldehydes to give ozonides;[447] and (iii) *cis* and *trans* alkenes generally give the same ozonide, which would be expected if they cleave first.[448] However, this was not true for $Me_3CCH{=}CHCMe_3$, where the *cis* alkene gave the *cis* ozonide (chiefly), and the *trans* alkene gave the *trans* ozonide.[449] The latter result is not compatible with the Criegee mechanism. Also incompatible with the Criegee mechanism was the finding that the *cis*/*trans* ratios of symmetrical (cross) ozonides obtained from *cis*- and *trans*-4-methylpent-2-ene were not the same.[450] If the Criegee mechanism operated as shown above, the *cis*/*trans* ratio for each of the two cross ozonides would have to be identical for the *cis* and *trans* alkenes, since in this mechanism they are completely cleaved. A discussion of highly oxidized multifunctional products for the ozonolysis of cyclohexene has been reported.[451]

The above stereochemical results have been explained[452] on the basis of the Criegee mechanism with the following refinements: (i) The formation of **7** is stereospecific, as expected from a 1,3-dipolar cycloaddition. (ii) Once formed, **8** and the aldehyde or ketone remain attracted to each other, much like an ion pair. (iii) Intermediate **8** exists in *syn* and *anti* forms, which are produced in different amounts and can hold their shapes, at least for a time. This is plausible if we remember that a C=O canonical form contributes to the structure. (iv) The combination of **8** and the aldehyde or ketone is also a 1,3-dipolar cycloaddition, so configuration is retained in this step too.[453]

Evidence that the basic Criegee mechanism operates even in these cases comes from ^{18}O labeling experiments, making use of the fact, mentioned above, that mixed ozonides (e.g., **8**) can be isolated when an external aldehyde is added. Both the normal and modified Criegee mechanisms predict that if ^{18}O-labeled aldehyde is added to the ozonolysis mixture, the label will appear in the ether oxygen, and this is what is found.[454] There is evidence that the *anti*-**8** (^-O is *anti* to R′) couples much more readily than the *syn*-**8** (^-O is *syn* to R′).[455]



syn-8 **anti-8**

The ozonolysis of ethylene[456] in the liquid phase (without a solvent) was shown to take place by the Criegee mechanism.[457] This reaction has been used to study the structure of

[446] Criegee, R.; Korber, H. *Chem. Ber.* ***1971***, *104*, 1812.
[447] Higley, D.P.; Murray, R.W. *J. Am. Chem. Soc.* ***1974***, *96*, 3330.
[448] See Murray, R.W.; Williams, G.J. *J. Org. Chem.* ***1969***, *34*, 1896.
[449] See Kolsaker, P. *Acta Chem. Scand. Ser. B* ***1978***, *32*, 557.
[450] Murray, R.W.; Youssefyeh, R.D.; Story, P.R. *J. Am. Chem. Soc.* ***1966***, *88*, 3143, 3655; Story, P.R.; Murray, R.W.; Youssefyeh, R.D. *J. Am. Chem. Soc.* ***1966***, *88*, 3144. Also see, Choe, J.; Srinivasan, M.; Kuczkowski, R.L. *J. Am. Chem. Soc.* ***1983***, *105*, 4703.
[451] Rissanen, M.P.; Kurtén, T.; Sipilä, M.; Thornton, J.A.; Kangasluoma, J.; Sarnela, N.; Junninen, H.; Jørgensen, S.; Schallhart, S.; Kajos, M.K.; Taipale, R.; Springer, M.; Mentel, T.F.; Ruuskanen, T.; Petäjä, T.; Worsnop, D.R.; Kjaergaard, H.G.; Ehn, M. *J. Am. Chem. Soc.* ***2014***, *136*, 15596.
[452] Keul, H.; Kuczkowski, R.L. *J. Am. Chem. Soc.* ***1985***, *50*, 3371.
[453] See Choe, J.; Painter, M.K.; Kuczkowski, R.L. *J. Am. Chem. Soc.* ***1984***, *106*, 2891.
[454] See Mazur, U.; Kuczkowski, R.L. *J. Org. Chem.* ***1979***, *44*, 3185.
[455] Mile, B.; Morris, G.M. *J. Chem. Soc., Chem. Commun.* ***1978***, 263.
[456] See Samuni, U.; Fraenkel, R.; Haas, Y.; Fajgar, R.; Pola, J. *J. Am. Chem. Soc.* ***1996***, *118*, 3687.
[457] Fong, G.D.; Kuczkowski, R.L. *J. Am. Chem. Soc.* ***1980***, *102*, 4763.

the dioxirane intermediate or a biradical (•CH_2—O—O•). The dioxirane was identified in the reaction mixture[458] at low temperatures and is probably in equilibrium with the biradical. Dioxirane has been produced in solution but it oxidatively cleaves dialkyl ethers (e.g., Et—O—Et) via a chain radical process,[459] so the choice of solvent is important.

Ozonolysis in the gas phase is not generally carried out in the laboratory. However, the reaction is important because it takes place in the atmosphere and contributes to air pollution.[460] There is much evidence that the Criegee mechanism operates in the gas phase too, although the products are more complex because of other reactions that also take place.[461]

OS **V**, 489, 493; **VI**, 976; **VII**, 168; **IX**, 314. Also see, OS **IV**, 554. For the preparation of ozone, see OS **III**, 673.

19-10 Oxidative Cleavage of Double Bonds and Aromatic Rings

$$R_2C{=}CHR \xrightarrow{CrO_3} R_2C{=}O + RCOOH$$

Carbon-carbon double bonds can be cleaved by many oxidizing agents,[462] the most common of which are permanganate in neutral or acid media and dichromate in acid media. The products are generally 2 molar equivalents of ketone, 2 molar equivalents of carboxylic acid, or 1 molar equivalent of each, depending on what groups are attached to the alkene. With ordinary solutions of permanganate or dichromate yields are generally low, and the reaction is seldom a useful synthetic method; but high yields can be obtained by oxidizing with $KMnO_4$ dissolved in benzene containing the crown ether dicyclohexano-18-crown-6 (Sec. 3.C.ii).[463] The crown ether coordinates with K^+, permitting the $KMnO_4$ to dissolve in benzene. Another reagent frequently used for synthetic purposes is the *Lemieux-von Rudloff reagent*, which is HIO_4 containing a trace of MnO_4^-.[464] The MnO_4^- is the actual oxidizing agent, being reduced to the manganate stage (MnO_4^{2-}), and the purpose of the HIO_4 is to reoxidize the manganate(VI) back to MnO_4^-. Another reagent that behaves similarly is $NaIO_4$/ruthenium tetroxide.[465] Oxidative cleavage of alkenes is catalyzed by Ru with $IO(OH)_5$.[466] Cyclic alkenes are cleaved to dialdehydes with $KMnO_4$•$CuSO_4$ in dichloromethane.[467]

[458] Suenram, R.D.; Lovas, F.J. *J. Am. Chem. Soc.* ***1978***, *100*, 5117. See, however, Ishiguro, K.; Hirano, Y.; Sawaki, Y. *J. Org. Chem.* ***1988***, *53*, 5397.

[459] Ferrer, M.; Sánchez-Baeza, F.; Casas, J.; Messeguer, A. *Tetrahedron Lett.* ***1994***, *35*, 2981.

[460] See Atkinson, R.; Carter, W.P.L. *Chem. Rev.* ***1984***, *84*, 437.

[461] See Atkinson, R.; Carter, W.P.L. *Chem. Rev.* ***1984***, *84*, 437 (pp. 452–454); Martinez, R.I.; Herron, J.T. *J. Phys. Chem.* ***1988***, *92*, 4644.

[462] See Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 77–84, 96–98; Badanyan, Sh.O.; Minasyan, T.T.; Vardapetyan, S.K. *Russ. Chem. Rev.* ***1987***, *56*, 740; Cainelli, G.; Cardillo, G. *Chromium Oxiations in Organic Chemistry*, Open Court Pub. Co., La Salle, IL, ***1981***, pp. 59–92. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 1634.

[463] Sam, D.J.; Simmons, H.E. *J. Am. Chem. Soc.* ***1972***, *94*, 4024. See also, Lee, D.G.; Chang, V.S. *J. Org. Chem.* ***1978***, *43*, 1532.

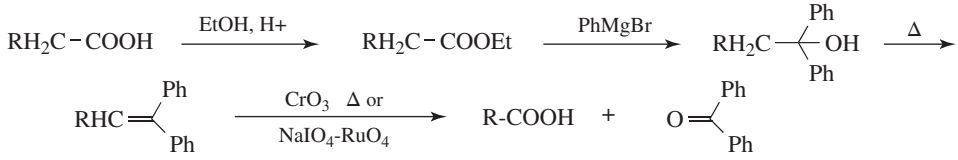
[464] von Rudloff, E. *Can. J. Chem.* ***1955***, *33*, 1714; ***1956***, *34*, 1413; ***1965***, *43*, 1784.

[465] Lee, D.G.; van den Engh, M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 186–192. See Cainelli, G.; Contento, M.; Manescalchi, F.; Plessi, L. *Synthesis* ***1989***, 47.

[466] Shoair, A.G.F.; Mohamed, R.H. *Synth. Commun.* ***2006***, *36*, 59; Griffith, W.P.; Shoair, A.G.; Suriaatmaja, M. *Synth. Commun.* ***2000***, *30*, 3091.

[467] Göksu, S.; Altundaş, R.; Sütbeyaz, Y. *Synth. Commun.* ***2000***, *30*, 1615.

The *Barbier-Wieland procedure* for decreasing the length of a chain by one carbon involves oxidative cleavage by acid dichromate ($NaIO_4/RuO_4$ has also been used), but this is cleavage of a 1,1-diphenyl alkene, which generally gives good yields.



Addition of a catalytic amount of OsO_4 to *Jones reagent* (**19-3**) leads to good yields of the carboxylic acid from simple alkenes.[468] A combination of Oxone® and OsO_4 in DMF cleaves alkenes to carboxylic acids.[469] Cleavage of alkynes is generally rather difficult, but treatment of internal alkynes with an excess of Oxone with a Ru catalyst leads to aliphatic carboxylic acids.[470]

With certain reagents, the oxidation of double bonds can be stopped at the aldehyde stage, and in these cases the products are the same as in the ozonolysis procedure. Among these reagents are *tert*-butyl iodoxybenzene[471] and $NaIO_4/OsO_4$.[472] Enol ethers, $RC(OR')=CH_2$, have been cleaved to carboxylic esters $RC(OR')=O$ by atmospheric oxygen.[473] Oxidative cleavage of alkenes is catalyzed by a Mn/porphyrin complex.[474]

The mechanism of oxidation in most cases probably involves the initial formation of a glycol (**15-25**) or cyclic ester,[475] and then further oxidation as in **19-7**.[476] In line with the electrophilic attack on the alkene, triple bonds are more resistant to oxidation than double bonds. Terminal triple-bond compounds can be cleaved to carboxylic acids with $Tl(III)NO_3$[477] or with [bis(trifluoroacetoxy)iodo]pentafluorobenzene [i.e., $C_6F_5I(OCOCF_3)_2$].[478]

Other methods have been developed for the oxidative cleavage of alkenes to give carbonyl derivatives. The *N*-hydroxyphthalimide-catalyzed oxidative cleavage of alkenes using O_2 as an oxidant gave the carbonyl derivatives.[479] Oxidative cleavage of C=C double bonds with a phenyl substituent by reaction with iodosylbenzene gave carbonyl compounds via a radical pathway.[480] When heating an alkene with Oxone in an acetonitrile/water mixture, the alkenes underwent oxidative cleavage to the corresponding acids.[481] Heating alkenes with an organoselenium catalyst alkene in ethanol with hydrogen peroxide gave

[468] Henry, J.R.; Weinreb, S.M. *J. Org. Chem.* ***1993***, *58*, 4745.
[469] Travis, B.R.; Narayan, R.S.; Borhan, B. *J. Am. Chem. Soc.* ***2002***, *124*, 3824. See also, Whitehead, D.C.; Travis, B.R.; Borhan, B. *Tetrahedron Lett.* ***2006***, *47*, 3797.
[470] Yang, D.; Chen, F.; Dong, Z.-M.; Zhang, D.-W. *J. Org. Chem.* ***2004***, *69*, 2221.
[471] Ranganathan, S.; Ranganathan, D.; Singh, S.K. *Tetrahedron Lett.* ***1985***, *26*, 4955.
[472] Pappo, R.; Allen Jr., D.S.; Lemieux, R.U.; Johnson, W.S. *J. Org. Chem.* ***1956***, *21*, 478.
[473] Taylor, R. *J. Chem. Res. (S)* ***1987***, 178. See Torii, S.; Inokuchi, T.; Kondo, K. *J. Org. Chem.* ***1985***, *50*, 4980.
[474] Liu, S.-T.; Reddy, K.V.; Lai, R.-Y. *Tetrahedron* ***2007***, *63*, 1821.
[475] See Lee, D.G.; Spitzer, U.A. *J. Org. Chem.* ***1976***, *41*, 3644; Lee, D.G.; Chang, V.S.; Helliwell, S. *J. Org. Chem.* ***1976***, *41*, 3644, 3646.
[476] For evidence of an epoxide intermediate: see Rocek, J.; Drozd, J.C. *J. Am. Chem. Soc.* ***1970***, *92*, 6668.
[477] McKillop, A.; Oldenziel, O.H.; Swann, B.P.; Taylor, E.C.; Robey, R.L. *J. Am. Chem. Soc.* ***1973***, *95*, 1296.
[478] Moriarty, R.M.; Penmasta, R.; Awasthi, A.K.; Prakash, I. *J. Org. Chem.* ***1988***, *53*, 6124.
[479] Lin, R.; Chen, F.; Jiao, N. *Org. Lett.* ***2012***, *14*, 4158.
[480] Atmaca, U.; Usanmaz, H.K.; Çelik, M. *Tetrahedron Lett.* ***2014***, *55*, 2230.
[481] Parida, K.N.; Moorthy, J.N. *Tetrahedron* ***2014***, *70*, 2280.

carbonyl compounds.[482] A Ru catalyst with an *N*-heterocyclic carbene ligand oxidatively cleaved C═C bonds to aldehydes and C≡C bonds to α-diketones.[483] The oxidative cleavage of alkenes with $PhI(OAc)_2$ and ammonium hydrogen carbonate gave the nitrile.[484]

Aromatic rings can be cleaved with sufficiently strong oxidizing agents. An important laboratory reagent for this purpose is RuO_4, along with a co-oxidant such as $NaIO_4$ or NaOCl (household bleach can be used). Ruthenium tetroxide is an expensive reagent, but the cost can be greatly reduced by the use of an inexpensive co-oxidant such as NaOCl, the function of which is to oxidize RuO_2 back to ruthenium tetroxide. Examples[485] are the oxidation of naphthalene to phthalic acid[486] and, even more remarkably, of cyclohexylbenzene to cyclohexanecarboxylic acid.[487] The latter conversion was also accomplished with ozone.[488] Another reagent that oxidizes aromatic rings is air catalyzed by V_2O_5. The oxidations of naphthalene to phthalic anhydride and of benzene to maleic anhydride by this reagent are important industrial procedures.[489] *o*-Diamines have been oxidized to hexa-2,4-dienedinitrile with nickel peroxide, with lead tetraacetate,[490] and with O_2 catalyzed by CuCl.[491] The latter reagent also cleaves *o*-dihydroxybenzenes (catechols) to give, in the presence of MeOH, the mono-methylated dicarboxylic acids $HO_2C{-}C{=}C{-}C{=}C{-}CO_2Me$.[492]

OS **II**, 53, 523; **III**, 39, 234, 449; **IV**, 136, 484, 824; **V**, 393; **VI**, 662, 690; **VII**, 397; **VIII**, 377, 490; **IX**, 530. Also see, OS **II**, 551.

19-11 Oxidation of Aromatic Side Chains

$$ArR \xrightarrow{KMnO_4} ArCOOH$$

Alkyl chains on aromatic rings can be oxidized to CO_2H groups by many oxidizing agents, including permanganate, nitric acid, and acid dichromate.[493] The method is most often applied to the methyl group ($CH_3 \rightarrow CO_2H$), although longer side chains can also be cleaved. Tertiary alkyl groups are resistant to oxidation, and when they *are* oxidized, ring cleavage usually occurs too.[494] It is usually difficult to oxidize an R group on a fused aromatic system without cleaving the ring or oxidizing it to a quinone (**19-19**). However, such oxidation has been done (e.g., 2-methylnaphthalene was converted to 2-naphthoic acid)

[482] Wang, T.; Jing, X.; Chen, C.; Yu, L. *J. Org. Chem.* ***2017***, *82*, 9342.
[483] Daw, P.; Petakamsetty, R.; Sarbajna, A.; Laha, S.; Ramapanicker, R.; Bera, J.K. *J. Am. Chem. Soc.* ***2014***, *136*, 13987.
[484] Xu, J.-H.; Jiang, Q.; Guo, C.-C. *J. Org. Chem.* ***2013***, *78*, 11881.
[485] See Nuñez, M.T.; Martín, V.S. *J. Org. Chem.* ***1990***, *55*, 1928.
[486] Spitzer, U.A.; Lee, D.G. *J. Org. Chem.* ***1974***, *39*, 2468.
[487] Caputo, J.A.; Fuchs, R. *Tetrahedron Lett.* ***1967***, 4729.
[488] Klein, H.; Steinmetz, A. *Tetrahedron Lett.* ***1975***, 4249. See Liotta, R.; Hoff, W.S. *J. Org. Chem.* ***1980***, *45*, 2887; Chakraborti, A.K.; Ghatak, U.R. *J. Chem. Soc., Perkin Trans. 1* ***1985***, 2605.
[489] See Pyatnitskii, Yu.I. *Russ. Chem. Rev.* ***1976***, *45*, 762.
[490] Nakagawa, K.; Onoue, H. *Tetrahedron Lett.* ***1965***, 1433; *Chem. Commun.* ***1966***, 396.
[491] Kajimoto, T.; Takahashi, H.; Tsuji, J. *J. Org. Chem.* ***1976***, *41*, 1389.
[492] Tsuji, J.; Takayanag, H.i. *Tetrahedron* ***1978***, *34*, 641; Bankston, D. *Org. Synth. 66*, 180.
[493] Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 105–109; Lee, D.G. *The Oxidation of Organic Compounds by Permanganate Ion and Hexavalent Chromium*, Open-Court Publishing Co., La Salle, IL, ***1980***, pp. 43–64. See Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Open Court Pub. Co., La Salle, IL, ***1981***, pp. 23–33.
[494] Brandenberger, S.G.; Maas, L.W.; Dvoretzky, I. *J. Am. Chem. Soc.* ***1961***, *83*, 2146.

with aqueous $Na_2Cr_2O_7$.[495] Aryl methyl groups are oxidized to aryl CO_2H with NaOCl in acetonitrile,[496] or with NBS in aqueous NaOH under photochemical conditions.[497] Functional groups can be present anywhere on the side chain and, if in the α position, greatly increase the ease of oxidation. An exception is an α-phenyl group. In such cases, the reaction stops at the diaryl ketone stage. Molecules containing aryl groups on different carbons cleave so that each ring gets one carbon atom, as in the cleavage of the 9,10 bond of dihydrophenanthrene to the diacid.

It is possible to oxidize only one alkyl group of a ring that contains more than one. The order of reactivity[498] toward most reagents is $CH_2Ar > CHR_2 > CH_2R > CH_3$.[499] Groups on the ring susceptible to oxidation (OH, NHR, NH_2, etc.) must be protected. The oxidation can be performed with oxygen, in which case it is autoxidation, and the mechanism is like that in **14-6**, with a hydroperoxide intermediate.[500] With this procedure it is possible to isolate ketones from $ArCH_2R$.[501]

The mechanism has been studied for the closely related reaction:[502]

$$Ar_2CH_2 + CrO_3 \rightarrow Ar_2C{=}O$$

A deuterium isotope effect of 6.4 was found, indicating that the rate-determining step is either $Ar_2CH_2 \rightarrow Ar_2CH\bullet$ or $Ar_2CH_2 \rightarrow Ar_2CH^+$. Either way this explains why tertiary groups are not converted to CO_2H and why the reactivity order is $CHR_2 > CH_2R > CH_3$, as mentioned above. Both free radicals and carbocations exhibit this order of stability (Chapter 5). Just how the radical or the cation goes on to the product is not known.

When the alkyl group is oxidizable to CO_2H (**19-11**), cupric salts are oxidizing agents, and the OH group is found in a position *ortho* to that occupied by the alkyl group.[503] This reaction is used industrially to convert toluene to phenol.

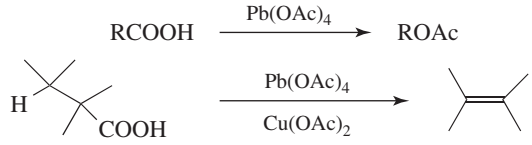
In another kind of reaction, an aromatic aldehyde ArCHO or ketone ArCOR′ is converted to a phenol ArOH on treatment with alkaline H_2O_2,[504] but there must be an OH or NH_2 group in the *ortho* or *para* position. This is called the *Dakin reaction*.[505] The mechanism may be similar to that of the *Baeyer-Villiger reaction* (**18-19**),[506] and an acetate intermediate has been isolated.[507] The reaction has been performed on aromatic aldehydes with an alkoxy group in the ring, and no OH or NH_2. In this case, acidic H_2O_2 was used.[508] The Dakin

[495] Friedman, L.; Fishel, D.L.; Shechter, H. *J. Org. Chem.* ***1965***, *30*, 1453.
[496] Yamazaki, S. *Synth. Commun.* ***1999***, *29*, 2211.
[497] Itoh, A.; Kodama, T.; Hashimoto, S.; Masaki, Y. *Synthesis* ***2003***, 2289.
[498] Onopchenko, A.; Schulz, J.G.D.; Seekircher, R. *J. Org. Chem.* ***1972***, *37*, 1414.
[499] See Foster, G.; Hickinbottom, W.J. *J. Chem. Soc.* ***1960***, 680; Ferguson, L.N.; Wims, A.I. *J. Org. Chem.* ***1960***, *25*, 668.
[500] Hermans, I.; Peeters, J.; Jacobs, P.A. *J. Org. Chem.* ***2007***, *72*, 3057.
[501] Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 508–543.
[502] Wiberg, K.B.; Evans, R.J. *Tetrahedron* ***1960***, *8*, 313.
[503] Kaeding, W.W. *J. Org. Chem.* ***1961***, *26*, 3144. See Lee, D.G.; van den Engh, M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt B, Academic Press, NY, ***1973***, pp. 91–94.
[504] For a convenient procedure, see Hocking, M.B. *Can. J. Chem.* ***1973***, *51*, 2384.
[505] See Schubert, W.M.; Kintner, R.R. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 749–752.
[506] See Hocking, M.B.; Bhandari, K.; Shell, B.; Smyth, T.A. *J. Org. Chem.* ***1982***, *47*, 4208.
[507] Hocking, M.B.; Ko, M.; Smyth, T.A. *Can. J. Chem.* ***1978***, *56*, 2646.
[508] Matsumoto, M.; Kobayashi, H.; Hotta, Y. *J. Org. Chem.* ***1984***, *49*, 4740.

reaction has been done in ionic liquids.[509] Flavin catalysts facilitated an organocatalytic Dakin oxidation of electron-rich aryl aldehydes to give phenols.[510]

OS **I**, 159, 385, 392, 543; **II**, 135, 428; **III**, 334, 420, 740, 791, 820, 822; **V**, 617, 810. OS **I**, 149; **III**, 759.

19-12 Oxidative Decarboxylation



Carboxylic acids can be decarboxylated[511] with lead tetraacetate to give a variety of products: an ester ROAc, the alkane RH (see **12-39**), an alkene if α,β hydrogens are present, as well as numerous other products arising from rearrangements, internal cyclizations,[512] and reactions with solvent molecules. When R is tertiary, the chief product is usually the alkene. High yields of alkenes can also be obtained when R is primary or secondary using $Cu(OAc)_2$ along with the $Pb(OAc)_4$.[513] In the absence of $Cu(OAc)_2$, primary acids give mostly alkanes (though yields are generally low) and secondary acids may give carboxylic esters or alkenes. Other oxidizing agents,[514] including Co(III), Ag(II), Mn(III), and Ce(IV), have also been used to effect oxidative decarboxylation.[515]

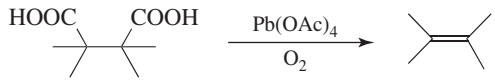
The mechanism with lead tetraacetate is generally accepted to be of the free-radical type.[516] First, there is an interchange of ester groups. A free-radical chain mechanism follows. (Other lead esters can behave similarly.) Products can then be formed either from R• or R^+. Primary R• abstract H from solvent molecules to give RH. The R^+ can lose H^+ to give an alkene, react with HOAc to give the carboxylic ester, react with solvent molecules or with another functional group in the same molecule, or rearrange, thus accounting for the large number of possible products. The radical R• can also dimerize to give RR. The effect of Cu^{2+} ions[517] is to oxidize the radicals to alkenes, thus producing good yields of alkenes from primary and secondary substrates. The Cu^{2+} ion has no effect on tertiary radicals, which are efficiently oxidized to alkenes by lead tetraacetate.

In another type of oxidative decarboxylation, aryl acetic acids can be oxidized to aldehydes with one less carbon ($ArCH_2COOH \rightarrow ArCHO$) by tetrabutylammonium

[509] Zambrano, J.L.; Dorta, R. *Synlett* ***2003***, 1545.
[510] Chen, S.; Hossain, M.S.; Foss Jr., F.W. *Org. Lett.* ***2012***, *14*, 2806.
[511] See Serguchev, Yu.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1980***, *49*, 1119; Sheldon, R.A.; Kochi, J.K. *Org. React.* ***1972***, *19*, 279.
[512] See Davies, D.I.; Waring, C. *J. Chem. Soc. C* ***1968***, 1865, 2337.
[513] Ogibin, Yu.N.; Katzin, M.I.; Nikishin, G.I. *Synthesis* ***1974***, 889.
[514] See Kochi, J.K. *Organometallic Mechanisms and Catalysis*, Academic Press, NY, ***1978***, pp. 99–106. See also, Fristad, W.E.; Fry, M.A.; Klang, J.A. *J. Org. Chem.* ***1983***, *48*, 3575; Barton, D.H.R.; Crich, D.; Motherwell, W.B. *J. Chem. Soc., Chem. Commun.* ***1984***, 242.
[515] For another method, see Barton, D.H.R.; Bridon, D.; Zard, S.Z. *Tetrahedron* ***1989***, *45*, 2615.
[516] See Cantello, B.C.C.; Mellor, J.M.; Scholes, G. *J. Chem. Soc., Perkin Trans. 2* ***1974***, 348; Beckwith, A.L.J.; Cross, R.T.; Gream, G.E. *Aust. J. Chem.* ***1974***, *27*, 1673, 1693.
[517] Kochi, J.K.; Bacha, J.D. *J. Org. Chem.* ***1968***, *33*, 2746; Torssell, K. *Ark. Kemi.* ***1970***, *31*, 401.

periodate.[518] Simple aliphatic carboxylic acids were converted to nitriles with one less carbon ($RCH_2COOH \rightarrow RC{\equiv}N$) by treatment with trifluoroacetic anhydride and $NaNO_2$ in F_3CCO_2H.[519]

19-13 Bis(decarboxylation)

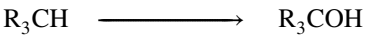


Compounds containing carboxyl groups on adjacent carbons (succinic acid derivatives) can be bis(decarboxylated) with lead tetraacetate in the presence of O_2.[509] The reaction is of wide scope. The elimination is stereoselective, but not stereospecific (both *meso*- and *dl*-2,3-diphenylsuccinic acid gave *trans*-stilbene);[520] a concerted mechanism is thus unlikely. Replacement of OAc of lead tetraacetate with a O_2CR unit of the diacid, followed by loss of the lead moiety to give a carbocation, and decarboxylation to give the alkene is compatible with the data. A free-radical mechanism seems to hold in some cases. Bis(decarboxylation) of succinic acid derivatives give alkenes.[521] Compounds containing geminal carboxyl groups (disubstituted malonic acid derivatives) can be bis(decarboxylated) with lead tetraacetate[522] and *gem*-diacetates (acylals) are produced, which are easily hydrolyzable to ketones.[523]

A related reaction involves α-substituted aryl nitriles having a sufficiently acidic α hydrogen, which can be converted to ketones by oxidation with air under phase-transfer conditions.[524] The nitrile is added to NaOH in benzene or DMSO containing a catalytic amount of triethylbenzylammonium chloride (TEBA).[525] This reaction could not be applied to aliphatic nitriles, but an indirect method for achieving this conversion is given in **19-65**.

C. Reactions Involving Replacement of Hydrogen by Heteroatoms

19-14 Hydroxylation at an Aliphatic Carbon



Compounds containing susceptible C—H bonds can be oxidized to alcohols (C—OH).[526] Nearly always, the C—H bond involved is tertiary, so the product is a tertiary alcohol. This is

[518] Santaniello, E.; Ponti, F.; Manzocchi, A. *Tetrahedron Lett.* ***1980***, *21*, 2655. Also see Doleschall, G.; Tóth, G. *Tetrahedron* ***1980***, *36*, 1649.
[519] Smushkevich, Yu.I.; Usorov, M.I.; Suvorov, N.N. *J. Org. Chem. USSR* ***1975***, *11*, 653.
[520] Corey, E.J.; Casanova, J. *J. Am. Chem. Soc.* ***1963***, *85*, 165.
[521] For a review, see De Lucchi, O.; Modena, G. *Tetrahedron* ***1984***, *40*, 2585 (pp. 2591–2608).
[522] See Salomon, R.G.; Roy, S.; Salomon, R.G. *Tetrahedron Lett.* ***1988***, *29*, 769.
[523] Tufariello, J.J.; Kissel, W.J. *Tetrahedron Lett.* ***1966***, 6145.
[524] For other methods of achieving this conversion, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 1260.
[525] See Kulp, S.S.; McGee, M.J. *J. Org. Chem.* ***1983***, *48*, 4097.
[526] Chinn, L.J. *Selection of Oxidants in Synthesis*, Marcel Dekker, NY, ***1971***, pp. 7–11; Lee, D.G. in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 2–6; Hill, C.L. *Activation and Functionalization of Alkanes*, Wiley, NY, ***1989***. See Goldberg, K.I.; Goldman, A.S. *Acc. Chem. Res.* ***2017***, *50*, 620.

partly because tertiary C—H bonds are more susceptible to free-radical attack than primary and secondary bonds and partly because the reagents involved would oxidize primary and secondary alcohols further. An arcane method is the reaction with ozone and the substrate is absorbed on silica gel.[527] Yields as high as 99% have been obtained by this method. Other reagents are chromic acid,[528] RuO_4,[529] thallium acetate,[530] sodium chlorite ($NaClO_2$) with a metalloporphyrin catalyst,[531] and OsO_4.[532] Alkanes and cycloalkanes have been oxidized at secondary positions, to a mixture of alcohols and trifluoroacetates, by 30% aqueous H_2O_2 in trifluoroacetic acid.[533] This reagent does not oxidize the alcohols further and ketones are not found. The $\omega - 1$ position is the most favored. Use of an optically active Fe(III)/porphyrin gave modest enantioselective hydroxylation.[534]

When chromic acid is the reagent, the mechanism is probably as follows: a Cr^{6+} species abstracts a hydrogen to give $R_3C\bullet$, which is held in a solvent cage near the resulting Cr^{5+} species. The two species then combine to give R_3COCr^{4+}, which is hydrolyzed to the alcohol. This mechanism predicts retention of configuration; this is largely observed.[535] The oxidation by permanganate also involves predominant retention of configuration, and a similar mechanism has been proposed.[536]

Hydroxylation can be accomplished using enzymatic systems. In the presence of *Bacillus megaterium* and oxygen, cyclohexane is converted to cyclohexanol.[537] Allylic oxidation to an allylic alcohol was accomplished with cultured cells of *Gossypium hirsutum*.[538] The reaction of tetradecanoic acid with the α-oxidase from *Pisum sativum*, in the presence of molecular oxygen, gives (2*R*)-hydroxytetradecanoic acid with high asymmetric induction.[539] Cyclodecane was oxidized to cyclodecanone by reaction with P450 monooxygenase BM-3 19A12 and then alcohol dehydrogenase from *L. kefir*., with 10% $NADP^+$ and oxygen.[540] The highly regio- and diastereoselective enzymatic hydroxylation of nonactivated disubstituted cyclohexane derivatives was catalyzed using wild-type P450-BM3.[541] The highly selective terminal hydroxylation of *gem*-difluorinated octanes by whole-cell catalysis using alkane hydroxylase derived from *Pseudomonas putida* Gpo1 gave *gem*-difluorinated octan-1-ols.[542] The fatty acid hydroxylase wild-type

[527] Cohen, Z.; Keinan, E.; Mazur, Y.; Varkony, T.H. *Org. Synth.* ***VI***, 43; Keinan, E.; Mazur, Y. *Synthesis* ***1976***, 523; McKillop, A.; Young, D.W. *Synthesis* ***1979***, 401 (see pp. 418–419).
[528] Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Springer, NY, ***1984***, pp. 8–23.
[529] See Drees, M.; Strassner, T. *J. Org. Chem.* ***2006***, *71*, 1755.
[530] Lee, J.C.; Park, C.; Choi, Y. *Synth. Commun.* ***1997***, *27*, 4079.
[531] Collman, J.P.; Tanaka, H.; Hembre, R.T.; Brauman, J.I. *J. Am. Chem. Soc.* ***1990***, *112*, 3689.
[532] Bales, B.C.; Brown, P.; Dehestani, A.; Mayer, J.M. *J. Am. Chem. Soc.* ***2005***, *127*, 2832.
[533] Deno, N.C.; Jedziniak, E.J.; Messer, L.A.; Meyer, M.D.; Stroud, S.G.; Tomezsko, E.S. *Tetrahedron* ***1977***, *33*, 2503.
[534] Groves, J.T.; Viski, P. *J. Org. Chem.* ***1990***, *55*, 3628.
[535] Wiberg, K.B.; Eisenthal, R. *Tetrahedron* ***1964***, *20*, 1151.
[536] Stewart, R.; Spitzer, U.A. *Can. J. Chem.* ***1978***, *56*, 1273.
[537] Adam, W.; Lukacs, Z.; Saha-Möller, C.R.; Weckerle, B.; Schreier, P. *Eur. J. Org. Chem.* ***2000***, 2923.
[538] Hamada, H.; Tanaka, T.; Furuya, T.; Takahata, H.; Nemoto, H. *Tetrahedron Lett.* ***2001***, *42*, 909.
[539] Adam, W.; Boland, W.; Hartmann-Schreier, J.; Humpf, H.-U.; Lazarus, M.; Saffert, A.; Saha-Möller, C.R.; Schreier, P. *J. Am. Chem. Soc.* ***1998***, *120*, 11044.
[540] Staudt, S.; Burda, E.; Giese, C.; Müller, C.A.; Marienhagen, J.; Schwaneberg, U.; Hummel, W.; Drauz, K.; Gröger, H. *Angew. Chem. Int. Ed.* ***2013***, *52*, 2359.
[541] Ilie, A.; Agudo, R.; Roiban, G.-D.; Reetz, M.T. *Tetrahedron* ***2015***, *71*, 470. See Munday, S.D.; Shoji, O.; Watanabe, Y.; Wong, L.-L.; Bel, S.G. *Chem. Commun.* ***2016***, *52*, 1036.
[542] Ramu, R.; Chang, C.-W.; Chou, H.-H.; Wu, L.-L.; Chiang, C.-H.; Yu, S.S.-F. *Tetrahedron Lett.* ***2011***, *52*, 2950.

P450BM3 is unable to oxidize gaseous alkanes unless a perfluorocarboxylic acid is added, in which case the P450BM3 catalytic cycle gave hydroxylation of butane and propane.[543] The terminal-selective cytochrome P450pyr has been successfully engineered through directed evolution for the hydroxylation of *n*-octane to (*S*)-octan-2-ol with excellent regio- and enantioselectivity.[544]

Hydroxylation of unactivated sp^3-hybridized bonds is possible using an oxaziridine-mediated, organocatalyzed reaction.[545] Hydrogen peroxide and trifluoroacetic acid has also been used for oxidation of alkanes.[546] The same type of conversion, with lower yields (20–30%), has been achieved with the *Gif system*.[547] One variation consists of pyridine/acetic acid, with H_2O_2 as oxidizing agent and tris(picolinato)iron(III) as catalyst.[548] Other Gif systems use O_2[549] as oxidizing agent and Zn as a reductant.[550] The mechanism of oxygen insertion into alkanes has been examined.[551] The selectivity of the Gif systems toward alkyl carbons is $CH_2 > CH \geq CH_3$, which is unusual, and shows that a simple free-radical mechanism (Sec. 14.A.iv) is not involved.[552] Another reagent that can oxidize the CH_2 of an alkane is methyl(trifluoromethyl)dioxirane, but this produces CH—OH more often than C—O (see **19-14**; **19-16**).[553] Cyclic alkanes are oxidized to a mixture of the alcohol and the ketone with $PhI(OAc)_2$ and a manganese complex in an ionic liquid.[554] Oxidation of cyclic alkanes to cyclic ketones was accomplished using a Ru catalyst.[555] The iron/thymine-1-acetate system catalyzed conversion of alkanes to ketones.[556]

Oxidation of CH_2 to C═O groups is possible indirectly, even if they are not near any functional groups, by the remote oxidation method of Breslow[76] (see **19-2**). Remote oxidations[557] have also been reported. Octan-2-ol was oxidized to give 2-propyl-5-methyl γ-butyrolactone with lead tetraacetate in a CO atmosphere.[558] Chloramine-T (see **15-50**), O_2, and an Fe catalyst give selective oxidation of hydrocarbons to ketones.[559]

Nanocrystalline cobalt oxide is another catalyst for alkane oxidation.[560] A tandem biocatalyst system of a monooxygenase-containing microorganism and an alcohol

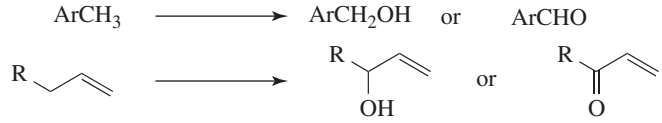
[543] Kawakami, N.; Shoji, O.; Watanabe, Y. *Angew. Chem. Int. Ed.* ***2011***, *50*, 5315.
[544] Yang, Y.; Liu, J.; Li, Z. *Angew. Chem. Int. Ed.* ***2014***, *53*, 3120.
[545] Brodsky, B.H.; Du Bois, J. *J. Am. Chem. Soc.* ***2005***, *127*, 15391.
[546] Camaioni, D.M.; Bays, J.T.; Shaw, W.J.; Linehan, J.C.; Birnbaum, J.C. *J. Org. Chem.* ***2001***, *66*, 789. See Tung, H.; Sawyer, D.T. *J. Am. Chem. Soc.* ***1990***, *112*, 8214.
[547] Named for Gif-sur-Yvette, France, where it was discovered. See Schuchardt, U.; Jannini, M.J.D.M.; Richens, D.T.; Guerreiro, M.C.; Spinacé, E.V. *Tetrahedron* ***2001***, *57*, 2685.
[548] About-Jaudet, E.; Barton, D.H.R.; Csuhai, E.; Ozbalik, N. *Tetrahedron Lett.* ***1990***, *31*, 1657. For a review of the mechanism, see Barton, D.H.R. *Chem. Soc. Rev.* ***1996***, *25*, 237.
[549] See Liang, Y.-F.; Jiao, N. *Acc. Chem. Res.* ***2017***, *50*, 1640.
[550] See Barton, D.H.R.; Csuhai, E.; Ozbalik, N. *Tetrahedron* ***1990***, *46*, 3743 and references cited therein.
[551] Freccero, M.; Gandolfi, R.; Sarzi-Amadé, M.; Rastelli, A. *Tetrahedron* ***2001***, *57*, 9843.
[552] Barton, D.H.R.; Csuhai, E.; Doller, D.; Ozbalik, N.; Senglet, N. *Tetrahedron Lett.* ***1990***, *31*, 3097. For mechanistic studies, see Barton, D.H.R.; Doller, D.; Geletii, Y.V. *Tetrahedron Lett.* ***1991***, *32*, 3911 and references cited therein. See Barton, D.H.R.; Hill, D.R. *Tetrahedron Lett.* ***1994***, *35*, 1431.
[553] D'Accolti, L.; Dinoi, A.; Fusco, C.; Russo, A.; Curci, R. *J. Org. Chem.* ***2003***, *68*, 7806.
[554] Li, Z.; Xiu, C.-G.; Xu, C.-Z. *Tetrahedron Lett.* ***2003***, *44*, 9229.
[555] Che, C.-M.; Cheng, K.-W.; Chan, M.C.W.; Lau, T.-C.; Mak, C.-K. *J. Org. Chem.* ***2000***, *65*, 7996.
[556] Al-hunaiti, A.; Räisänen, M.; Repo, T. *Chem. Commun.* ***2016***, *52*, 2043.
[557] See also, Beckwith, A.L.J.; Duong, T. *J. Chem. Soc., Chem. Commun.* ***1978***, 413.
[558] Tsunoi, S.; Ryu, I.; Okuda, T.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* ***1998***, *120*, 8692. Also see, Tsunoi, S.; Ryu, I.; Sonoda, N. *J. Am. Chem. Soc.* ***1994***, *116*, 5473.
[559] Li, S.-J.; Wan, Y.-G. *Tetrahedron Lett.* ***2005***, *46*, 8013.
[560] Davies, T.E.; García, T.; Solsona, B.; Taylor, S.H. *Chem. Commun.* ***2006***, 3417.

dehydrogenase was developed for the oxidations of methylene groups to ketones.[561] Methylene units of hydrocarbons were oxidize to the corresponding ketone using a benzimidazole-based nonheme manganese complex with hydrogen peroxide in the presence of acetic acid as an additive.[562] The oxidation of the C—H of an isopropyl group distal to a pyridine moiety using a Mn-mediated, Ru-catalyzed reaction with peroxyacetic acid in acetic acid gave the corresponding alcohol.[563] Copper complexes were used to catalyzed the oxidation of alkanes with H_2O_2 to give the alcohol is modest yield.[564] The Os-catalyzed oxidation of cyclohexane with H_2O_2 gave a mixture of 61% of cyclohexanol plus 12% of cyclohexanone.[565] The conversion of methane to methanol by reaction with methyl(trifluoromethyl)dioxirane was reported at subambient temperatures.[566] The aryl trifluoromethyl ketone-catalyzed reaction using hydrogen peroxide for oxidation of alkanes gave the alcohol with selectivity for tertiary over secondary C—H bonds.[567]

Simple alkanes can be converted to esters with dialkyloxiranes. Cyclic alkanes are oxidized to alcohols with dimethyl dioxirane.[568] Cyclohexane was converted to cyclohexyl trifluoroacetate with di(trifluoromethyl)dioxirane and trifluoroacetic anhydride[569] and also with $RuCl_3/MeCO_3H/CF_3CO_2H$.[570] A Pd-catalyzed alkoxylation of unactivated methylene and methyl groups using a cyclic hypervalent iodine oxidant gave amides with a distal hydroxyl unit.[571]

OS **IV**, 23; **VI**, 43, 946; **VII**, 263, 277, 282.

19-15 Oxidation of Benzylic or Allylic Positions



Benzylic and allylic methylene groups are more readily oxidized to benzylic alcohols when compared to simple alkanes. Methyl groups on an aromatic ring can be oxidized to an aldehyde by several oxidizing agents.

When the reagent is chromyl chloride (CrO_2Cl_2), the reaction is called the *Étard reaction*[572] and the yields are high.[573] The mechanism of the Étard reaction is not completely

[561] Zhang, W.; Tang, W.L.; Wang, D.I.C.; Li, Z. *Chem. Commun.* ***2011***, *47*, 3284.
[562] Shen, D.; Miao, C.; Wang, S.; Xia, C.; Sun, W. *Org. Lett.* ***2014***, *16*, 1108.
[563] Adams, A.M.; Du Bois, J.; Malik, H.A. *Org. Lett.* ***2015***, *17*, 6066. See Roizen, J.L.; Harvey, M.E.; Du Bois, J. *Acc. Chem. Res.* ***2012***, *45*, 911.
[564] Garcia-Bosch, I.; Siegler, M.A. *Angew. Chem. Int. Ed.* ***2016***, *55*, 12873; Garcia-Bosch, I. *Synlett.* ***2017***, *28*, 1237.
[565] Chen, M.; Pan, Y.; Kwong, H.-K.; Zeng, R.J.; Lau, K.-C.; Lau, T.-C. *Chem. Commun.* ***2015***, *51*, 13686. See Xie, Y.; Zhang, F.; Liu, P.; Hao, F.; Luo, H. *Can. J. Chem.* ***2014***, *92*, 49.
[566] Annese, C.; D'Accolti, L.; Fusco, C.; Curci, R. *Org. Lett.* ***2011***, *13*, 2142.
[567] Pierce, C.J.; Hilinski, M.K. *Org. Lett.* ***2014***, *16*, 6504.
[568] See Yang, Z.; Yu, P.; Houk, K.N. *J. Am. Chem. Soc.* ***2016***, *138*, 4237.
[569] Asensio, G.; Mello, R.; González-Nuñez, M.E.; Castellano, G.; Corral, J. *Angew. Chem. Int. Ed.* ***1996***, *35*, 217.
[570] Komiya, N.; Noji, S.; Murahashi, S.-I. *Chem. Commun.* ***2001***, 65.
[571] Shan, G.; Yang, X.; Zong, Y.; Rao, Y. *Angew. Chem. Int. Ed.* ***2013***, *52*, 13606; Chen, F.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.; Shi, B. *Chem. Sci.* ***2013***, *4*, 4187.
[572] The name *Étard reaction* is often applied to any oxidation with chromyl chloride, for example, oxidation of glycols (**19-7**), alkenes (**19-10**), etc.
[573] See Hartford, W.H.; Darrin, M. *Chem. Rev.* ***1958***, *58*, 1 (see pp. 25–53).

known.[574] An insoluble complex is formed on addition of the reagents, which is hydrolyzed to the aldehyde. The complex is probably a kind of acylal, but the identity of the structure is not fully settled, although many proposals have been made as to its structure and as to how it is hydrolyzed. It is known that $ArCH_2Cl$ is not an intermediate (see **19-20**), since it reacts only very slowly with chromyl chloride. Magnetic susceptibility measurements[575] indicate that the complex from toluene is $PhCH(O{-}CrCl_2OH)_2$, a structure first proposed by Étard. According to this proposal, the reaction stops after only two hydrogen atoms have been replaced because of the insolubility of the Cr complex. There is a disagreement on how the Cr complex is formed, assuming that the complex has this structure. Both ionic[576] and free-radical[577] processes have been proposed. An entirely different structure for the complex was proposed by Nenitzescu and co-workers.[578] On the basis of ESR studies they proposed that the complex is $PhCH_2OCrCl_2OCrOCl_2OH$, which is isomeric with the other Cr complex. However, this view has been challenged by Wiberg and Eisenthal,[577] who interpret the ESR result as being in accord with $PhCH(O{-}CrCl_2OH)_2$. Still another proposal is that the complex is composed of benzaldehyde coordinated with reduced chromyl chloride.[579]

Another oxidizing agent is a mixture of CrO_3 and Ac_2O, where the reaction stops at the aldehyde stage because the initial product is $ArCH(OAc)_2$ (an acylal), which is resistant to further oxidation. Hydrolysis of the acylal gives the aldehyde. Many oxidizing agents[580] have been used to accomplish the conversion of $ArCH_3$ to ArCHO, including ceric ammonium nitrate,[581] *N*-hydroxyphthalimide/Co,[582] hypervalent iodoso compounds,[583] Bi/*t*-BuOOH,[584] and urea/H_2O_2 with microwave irradiation.[585] Other oxidizing agents include the Jones reagent,[586] DDQ,[587] $KMnO_4$ supported on MnO_2,[588] $KMnO_4/CuSO_4$ neat[589] or with ultrasound,[590] *tert*-butylhydroperoxide and a Ru catalyst,[591] or hydrogen peroxide with a Cu catalyst.[592] The reaction of ethylarenes with *N*-bromosuccinimide and a catalytic amount of AIBN in aqueous solvents, followed by reaction with molecular iodine and aqueous NH_3 gave primary aromatic amides.[593] Oxidation of benzylic positions to the

[574] For a review, see Nenitzescu, C.D. *Bull. Soc. Chim. Fr.* ***1968***, 1349.
[575] Wheeler, O.H. *Can. J. Chem.* ***1960***, *38*, 2137. See also, Makhija, R.C.; Stairs, R.A. *Can. J. Chem.* ***1968***, *46*, 1255.
[576] Stairs, R.A. *Can. J. Chem.* ***1964***, *42*, 550.
[577] Wiberg, K.B.; Eisenthal, R. *Tetrahedron* ***1964***, *20*, 1151. See also, Gragerov, I.P.; Ponomarchuk, M.P. *J. Org. Chem. USSR* ***1969***, *6*, 1125.
[578] Necsoiu, I.; Przemetchi, V.; Ghenciulescu, A.; Rentea, C.N.; Nenitzescu, C.D. *Tetrahedron* ***1966***, *22*, 3037.
[579] Duffin, H.C.; Tucker, R.B. *Chem. Ind. (London)* ***1966***, 1262; *Tetrahedron* ***1968***, *24*, 6999.
[580] See Steckhan, E. *Top. Curr. Chem.* ***1987***, *142*, 1 (pp. 12–17).
[581] See Syper, L. *Tetrahedron Lett.* ***1967***, 4193. See Ganin, E.; Amer, I. *Synth. Commun.* ***1995***, *25*, 3149.
[582] Gaster, E.; Kozuch, S.; Pappo, D. *Angew. Chem. Int. Ed.* ***2017***, *56*, 5912.
[583] Nicolaou, K.C.; Baran, P.S.; Zhong, Y.-L. *J. Am. Chem. Soc.* ***2001***, *123*, 3183.
[584] Bonvin, Y.; Callens, E.; Larrosa, I.; Henderson, D.A.; Oldham, J.; Burton, A.J.; Barrett, A.G.M. *Org. Lett.* ***2005***, *7*, 4549. See Han, X.; Zhou, Z.; Wan, C.; Xiao, Y.; Qin, Z. *Synthesis* ***2013***, *45*, 615.
[585] Paul, S.; Nanda, P.; Gupta, R. *Synlett* ***2004***, 531.
[586] Rangarajan, R.; Eisenbraun, E.J. *J. Org. Chem.* ***1985***, *50*, 2435.
[587] Lee, H.; Harvey, R.G. *J. Org. Chem.* ***1988***, *53*, 4587.
[588] Wei, H.-X.; Jasoni, R.L.; Shao, H.; Hu, J.; Paré, P.W. *Tetrahedron* ***2004***, *60*, 11829.
[589] Shaabani, A.; Lee, D.G. *Tetrahedron Lett.* ***2001***, *42*, 5833.
[590] Mečiarová, M.; Toma, S.; Heribanová, A. *Tetrahedron* ***2000***, *56*, 8561.
[591] Murahashi, S.-I.; Komiya, N.; Oda, Y.; Kuwabara, T.; Naota, T. *J. Org. Chem.* ***2000***, *65*, 9186.
[592] Velusamy, S.; Punniyamurthy, T. *Tetrahedron Lett.* ***2003***, *44*, 8955.
[593] Shimokawa, S.; Kawagoe, Y.; Moriyama, K.; Togo, H. *Org. Lett.* ***2016***, *18*, 784.

corresponding carbonyl has been reported using two heterogeneous catalysts.[594] Oxidation of $ArCH_3$ to carboxylic acids is considered at **19-11**. Typical reagents include manganese salen and PhIO[595] or peroxides.[596] With minimal water, cerium(IV) triflate converts benzylic arenes to benzylic alcohols, although the major product is the ketone when >15% of water is present.[597] Benzylic arenes are converted to the corresponding α-hydroxy compounds by treatment with the enzymes of *Bacillus megaterium*, with modest enantioselectivity.[598] Benzylic and allylic C—H have been oxidized in aqueous media.[599]

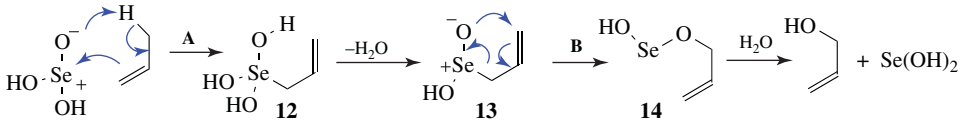
Much research continues in this area. An aerobic photooxidation of methylarenes to benzoic acid derivatives in a continuous-flow microreactor (Sec. 7.D) utilized a reaction with oxygen and 2-*tert*-butylanthraquinone as a photosensitizer.[600] The aerobic benzylic oxidation with air and tetrabutylammonium hydrogensulfate gave α-keto amides.[601] The $Rh/AgSbF_6$ system catalyzed the reaction of the methyl group of 8-methylquinoline with 3-phenyl-1,4,2-dioxazol-5-one to give the corresponding amide.[602] Oxidation of the methyl group of 2-methylquinolines in the presence of phenyliodine diacetate (PIDA), under microwave irradiation, gave 2-quinolinecarboxaldehydes.[603] The benzylic CH_2 units of heteroaryl compounds were oxidized to the corresponding ketone with O_2 mediated by ethyl chloroactate and a Cu catalyst.[604] The (hetero)benzylic sp^3 C—H oxidation to the corresponding ketone used KO*t*-Bu as a promoter and oxygen in the presence of 18-crown-6.[605] (Hetero)aryl acetimidates were oxidized to aryl α-keto esters using molecular oxygen with a Cu catalyst, followed by hydrolysis.[606]

The benzylic oxidation of alkylarenes to aryl ketones used alkali metal bromides and Oxone via thermal oxidation or photooxidation.[607] The reaction of methyl arenes and *N*-chloroamines in the presence of MnO_2 and TBHP gave the corresponding amide.[608] Heating benzylic compounds with CO and an alcohol with a Pd catalyst and di-*tert*-butylperoxide gave the corresponding benzylic ester.[609] Benzylic compounds were oxidized to the corresponding aryl ketone using a zinc catalyst with H_2O_2 in the presence of TFA.[610] The oxidation of ethylbenzene to acetophenone used (diacetoxyiodo)benzene, mcpba, and TBHP.[611] Benzylic bromides reacted with tertiary amine *N*-oxides to give aryl aldehydes.[612] Diarylmethanes were converted to diaryl ketones using O_2, mediated by

[594] Rajabi, F.; Clark, J.H.; Karimi, B.; Macquarrie, D.J. *Org. Biomol. Chem.* ***2005***, *3*, 725.
[595] Hamada, T.; Irie, R.; Mihara, J.; Hamachi, K.; Katsuki, T. *Tetrahedron* ***1998***, *54*, 10017.
[596] Kawasaki, K.; Tsumura, S.; Katsuki, T. *Synlett* ***1995***, 1245.
[597] Laali, K.K.; Herbert, M.; Cushnyr, B.; Bhatt, A.; Terrano, D. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 578.
[598] Adam, W.; Lukacs, Z.; Harmsen, D.; Saha-Möller, C.R.; Schreier, P. *J. Org. Chem.* ***2000***, *65*, 878.
[599] Ang, W.J.; Lam, Y. *Org. Biomol. Chem.* ***2015***, *13*, 1048.
[600] Nagasawa, Y.; Tanba, K.; Tada, N.; Yamaguchi, E.; Itoh, A. *Synlett* ***2015***, *26*, 412.
[601] Shao, J.; Huang, X.; Wang, S.; Liu, B.; Xu, B. *Tetrahedron* ***2012***, *68*, 573.
[602] Wang, H.; Tang, G.; Li, X. *Angew. Chem. Int. Ed.* ***2015***, *54*, 13049.
[603] Jiang, L.; Huang, Y.; Yan, Y.; Xie, Y. *Tetrahedron Lett.* ***2016***, *57*, 4149.
[604] Liu, J.; Zhang, X.; Yi, H.; Liu, C.; Liu, R.; Zhang, H.; Zhuo, K.; Lei, A. *Angew. Chem. Int. Ed.* ***2015***, *54*, 1261.
[605] Wang, H.; Wang, Z.; Huang, H.; Tan, J.; Xu, K. *Org. Lett.* ***2016***, *18*, 5680.
[606] Kumar, Y.; Jaiswal, Y.; Kumar, A. *J. Org. Chem.* ***2016***, *81*, 12247.
[607] Moriyama, K.; Takemura, M.; Togo, H. *Org. Lett.* ***2012***, *14*, 2414; Yin, L.; Wu, J.; Xiao, J.; Cao, S. *Tetrahedron Lett.* ***2012***, *53*, 4418.
[608] Vanjari, R.; Guntreddi, T.; Singh, K.-N. *Org. Lett.* ***2013***, *15*, 4908.
[609] Xie, P.; Xie, Y.; Qian, B.; Zhou, H.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* ***2012***, *134*, 9902.
[610] Wu, X.-F. *Tetrahedron Lett.* ***2012***, *53*, 6123.
[611] Xu, Y.; Yang, Z.; Hu, J.; Yan, J. *Synthesis* ***2013***, *45*, 370.
[612] Tabata, M.; Moriyama, K.; Togo, H. *Eur. J. Org. Chem.* ***2014***, 3402. See Patil, R.D.; Adimurthy, S. *Synth. Commun.* ***2010–2011***, *41*, 2712.

t-BuONa.[613] 2-Methylbenzoic acid derivatives were converted to benzolactones by the Pd-catalyzed, intramolecular insertion of the carboxyl oxygen to the methyl C—H.[614] An Fe-catalyzed oxidation of allyl arenes with DDQ in the presence of water gave alkenyl aldehydes.[615] Diarylmethanes reacted with a catalytic amount of DDQ/*tert*-butyl nitrite with O_2 in acetic acid to give the diaryl ketone.[616] Alkyl aromatics were oxidized to diaryl ketones using nanoamorphous MnO_2 as a catalyst and *t*-BuOOH as the oxidant.[617] Benzylic oxidation to the ketone used a Co catalyst in the presence of Oxone.[618]

Alkenes of the form C=C—CH_2 (an allylic position) have been oxidized to α,β-unsaturated ketones[619] by sodium dichromate in HOAc/Ac_2O, by *t*-BuOOH and Cr compounds,[620] and by *t*-BuOOH and a Pd[621] or Rh[622] catalyst. Thallium(III) nitrate in aqueous acetic acid converts allylic alkenes to the corresponding saturated ketone, even in the presence of a primary alcohol elsewhere in the molecule.[623] The propargylic position of internal alkynes are oxidized to give propargylic ketones with an Fe catalyst,[624] with a dirhodium catalyst in water,[625] or with O_2/*t*-BuOOH in the presence of a Cu catalyst.[626] Treatment of double-bond compounds with selenium dioxide introduces an OH group into the allylic position.[627] This reaction also produces conjugated aldehydes in some cases.[628] Allylic rearrangements are common. There is evidence that the mechanism does not involve free radicals, but includes two pericyclic steps (**A** and **B**).[629] The step marked **A** to give **12** is similar to the ene synthesis (**15-23**). Subsequent reaction with water gives **13**, and a rearrangement gives **14**. The step marked **B** to give **14** is a [2,3]-sigmatropic rearrangement (see **18-35**).



[613] Li, J.-S.; Yang, F.; Yang, Q.; Li, Z.-W.; Chen, G.-Q.; Da, Y.-D.; Huang, P.-M.; Chen, C.; Zhang, Y.; Huang, L.-Z. *Synlett* ***2017***, *28*, 994.
[614] Novák, P.; Correa, A.; Gallardo-Donaire, J.; Martin, R. *Angew. Chem. Int. Ed.* ***2011***, *50*, 12236.
[615] Wang, T.; Xiang, S.-K.; Qin, C.; Ma, J.-A.; Zhang, L.-H.; Jiao, N. *Tetrahedron Lett.* ***2011***, *52*, 3208.
[616] Ma, J.; Hu, Z.; Li, M.; Zhao, W.; Hu, X.; Mo, W.; Hu, B.; Sun, N.; Shen, Z. *Tetrahedron* ***2015***, *71*, 6733.
[617] Burange, A.S.; Kale, S.R.; Jayaram, R.V. *Tetrahedron Lett.* ***2012***, *53*, 2989. See Nammalwar, B.; Fortenberry, C.; Bunce, R.A.; Lageshetty, S.K.; Ausman, K.D. *Tetrahedron Lett.* ***2013***, *54*, 2010.
[618] Yang, Y.; Ma, H. *Tetrahedron Lett.* ***2016***, *57*, 5278.
[619] See Muzart, J. *Bull. Soc. Chim. Fr.* ***1986***, 65. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1207–1210.
[620] Muzart, J. *Tetrahedron Lett.* ***1987***, *28*, 2131; Chidambaram, N.; Chandrasekaran, S. *J. Org. Chem.* ***1987***, *52*, 5048.
[621] Yu, J.-Q.; Corey, E.J. *J. Am. Chem. Soc.* ***2003***, *125*, 3232.
[622] Catino, A.J.; Forslund, R.E.; Doyle, M.P. *J. Am. Chem. Soc.* ***2004***, *126*, 13622.
[623] Ferraz, H.M.C.; Longo Jr., L.S.; Zukerman-Schpector, J. *J. Org. Chem.* ***2002***, *67*, 3518.
[624] Pérollier, C.; Sorokin, A.B. *Chem. Commun.* ***2002***, 1548.
[625] McLaughlin, E.C.; Doyle, M.P. *J. Org. Chem.* ***2008***, *73*, 4317.
[626] Ajjou, A.N.; Ferguson, G. *Tetrahedron Lett.* ***2006***, *47*, 3719.
[627] See Rabjohn, N. *Org. React.* ***1976***, *24*, 261; Jerussi, R.A. *Sel. Org. Transform.* ***1970***, *1*, 301; Trachtenberg, E.N. in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 123–153.
[628] Singh, J.; Sharma, M.; Kad, G.L.; Chhabra, B.R. *J. Chem. Res. (S)* ***1997***, 264.
[629] Arigoni, D.; Vasella, A.; Sharpless, K.B.; Jensen, H.P. *J. Am. Chem. Soc.* ***1973***, *95*, 7917; Woggon, W.; Ruther, F.; Egli, H. *J. Chem. Soc., Chem. Commun.* ***1980***, 706. Also see Stephenson, L.M.; Speth, D.R. *J. Org. Chem.* ***1979***, *44*, 4683.

The reaction can also be accomplished with *tert*-butyl hydroperoxide, if SeO_2 is present in catalytic amounts (the *Sharpless method*).[630] The SeO_2 is the actual reagent; the peroxide reoxidizes the $Se(OH)_2$.[631] This method makes workup easier, but gives significant amounts of side products when the double bond is in a ring.[632]

Alkynes generally give α,α′-dihydroxylation.[633] Allylic hydroxylation[634] with selenium dioxide often gives aldehydes. Allylic benzyloxylation occurs when an alkene is treated with *t*-BuOOCOPh and a Cu/Na zeolite[635] or a Cu catalyst.[636] A chiral Lewis acid has been used for an enantioselective allylic CH oxidation to an allylic acyl derivative.[637] α-Acetoxylation of allylic alkenes can proceed with allylic rearrangement.[638]

Allylic oxidation is an active area of research. Allylic alcohols have been oxidized to enones.[639] Electrolysis was used to oxidize allylic hydrocarbons to the corresponding enone.[640] The Ir-catalyzed reaction of aryl cycloalkenes with 2.2 equivalents of *N*-propylthiosuccinimide and alcohols gave the corresponding allylic ether.[641] The reaction of cyclic alkenes with *tert*-butyl perbenzoate to give allylic esters was catalyzed by self-assembly of a coordination polymer. With a coordinating solvent, such as acetone or acetonitrile, the coordination polymer disassembles, allowing catalysis to take place in homogeneous phase, but after the reaction is complete, the catalyst reassembles upon evaporation of the solvent and addition of hexane, and the catalyst is recovered as an insoluble solid.[642]

The Co-catalyzed oxidative reaction of allylic/benzylic bonds with carboxylic acids gave the ester.[643] The Cu-catalyzed asymmetric allylic oxidation of cyclohexene with *t*-butyl *p*-nitroperbenzoate gave the allylic 4-nitrobenzoate with good enantioselectivity.[644] The Cu-catalyzed allylic oxidation of alkenes with $PhCO_3t$-Bu gave the allylic benzoate with good enantioselectivity.[645] Cyclohexene was oxidized to give the allylic benzoate by reaction with CuCl, DBU, and *tert*-butyl peroxybenzoate.[646]

OS **II**, 441; **III**, 641; **IV**, 31, 713.

[630] Umbreit, M.A.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1977***, *99*, 5526. See also Singh, J.; Sabharwal, A.; Sayal, P.K.; Chhabra, B.R. *Chem. Ind. (London)* ***1989***, 533.

[631] See Sabol, M.R.; Wiglesworth, C.; Watt, D.S. *Synth. Commun.* ***1988***, *18*, 1.

[632] Warpehoski, M.A.; Chabaud, B.; Sharpless, K.B. *J. Org. Chem.* ***1982***, *47*, 2897.

[633] Chabaud, B.; Sharpless, K.B. *J. Org. Chem.* ***1979***, *44*, 4202.

[634] For a review, see Andrus, M.B.; Lashley, J.C. *Tetrahedron* ***2002***, *58*, 845.

[635] Carloni, S.; Frullanti, B.; Maggi, R.; Mazzacani, A.; Bigi, F.; Sartori, G. *Tetrahedron Lett.* ***2000***, *41*, 8947.

[636] LeBras, J.; Muzart, J. *Tetrahedron: Asymmetry* ***2003***, *14*, 1911. See García-Cabeza, A.L.; Moreno-Dorado, F.J.; Ortega, M.J.; Guerra, F.M. *Synthesis* ***2016***, *48*, 2323.

[637] Covell, D.J.; White, M.C. *Angew. Chem. Int. Ed.* ***2008***, *47*, 6448.

[638] Chen, M.S.; White, M.C. *J. Am. Chem. Soc.* ***2004***, *126*, 1346.

[639] Weidmann, V.; Maison, W. *Synthesis* ***2013***, *45*, 2201.

[640] Waldvogel, S.R.; Selt, M. *Angew. Chem. Int. Ed.* ***2016***, *55*, 12578. See Meng, L.; Su, J.; Zha, Z.; Zhang, L.; Zhang, Z.; Wang, Z. *Chem. Eur. J.* ***2013***, *19*, 5542.

[641] Huang, D.; Wang, H.; Guan, H.; Huang, H.; Shi, Y. *Org. Lett.* ***2011***, *13*, 1548.

[642] Aldea, L.; Delso, I.; Hager, M.; Glos, M.; García, J.I.; Mayoral, J.A.; Reiser, O. *Tetrahedron* ***2012***, *68*, 3417.

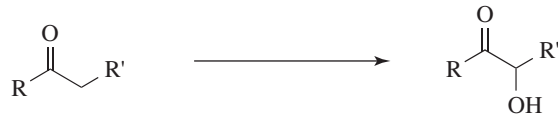
[643] Ren, T.-L.; Xu, B.-H.; Mahmood, S.; Sun, M.-X.; Zhang, S.-J. *Tetrahedron* ***2017***, *73*, 2943.

[644] Zhou, Z.; Andrus, M.B. *Tetrahedron Lett.* ***2012***, *53*, 4528.

[645] Zhang, B.; Zhu, S.-F.; Zhou, Q.-L. *Tetrahedron Lett.* ***2013***, *54*, 2665.

[646] Marín-Barrios, R.; Guerra, F.M.; García-Cabeza, A.L.; Moreno-Dorado, F.J.; Massanet, G.M. *Tetrahedron* ***2012***, *68*, 1105.

19-16 Oxidation of Activated Methylene to OH, O_2CR, or OR

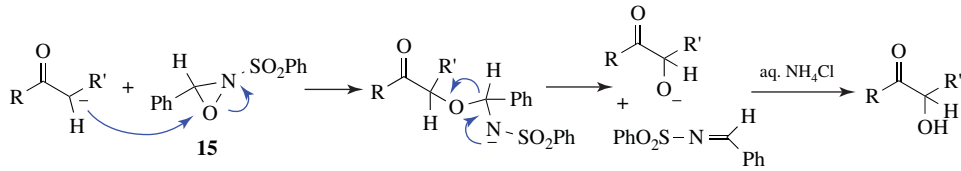


Methyl or methylene groups α to a carbonyl can be oxidized to give α-hydroxy ketones,[647] aldehydes, or carboxylic acid derivatives. Ketones can be α-hydroxylated in good yields, without conversion to the enolates, by treatment with the hypervalent iodine reagents[648] *o*-iodosobenzoic acid.[649] Dioxygen (O_2) and a chiral phase-transfer catalyst gave enantioselective α-hydroxylation of ketones, if the α position was tertiary.[650] Dimethyl dioxirane is quite effective for hydroxylation of 1,3-dicarbonyl compounds,[651] and O_2 with a Mn or Ce catalyst also gives hydroxylation.[652] The hydroxylation of the more substituted position α to a carbonyl group used a dinuclear Pd(II) complex in the presence of bimolecular oxygen.[653] The Pd/C-catalyzed[654] and the Au-catalyzed[655] α-oxygenation of 1,3-dicarbonyl compounds can be accomplished using O_2. An engineered cytochrome P450 BM-3 is effective for the enantioselective α-hydroxylation of esters of benzylic acids.[656] Hypervalent iodine(III) sulfonate has been used for the α-hydroxylation of aryl ketones.[657]

Ketones and carboxylic esters can be α-hydroxylated by treatment of their enolate anions (prepared by adding the ketone or ester to LDA) with *MoO_5/pyridine/HMPA* (called MoOPH) in THF/hexane at −70 °C.[658] The enolate forms of amides and esters[659] and the enamine derivatives of ketones[660] can similarly be converted to their α-hydroxy derivatives by reaction with molecular oxygen. The MoO_5 method can also be applied to certain nitriles.[661]

Ketones are converted to α-hydroxy ketones by reaction of the enolate anion with a 2-sulfonyloxaziridine (e.g., **15**).[662] The mechanism shown is likely.

[647] For strategies for the synthesis of α-hydroxy ketones, see Streuff, J. *Synlett* ***2013***, *24*, 276.
[648] See Moriarty, R.M.; Prakash, O. *Acc. Chem. Res.* ***1986***, *19*, 244. Also see, Reddy, D.R.; Thornton, E.R. *J. Chem. Soc., Chem. Commun.* ***1992***, 172; Beaulieu, S.; Legault, C.Y. *Chem. Eur. J.* ***2015***, *21*, 11206.
[649] Moriarty, R.M.; Hou, K.; Prakash, O.; Arora, S.K. *Org. Synth.* ***VII***, 263.
[650] Masui, M.; Ando, A.; Shioiri, T. *Tetrahedron Lett.* ***1988***, *29*, 2835.
[651] Curci, R.; D'Accolti, L.; Fusco, C. *Acc. Chem. Res.* ***2006***, *39*, 1.
[652] See Christoffers, J.; Werner, T. *Synlett* ***2002***, 119.
[653] Chuang, G.J.; Wang, W.; Lee, E.; Ritter, T. *J. Am. Chem. Soc.* ***2011***, *133*, 1760.
[654] Monguchi, Y.; Takahashi, T.; Iida, Y.; Fujiwara, Y.; Inagaki, Y.; Maegawa, T.; Sajiki, H. *Synlett* ***2008***, 2291.
[655] Miyamura, H.; Kobayashi, S. *Chem. Lett.* ***2012***, *41*, 976.
[656] Landwehr, M.; Hochrein, L.; Otey, C.R.; Kasrayan, A.; Bäckvall, J.-E.; Arnold, F.H. *J. Am. Chem. Soc.* ***2006***, *128*, 6058. See Agudo, R.; Roiban, G.-D.; Lonsdale, R.; Ilie, A.; Reetz, M.T. *J. Org. Chem.* ***2015***, *80*, 950.
[657] Huang, H.-Y.; Hou, R.-S.; Wang, H.-M.; Chen, L.-C. *Org. Prep. Proceed. Int.* ***2006***, *38*, 473.
[658] Vedejs, E.; Larsen, S. *Org. Synth.* ***VII***, 277; Gamboni, R.; Tamm, C. *Tetrahedron Lett.* ***1986***, *27*, 3999. See also, Hara, O.; Takizawa, J.-i.; Yamatake, T.; Makino, K.; Hamada, Y. *Tetrahedron Lett.* ***1999***, *40*, 7787.
[659] Wasserman, H.H.; Lipshutz, B.H. *Tetrahedron Lett.* ***1975***, 1731. For another method, see Pohmakotr, M.; Winotai, C. *Synth. Commun.* ***1988***, *18*, 2141.
[660] Cuvigny, T.; Valette, G.; Larcheveque, M.; Normant, H. *J. Organomet. Chem.* ***1978***, *155*, 147.
[661] Rubottom, G.M.; Gruber, J.M.; Juve Jr., H.D.; Charleson, D.A. *Org. Synth.* ***VII***, 282. See also, Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* ***1989***, *30*, 3323.
[662] Davis, F.A.; Vishwakarma, L.C.; Billmers, J.M.; Finn, J. *J. Org. Chem.* ***1984***, *49*, 3241.



The method is also successful for carboxylic esters[663] and *N*,*N*-disubstituted amides,[664] and can be made enantioselective by the use of a chiral oxaziridine.[665] Dimethyldioxirane also oxidizes the enolate anions of ketones to α-hydroxy ketones.[666] Titanium enolates are oxidized with *tert*-butyl hydroperoxide[667] or with dimethyl dioxirane[668] and hydrolyzed with aqueous ammonium fluoride to give the α-hydroxy ketone. α-Lithio sulfones have been hydroxylated with Me_3SiOOt-Bu.[669]

Ketones have been α-hydroxylated by conversion to the silyl enol ether, followed by treatment with *m*-chloroperoxybenzoic acid,[156] or with certain other oxidizing agents.[670] α-Hydroxy ketones can be prepared from silyl enol ethers with a catalytic amount of $MeReO_3$ and H_2O_2.[671] When the silyl enol ethers are treated with iodosobenzene in the presence of trimethylsilyl trifluoromethyl sulfonate, the product is the α-keto triflate.[672] Silyl ketene ethers are converted to α-hydroxy esters with H_2O_2 and $MeReO_3$.[673] The α′ position of α,β-unsaturated ketones can be selectively oxidized.[674]

α-Acetoxylation of ketones with concurrent α-arylation occurs when ketones react with $Mn(OAc)_3$ in benzene.[675] Iodobenzene with 30% aqueous hydrogen peroxide and acetic anhydride generates α-acetoxy ketones.[676] Thallium(III) triflate converts acetophenone to α-formyloxy acetophenone.[677] The reaction of PhI(OH)OTs and ketones gave α-tosyloxy (OTs) ketones.[678] *N*-Methyl-*O*-tosylhydroxylamine is another reagent that effects direct α-oxytosylation of ketones and aldehydes.[679] α-Acetoxylation of ketones results from *in situ* generation of hypervalent iodine species in the presence of acetic acid.[680]

Tetrahydrofuran was converted to the hemiacetal 2-hydroxytetrahydrofuran (which was relatively stable under the conditions used) by electrolysis in water.[681] α-Hydroxy ethers are generated by reaction of SO_2/O_2 and a V catalyst with ethers.[682]

[663] For formation of α-benzyloxy lactones, see Brodsky, B.H.; DuBois, J. *Org. Lett.* ***2004***, *6*, 2619.
[664] Davis, F.A.; Vishwakarma, L.C. *Tetrahedron Lett.* ***1985***, *26*, 3539.
[665] See Davis, F.A.; Sheppard, A.C.; Chen, B.; Haque, M.S. *J. Am. Chem. Soc.* ***1990***, *112*, 6679.
[666] Guertin, K.R.; Chan, T.H. *Tetrahedron Lett.* ***1991***, *32*, 715.
[667] Schulz, M.; Kluge, R.; Schüßler, M.; Hoffmann, F. *Tetrahedron* ***1995***, *51*, 3175.
[668] Adam, W.; Müller, M.; Prechtl, F. *J. Org. Chem.* ***1994***, *59*, 2358.
[669] Chemla, F.; Julia, M.; Uguen, D. *Bull. Soc. Chim. Fr.* ***1993***, *130*, 547; ***1994***, *131*, 639.
[670] See Takai, T.; Yamada, T.; Rhode, O.; Mukaiyama, T. *Chem. Lett.* ***1991***, 281.
[671] Stankovic, S.; Espenson, J.H. *J. Org. Chem.* ***1998***, *63*, 4129.
[672] Moriarty, R.M.; Epa, W.R.; Penmasta, R.; Awasthi, A.K. *Tetrahedron Lett.* ***1989***, *30*, 667.
[673] Stankovic, S.; Espenson, J.H. *J. Org. Chem.* ***2000***, *65*, 5528.
[674] Demir, A.S.; Jeganathan, A. *Synthesis* ***1992***, 235.
[675] Tanyeli, C.; Özdemïrhan, D.; Sezen, B. *Tetrahedron* ***2002***, *58*, 9983.
[676] Sheng, J.; Li, X.; Tang, M.; Gao, B.; Huang, G. *Synthesis* ***2007***, 1165.
[677] Lee, J.C.; Jin, Y.S.; Choi, J.-H. *Chem. Commun.* ***2001***, 956.
[678] See Akiike, J.; Yamamoto, Y.; Togo, H. *Synlett* ***2007***, 2168.
[679] John, O.R.S.; Killeen, N.M.; Knowles, D.A.; Yau, S.C.; Bagley, M.C.; Tomkinson, N.C.O. *Org. Lett.* ***2007***, *9*, 4009.
[680] Ochiai, M.; Takeuchi, Y.; Katayama, T.; Sueda, T.; Miyamoto, K. *J. Am. Chem. Soc.* ***2005***, *127*, 12244.
[681] Wermeckes, B.; Beck, F.; Schulz, H. *Tetrahedron* ***1987***, *43*, 577.
[682] Miyafuji, A.; Katsuki, T. *Synlett* ***1997***, 836.

This type of oxidation is an active area of research. The 2-hydroxylation of 1,3-diketones was reported by heating with atmospheric oxygen in the presence of CsF, CaF_2, KF, or TBAF and NaOH.[683] The iodine-catalyzed α-hydroxylation using air has also been reported.[684] A transition metal-free Cs_2CO_3-catalyzed α-hydroxylation of carbonyl compounds with O_2, and triethylphosphine as an additive, gave tertiary α-hydroxycarbonyl compounds.[685] The reaction of ketones and DMSO was catalyzed by I_2 or NBS to give the α-hydroxy carbonyl, where DMSO is the oxidant, oxygen source, and solvent.[686]

The α-hydroxylation of β-oxo esters and β-oxo amides used *m*-chloroperbenzoic acid as the oxidant and the hydroxylated products were converted into vicinal tricarbonyl compounds by reaction with cupric acetate.[687] *Cinchona* alkaloid-derived organocatalysts were used for the enantioselective α-hydroxylation of β-oxo esters with hydroperoxides to give α-hydroxy-β-oxo esters.[688] A mixture of $Pr(OiPr)_3$ and a fluoro-substituted amide-based ligand was used to catalyze the asymmetric hydroxylation of α-alkoxycarbonyl primary amides using oxaziridine as the oxidizing reagent to give the α-hydroxy compound.[689] The base-free α-hydroxylation of β-keto esters and amides used air as the oxygen source and catalytic amounts of SmI_3 and I_2 to give α-hydroxylated 1,3-dicarbonyl products.[690] In a related reaction, the reaction of phenylglyoxyic acids with amides or cyclic ethers, TBHP and TBAI gave decarboxylative acyloxylation and formation of *N*-acyloxymethylamides and α-acyloxy ethers.[691] Note that homoallylic-type oxidation occurs when an α,α-dimethyl oxime ether is treated with $PhI(OAc)_2$ and a Pd catalyst in acetic acid/acetic anhydride, converting one of the methyl groups to an acetoxymethyl.[692] The α-hydroxylation of ketones was catalyzed by $CuBr_2$ or HBr in DMSO to give secondary/tertiary α-hydroxy carbonyl compounds.[693]

The terminal-selective, Pt-catalyzed oxidation of methyl units of a long-chain aliphatic amine proceeds without using $CuCl_2$.[694] A primary amine catalyst for the asymmetric α-hydroxylation by reaction with an oxaziridine and α-fluorination has been developed for the reaction of *N*-fluorobenzenesulfonimide with α-branched aldehydes.[695] Heating a series of phthaloyl-protected primary amines and amino acid derivatives that have a CH_3CH_2- unit oxidized this unit to a methyl ketone moiety by reaction with $Na_2S_2O_8$ in aqueous methanol.[696] A distal $-CH_2-$ unit of the ammonium salt of aliphatic amines was selectively oxidized to an alcohol (—CHOH—) by reaction with $K_2S_2O_8$ in water.[697] The Cu-catalyzed reaction of *N*-alkyl-3-aryl-3-(4-pentenyl)oxaziridine derivatives gave the

[683] Li, Z.; Li, T.; Li, J.; He, L.; Jia, X.; Yang, J. *Synlett* ***2015***, *26*, 2863.
[684] Miao, C.-B.; Wang, Y.-H.; Xing, M.-L.; Lu, X.-L.; Sun, X.-Q.; Yang, H.-T. *J. Org. Chem.* ***2013***, *78*, 11584.
[685] Liang, Y.-F.; Jiao, N. *Angew. Chem. Int. Ed.* ***2014***, *53*, 548. Also see Chaudhari, M.B.; Sutar, Y.; Malpathak, S.; Hazra, A.; Gnanaprakasam, B. *Org. Lett.* ***2017***, *19*, 3628.
[686] Liang, Y.-F.; Wu, K.; Song, S.; Li, X.; Huang, X.; Jiao, N. *Org. Lett.* ***2015***, *17*, 876.
[687] Asahara, H.; Nishiwaki, N. *J. Org. Chem.* ***2014***, *79*, 11735.
[688] Yao, H.; Lian, M.; Li, Z.; Wang, Y.; Meng, Q. *J. Org. Chem.* ***2012***, *77*, 760.
[689] Takechi, S.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* ***2011***, *52*, 2140.
[690] Yu, S.-M.; Cui, K.; Lv, F.; Yang, Z.-Y.; Yao, Z.-J. *Tetrahedron Lett.* ***2016***, *57*, 2818.
[691] Zhang, S.; Guo, L.-N.; Wang, H.; Duan, X.-H. *Org. Biomol. Chem.* ***2013***, *11*, 4308.
[692] Desai, L.; Hull, K.L.; Sanford, M.S. *J. Am. Chem. Soc.* ***2004***, *126*, 9542.
[693] Li, H.-L.; An, X.-L.; Ge, L.-S.; Luo, X.; Deng, W.-P. *Tetrahedron* ***2015***, *71*, 3247.
[694] Lee, M.; Sanford, M.S. *J. Am. Chem. Soc.* ***2015***, *137*, 12796.
[695] Witten, M.R.; Jacobsen, E.N. *Org. Lett.* ***2015***, *17*, 2772.
[696] Li, X.; Che, X.; Chen, G.-H.; Zhang, J.; Yan, J.L.; Zhang, Y.-F.; Zhang, L.-S.; Hsu, C.-P.; Gao, Y.-Q.; Shi, Z.-J, *Org. Lett.* ***2016***, *18*, 1234.
[697] Lee, M.; Sanford, M.S. *Org. Lett.* ***2017***, *19*, 572.

rearrangement product, 1-aryl-4-hydroxyhex-1-one-5-ene derivatives.[698] 1-Iodopropane was oxidized to iodosylpropane, which decomposed to form hypoiodous acid as a catalyst; reaction with mcpba and tosic acid gave α-tosyloxy ketones.[699] In a Pd-catalyzed annulation of an oxime-masked alcohols with internal alcohol nucleophiles, annulation occurred at the β position to give aliphatic cyclic ethers.[700]

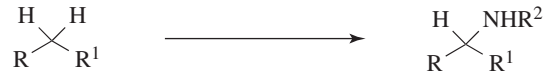
N-Acyl amines are converted to α-hydroxy derivatives with PhIO and a Mn salen catalyst.[701] Cyclic amines react with *Pseudomonas oleovorans* GPol to give hydroxy amines; *N*-benzylpyrrolidine is converted to 3-hydroxy *N*-benzylpyrrolidine.[702] *Sphingomonas* sp. HXN-200 gives similar results,[703] and lactams are converted to the corresponding 3-hydroxy lactam with *sphingomonas* sp. HXN-200.[704] *N*-Benzyl piperidine is converted to the 4-hydroxy derivative under the same conditions.[705] *N*-Benzylphthalimide reacts with NBS, NaOAc, and acetic acid to give *N*-(α-acetoxybenzyl)phthalimide.[706]

In some cases, similar reactions are possible, producing sulfur-containing compounds. Longifolene, as well as other hydrocarbons, reacted with a *N*-xanthylamide derivative in the presence of a blue LED to give the xanthate derivative.[707] Cyclic alkanes are converted to the corresponding alkylsulfonic acid with SO_2/O_2 and a V catalyst.[708] A Pd-catalyzed intermolecular reaction of the methyl group 8-methylquionoline with *N*-fluorobis(phenylsulfonyl)imide gave the corresponding (bis)sulfonimide.[709]

The Cu-catalyzed hydroxylation of phosphonate compounds by reaction with *N*-hydroxyphthalimide, O_2, and PPh_3, gave quaternary α-hydroxy phosphonates.[710] Quaternary α-hydroxy phosphonates were prepared by the [bmIm]OH-catalyzed α-hydroxylation of phosphonates using O_2.[711]

OSCV 7, 277; *OSCV 7*, 263; *OSCV 6*, 43

19-17 Oxidation of Methylene to Heteroatom Functional Groups Other Than O, S, or Carbonyl

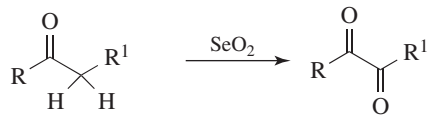


α-Amination or α-amidation of a CH unit is possible in some cases. Cyclic alkanes are converted to the *N*-alkyl *N*-tosylamine with PhI=NTs and a Cu complex.[712] Benzylic CH,

[698] Motiwala, H.F.; Gülgeze, B.; Aubé, J. *J. Org. Chem.* ***2012***, *77*, 7005.
[699] See Zhang, B.; Han, L.; Hu, J.; Yan, J. *Tetrahedron Lett.* ***2014***, *55*, 5851. See Tanaka, A.; Moriyama, K.; Togo, H. *Synlett* ***2011***, *22*, 1853; Brenet, S.; Minozzi, C.; Clarens, B.; Amiri, L.; Berthiol, F. *Synthesis* ***2015***, *47*, 3859; Yu, J.; Cui, J.; Hou, X.-S.; Liu, S.-S.; Gao, W.-C.; Jiang, S.; Tian, J.; Zhang, C. *Tetrahedron: Asymmetry* ***2011***, *22*, 2039; Guilbault, A.-A.; Basdevant, B.; Wanie, V.; Legault, C.Y. *J. Org. Chem.* ***2012***, *77*, 11283.
[700] Thompson, S.J.; Thach, D.Q.; Dong, G. *J. Am. Chem. Soc.* ***2015***, *137*, 11586.
[701] Punniyamurthy, T.; Katsuki, T. *Tetrahedron* ***1999***, *55*, 9439.
[702] Li, Z.; Feiten, H.-J.; van Beilen, J.B.; Duetz, W.; Witholt, B. *Tetrahedron: Asymmetry* ***1999***, *10*, 1323.
[703] Li, Z.; Feiten, H.-J.; Chang, D.; Duetz, W.A.; Beilen, J.B.; Witholt, B. *J. Org. Chem.* ***2001***, *66*, 8424.
[704] Chang, D.; Witholt, B.; Li, Z. *Org. Lett.* ***2000***, *2*, 3949.
[705] Chang, D.; Feiten, H.-J.; Engesser, K.-H.; van Beilen, J.; Witholt, B.; Li, Z. *Org. Lett.* ***2002***, *4*, 1859.
[706] Cho, S.-D.; Kim, H.-J.; Ahn, C.; Falck, J.R.; Shin, D.-S. *Tetrahedron Lett.* ***1999***, *40*, 8215.
[707] Czaplyski, W.L.; Na, C.G.; Alexanian, E.J. *J. Am. Chem. Soc.* ***2016***, *138*, 13854.
[708] Ishii, Y.; Matsunaka, K.; Sakaguchi, S. *J. Am. Chem. Soc.* ***2000***, *122*, 7390.
[709] Iglesias, Á.; Álvarez, R.; de Lera, Á.R.; Muñiz, K. *Angew. Chem. Int. Ed.* ***2012***, *51*, 2225.
[710] Gu, L.; Jin, C.; Zhang, H. *New J. Chem.* ***2015***, 1579.
[711] Li, X.; Jin, C.; Gu, L. *J. Org. Chem.* ***2015***, *80*, 2443.
[712] Díaz-Requejo, M.M.; Belderraín, T.R.; Nicasio, M.C.; Trofimenko, S.; Pérez, P.J. *J. Am. Chem. Soc.* ***2003***, *125*, 12078.

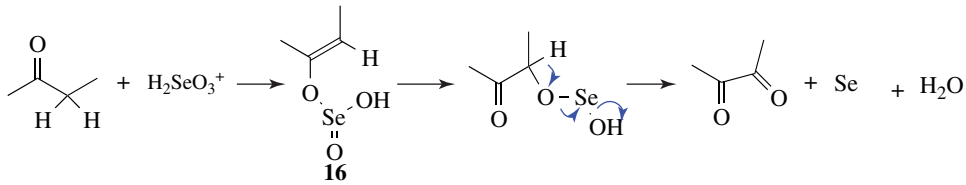
as in ethylbenzene, is oxidized with $PhI(OAc)_2$ in the presence of $TsNH_2$ and a fluorinated manganese porphyrin to give the corresponding *N*-tosylamine, PhCHMe(NHTs).[713] Alkenes with an allylic CH react with PhI=NTs and a Ru catalysts to give an allylic *N*-tosylamine.[714] When an α-keto ester reacts with DEAD (diethyl azodicarboxylate) and a chiral Cu complex, an α-carbamate is formed, $RCH(NHCO_2Et)C(=O)CO_2Et$, with modest enantioselectivity.[715] The oxidation of amides to imides has been reviewed.[716]

19-18 Oxidation of Methylene to Carbonyl



Methyl or methylene groups α to a carbonyl can be oxidized with selenium dioxide to give, respectively, α-keto aldehydes (see **19-15**) and α-diketones.[717] The reaction can also be carried out α to an aromatic ring or to a double bond, although in the latter case, hydroxylation (see **19-14**) is the more common result. Selenium dioxide, SeO_2 is often used, but the reaction has also been carried out with other oxidizing agents,[718] including hypervalent iodine compounds.[719]

Two mechanisms have been suggested for the reaction with SeO_2. One of these involves a selenate ester of the enol, **16**.[720]



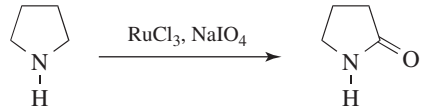
In the other proposed mechanism,[721] the principal intermediate is α,β-ketoseleninic acid O=C–CH–SeO_2H, and a selenate ester is not involved.

Sodium nitrite/HCl oxidizes cyclic ketones to the diketone.[722] Substrates most easily oxidized contain two aryl groups on CH_2, and these substrates can be oxidized with many oxidizing agents (see **19-11**). Methyl ketones are oxidized to the α-keto ester in a two-step procedure using a fluorous selenic acid with an iodoxy benzene, followed by treatment with sodium metabisulfite ($Na_2S_2O_5$).[723] The distal oxidation of a methylene unit in alkyl

[713] Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* ***2000***, *2*, 2233.
[714] Au, S.-M.; Huang, J.-S.; Che, C.-M.; Yu, W.-Y. *J. Org. Chem.* ***2000***, *65*, 7858.
[715] Juhl, K.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2002***, *124*, 2420.
[716] Sperry, J. *Synthesis* ***2011***, *43*, 3569.
[717] See Krief, A.; Hevesi, L. *Organoselenium Chemistry I*, Springer, NY, ***1988***, pp. 115–180; Krongauz, E.S. *Russ. Chem. Rev.* ***1977***, *46*, 59; Rabjohn, N. *Org. React.* ***1976***, *24*, 261; Trachtenberg, E.N. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Marcel Dekker, NY, pp. 119–187.
[718] See Wasserman, H.H.; Ives, J.L. *J. Org. Chem.* ***1985***, *50*, 3573.
[719] Lee, J.C.; Park, H.-J.; Park, J.Y. *Tetrahedron Lett.* ***2002***, *43*, 5661.
[720] Corey, E.J.; Schaefer, J.P. *J. Am. Chem. Soc.* ***1960***, *82*, 918.
[721] Sharpless, K.B.; Gordon, K.M. *J. Am. Chem. Soc.* ***1976***, *98*, 300.
[722] Rüedi, G.; Oberli, M.A.; Nagel, M.; Weymuth, C.; Hansen, H.-J. *Synlett* ***2004***, 2315.
[723] Crich, D.; Zou, Y. *J. Org. Chem.* ***2005***, *70*, 3309.

esters and amides to a keto unit used bis(*tert*-butylperoxy)iodobenzene as a peroxy radical source.[724] The conversion of cyclic amines to lactams with a Ru catalyst used NaOH and water.[725] The C—H to C—O conversion through oxidative cyclization of carboxylic acids using a Cu catalyst and potassium persulfate gave the lactone.[726] Amides were oxidized to imides using a Cu-catalyzed reaction with Selectfluor.[727] Amines were oxidized to the amide by reaction with $PhCO_3t$-Bu ad 2-pyridinecarboxyic acid with an Fe catalyst.[728] Benzylamines ere oxidized to benzamides by reaction with MnO_2.[729]

Cyclic amines are oxidized to lactams using a mixture of $RuCl_3$ and $NaIO_4$.[730]



Lactams are also formed using $KMnO_4$ with benzyltriethylammonium chloride.[731] Tertiary amines are converted to amides[732] and cyclic tertiary amines can be converted to lactams by oxidation with Hg(II)/EDTA complex in basic solution.[733] Lactams, which need not be *N*-substituted, can be converted to cyclic imides by oxidation with a hydroperoxide or peroxyacid and an Mn(II) or Mn(III) salt.[734] Lactams are oxidized to cyclic imides with oxygen and $Co(OAc)_2$ in the presence *N*-hydroxysuccinimide.[735] Primary amines were oxidized to primary amides using a MnO_2 catalyst under solvent-free conditions.[736] 1,2,3,4-Tetrahydroquinoline was converted to the corresponding lactam by reaction with 2 equivalents of NaOH and a Au/(poly)-*N*-vinyl-2-pyrrlidinone catalyst in aqueous ethanol.[737] The Cu-catalyzed conversion of *N*,*N*-dimethylanilines by reaction with O_2 and an anhydride gave the corresponding tertiary amide.[738]

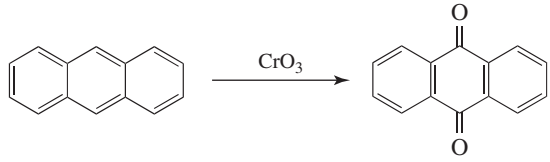
Ethers in which at least one group is primary alkyl can be oxidized to the corresponding carboxylic esters in high yields with ruthenium tetroxide.[739] Molecular oxygen with a binuclear copper(II) complex[740] or $PdCl_2/CuCl_2/CO$[741] also converts ethers to esters. Cyclic ethers are oxidized to lactones.[742] Cyclic ethers are oxidized to lactones with

[724] Zhao, Y.; Yim, W.-L.; Tan, C.K.; Yeung, Y.-Y. *Org. Lett.* ***2011***, *13*, 4308.
[725] Khusnutdinova, J.R.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* ***2014***, *136*, 2998.
[726] Sathyamoorthi, S.; Du Bois, J. *Org. Lett.* ***2016***, *18*, 6308.
[727] Jin, Z.; Xu, B.; Hammond, G.B. *Tetrahedron Lett.* ***2011***, *52*, 1956.
[728] Legacy, C.J.; Emmert, M.H. *Synlett* ***2016***, *27*, 1893.
[729] Poeschl, A.; Mountford, D.M. *Org. Biomol. Chem.* ***2014***, *12*, 7150.
[730] Sharma, N.K.; Ganesh, K.N. *Tetrahedron Lett.* ***2004***, *45*, 1403. See Gellrich, U.; Khusnutdinova, J.R.; Leitus, G.M.; Milstein, D. *J. Am. Chem. Soc.* ***2015***, *137*, 4851.
[731] Markgraf, J.H.; Stickney, C.A. *J. Heterocycl. Chem.* ***2000***, *37*, 109.
[732] Markgraf, J.H.; Sangani, P.K.; Finkelstein, M. *Synth. Commun.* ***1995***, *27*, 1285.
[733] Wenkert, E.; Angell, E.C. *Synth. Commun.* ***1988***, *18*, 1331.
[734] Doumaux Jr., A.R.; Trecker, D.J. *J. Org. Chem.* ***1970***, *35*, 2121.
[735] Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G.F. *J. Org. Chem.* ***2002***, *67*, 2671.
[736] Yamaguchi, K.; Wang, Y.; Mizuno, N. *Chem. Lett.* ***2012***, *41*, 633.
[737] Preedasuriyachai, P.; Chavasiri, W.; Sakurai, H. *Synlett* ***2011***, *22*, 1121.
[738] Cheng, H.-C.; Hou, W.-J.; Li, Z.-W.; Li, M.-Y.; Guan, B.-T. *Chem. Commun.* ***2015***, *51*, 17596.
[739] Bakke, J.M.; Frøhaug, Az. *Acta Chem. Scand. B* ***1995***, *49*, 615; Lee, D.G.; van den Engh, M. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 222–225; Carlsen, P.H.J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. *J. Org. Chem.* ***1981***, *46*, 3936.
[740] Minakata, S.; Imai, E.; Ohshima, Y.; Inaki, K.; Ryu, I.; Komatsu, M.; Ohshiro, Y. *Chem. Lett.* ***1996***, 19.
[741] Miyamoto, M.; Minami, Y.; Ukaji, Y.; Kinoshita, H.; Inomata, K. *Chem. Lett.* ***1994***, 1149.
[742] See Ferraz, H.M.C.; Longo Jr., L.S. *Org. Lett.* ***2003***, *5*, 1337.

CrO_3/Me_3SiONO_2.[743] Lactones are also formed from cyclic ethers with $NaBrO_3/KHSO_4$ in water.[744] The reaction has also been accomplished with CrO_3 in sulfuric acid,[745] and with benzyltriethylammonium permanganate.[746] Selenium-doped TiO_2 has been used as a photocatalyst for the oxidation of tetrahydrofuran to γ-butyrolactone.[747] Secondary methyl ethers were converted to ketones by reaction with calcium hypochlorite and acetic acid in aqueous acetonitrile.[748]

OS **I**, 266; **II**, 509; **III**, 1, 420, 438; **IV**, 189, 229, 579; **VI**, 48; **IX**, 396. Also see, OS **IV**, 23.

19-19 Oxidation of Aromatic Hydrocarbons to Quinones



Condensed aromatic systems (including naphthalenes) can be directly oxidized to quinones by various oxidizing agents.[749] Yields are generally not high, although good yields have been reported with ceric ammonium sulfate.[750] Benzene cannot be oxidized this way by strong oxidizing agents, but can be electrolytically oxidized to benzoquinone.[751] Naphthalene derivatives, however, are oxidized to naphthoquinones with H_5IO_6 and CrO_3.[752] 1,4-Dimethoxy aromatic compounds are oxidized to para-quinones with an excess of CoF_3 in water/dioxane.[753]

OS **IV**, 698, 757. Also see, OS **II**, 554.

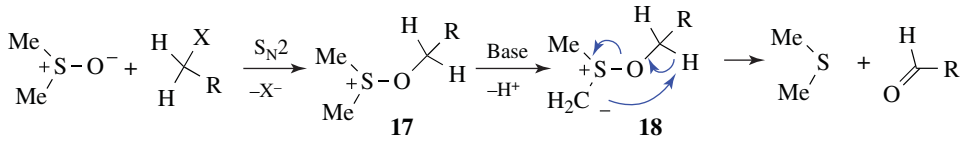
19-20 Oxidation of Primary Halides and Esters of Primary Alcohols to Aldehydes[754]

$$RCH_2Cl \xrightarrow{DMSO} RCHO$$

[743] Shahi, S.P.; Gupta, A.; Pitre, S.V.; Reddy, M.V.R.; Kumareswaran, R.; Vankar, Y.D. *J. Org. Chem.* ***1999***, *64*, 4509.
[744] Metsger, L.; Bittner, S. *Tetrahedron* ***2000***, *56*, 1905.
[745] Harrison, I.T.; Harrison, S. *Chem. Commun.* ***1966***, 752.
[746] Schmidt, H.; Schäfer, H.J. *Angew. Chem. Int. Ed.* ***1979***, *18*, 69.
[747] Padmalatha, P.; Khatri, P.K.; Jain, S.L. *Synlett* ***2013***, *24*, 1405.
[748] Gilissen, P.J.; Blanco-Ania, D.; Rutjes, F.P.J.T. *J. Org. Chem.* ***2017***, *82*, 6671.
[749] Naruta, Y.; Maruyama, K. in Patai, S.; Rappoport, Z. *The Chemistry of the Quinoid Compounds*, Vol. 2, pt. 1, Wiley, NY, ***1988***, pp. 242–247; Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 94–96; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 1, Academic Press, NY, ***1985***, pp. 182–185, 358–360; Thomson, R.H. in Patai, S. *The Chemistry of the Quinoid Compounds*, Vol. 1, pt. 1, Wiley, NY, ***1974***, pp. 132–134.
[750] See Balanikas, G.; Hussain, N.; Amin, S.; Hecht, S.S. *J. Org. Chem.* ***1988***, *53*, 1007.
[751] See Ito, S.; Katayama, R.; Kunai, A.; Sasaki, K. *Tetrahedron Lett.* ***1989***, *30*, 205.
[752] Yamazaki, S. *Tetrahedron Lett.* ***2001***, *42*, 3355.
[753] Tomatsu, A.; Takemura, S.; Hashimoto, K.; Nakata, M. *Synlett* ***1999***, 1474.
[754] For reviews, see Tidwell, T.T. *Org. React.* ***1990***, *39*, 297; *Synthesis* ***1990***, 857; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, pp. 171–181, 402–406; Epstein, W.W.; Sweat, F.W. *Chem. Rev.* ***1967***, *67*, 247. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1222–1225.

Primary alkyl halides (chlorides, bromides, and iodides) can be oxidized to aldehydes easily and in good yields with dimethyl sulfoxide,[755] in what has been called the *Kornblum reaction*. In Kornblum's original work, the reaction of α-halo ketones with DMSO at elevated temperatures gave good yields of the corresponding glyoxal (an α-keto aldehyde).[756] If the glyoxal could be removed from the reaction medium by distillation as it was formed, the reaction was very efficient. In many cases it was difficult to isolate high boiling glyoxals from DMSO. Primary and secondary[757] alkyl iodides or tosylates[758] can be converted to aldehydes or ketones, although they are much less reactive than α-halo ketones. Primary chlorides reacted with DMSO, NaBr, and ZnO give the corresponding aldehyde when heated to 140 °C.[759] Benzylic halides are oxidized to aryl aldehydes with MnO_2[760] or with $NaIO_4$/LiBr.[761] Hydrogen peroxide in ethanol oxidizes organic halides to carbonyl compounds.[762] Pyridine *N*-oxide in the presence of silver oxide oxidizes benzylic and allylic halides.[763]

The mechanism of these DMSO oxidations is probably that shown, with **17** and **18** as intermediates[764] although in some cases the base abstracts a proton directly from the carbon being oxidized, in which case the ylid **18** is not an intermediate.



Alkoxysulfonium salts (**17**) have been isolated.[765] This mechanism predicts that secondary compounds should be oxidizable to ketones, and this is the case. In a related procedure for the oxidation of alcohols, the intermediate **17**[766] is formed without the use of DMSO by treating the substrate with a complex generated from chlorine or NCS and dimethyl sulfide.[767] Also see the *Swern oxidation* in **19-3**.

Another way to oxidize primary alkyl halides to aldehydes is by the use of hexamethylenetetramine followed by water. However, this reaction, called the *Sommelet reaction*,[768] is limited to benzylic halides. The reaction is seldom useful when the R in RCH_2Cl

[755] Nace, H.R.; Monagle, J.J. *J. Org. Chem.* ***1959***, *24*, 1792; Kornblum, N.; Jones, W.J.; Anderson, G.J. *J. Am. Chem. Soc.* ***1959***, *81*, 4113. See Su, Y.; Zhang, L.; Jiao, N. *Org. Lett.* ***2011***, *13*, 2168. Also see Villemin, D.; Hammadi, M. *Synth. Commun.* ***1995***, *25*, 3141.

[756] Kornblum, N.; Powers, J.W.; Anderson, G.J.; Jones, W.J.; Larson, H.O.; Levand, O.; Weaver, W.M. *J. Am. Chem. Soc.* ***1957***, *79*, 6562. Mg-Al hydrotalcites have been used as heterogeneous basic catalysts: see Kshirsagar, S.W.; Patil, N.R.; Samant, S.D. *Tetrahedron Lett.* ***2008***, *49*, 1160.

[757] Baizer, M.M. *J. Org. Chem.,* ***1960***, *25*, 670.

[758] Kornblum, N.; Jones, W.J.; Anderson, G.J. *J. Am. Chem. Soc.* ***1959***, *81*, 4113.

[759] Guo, Z.; Sawyer, R.; Prakash, I. *Synth. Commun.* ***2001***, *31*, 667; Guo, Z.; Sawyer, R.; Prakash, I. *Synth. Commun.* ***2001***, *31*, 3395.

[760] Goswami, S.; Jana, S.; Dey, S.; Adak, A.K. *Chem. Lett.* ***2005***, *34*, 194.

[761] Ali Shaikh, T.M.; Emmanuvel, L.; Sudalai, A. *Synth. Commun.* ***2007***, *37*, 2641.

[762] Tang, J.; Zhu, J.; Shen, Z.; Zhang, Y. *Tetrahedron Lett.* ***2007***, *48*, 1919.

[763] Chen, D.X.; Ho, C.M.; Wu, Q.Y.R.; Wu, P.R.; Wong, F.M.; Wu, W. *Tetrahedron Lett.* ***2008***, *49*, 4147.

[764] See Johnson, C.R.; Phillips, W.G. *J. Org. Chem.* ***1967***, *32*, 1926; Torssell, K. *Acta Chem. Scand.* ***1967***, *21*, 1.

[765] Khuddus, M.A.; Swern, D. *J. Am. Chem. Soc.* ***1973***, *95*, 8393.

[766] For an alternative, see Moffatt, J.G. *J. Org. Chem.* ***1971***, *36*, 1909 and references cited therein.

[767] See Katayama, S.; Fukuda, K.; Watanabe, T.; Yamauchi, M. *Synthesis* ***1988***, 178.

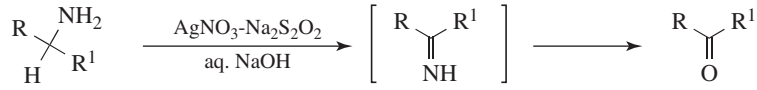
[768] See Angyal, S.J. *Org. React.* ***1954***, *8*, 197.

is alkyl. The first part of the reaction is conversion to the amine, $ArCH_2NH_2$, which can be isolated. Reaction of the amine with excess hexamethylenetetramine gives the aldehyde. It is this last step that is the actual Sommelet reaction, although the entire process can be conducted without isolation of intermediates. Once the amine is formed, it is converted to an imine ($ArCH_2N{=}CH_2$) with formaldehyde liberated from the reagent. The key step then follows: transfer of hydrogen from another mole of the arylamine to the imine. This last imine is then hydrolyzed by water to the aldehyde. Alternatively, the benzylamine may transfer hydrogen directly to hexamethylenetetramine.

Organic halides were converted into carbonyl derivatives via microwave-assisted oxidation with *N*-methylmorpholine *N*-oxide in an ionic liquid.[769] Benzylic halides were oxidized to aryl aldehydes via reaction with trimethylamine/H_2O_2 in aqueous media.[770] Use of pyridine followed by *p*-nitrosodimethylaniline and then water converts benzylic halides to aldehydes, and is called the *Kröhnke reaction*. Primary halides and tosylates have been oxidized to aldehydes by trimethylamine *N*-oxide,[771] and by pyridine *N*-oxide with microwave irradiation.[772]

OS **II**, 336: **III**, 811; **IV**, 690, 918, 932; **V**, 242, 668, 825, 852, 872. Also see, OS **V**, 689; **VI**, 218.

19-21 Oxidation of Amines or Nitro Compounds to Aldehydes, Ketones, or Dihalides



Primary aliphatic amines can be oxidized to aldehydes or ketones, using silver compounds as shown.[773] Other reagents have been used,[774] including *N*-bromoacetamide[775] (for benzylic amines) or aqueous NaOCl with phase-transfer catalysts.[776] Several indirect methods for achieving the conversion $RR'CHNH_2 \rightarrow RR'C{=}O$ (R′ = alkyl, aryl, or H) have been reported.[777]

Primary, secondary, and tertiary aliphatic amines have been cleaved to give aldehydes, ketones, or carboxylic acids with aqueous bromine[778] and with neutral permanganate.[779] The other product of this reaction is the amine with one less alkyl group. Reaction of a

[769] Khumraksa, B.; Phakhodee, W.; Pattarawarapan, M. *Tetrahedron Lett.* ***2013***, *54*, 1983.
[770] Zheg, P.; Yan, L.; Ji, X.; Duan, X. *Synth. Commun.* ***2010–2011***, *41*, 16.
[771] Franzen, V.; Otto, S. *Chem. Ber.* ***1961***, *94*, 1360. For the use of other amine oxides, see Suzuki, S.; Onishi, T.; Fujita, Y.; Misawa, H.; Otera, J. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 3287.
[772] Barbry, D.; Champagne, P. *Tetrahedron Lett.* ***1996***, *37*, 7725.
[773] See Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, pp. 200–220, 411–415.
[774] For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1225–1227; Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, p. 240.
[775] Banerji, K.K. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 3717.
[776] Lee, G.A.; Freedman, H.H. *Tetrahedron Lett.* ***1976***, 1641.
[777] See Babler, J.H.; Invergo, B.J. *J. Org. Chem.* ***1981***, *46*, 1937.
[778] Deno, N.C.; Fruit Jr., R.E. *J. Am. Chem. Soc.* ***1968***, *90*, 3502.
[779] Rawalay, S.S.; Shechter, H. *J. Org. Chem.* ***1967***, *32*, 3129. For another procedure, see Monkovic, I.; Wong, H.; Bachand, C. *Synthesis* ***1985***, 770.

primary amine with benzoyl peroxide/$CsCO_3$ and subsequent heating of the hydroxylamine product gives the ketone.[780] In a different type of procedure, primary alkyl primary amines can be converted to *gem*-dihalides [$RCH_2NH_2 \rightarrow RCHX_2$ (X = Br or Cl)] by treatment with an alkyl nitrite and the anhydrous copper(I) halide.[781] The oxidation of benzylic amines to give an aryl aldehyde was reported using $PhI(OAc)_2$ as an oxidant.[782] Benzylic amines were oxidized to aldehydes with Selectfluor.[783]

Primary and secondary aliphatic nitro compounds have been oxidized to aldehydes and ketones, respectively ($RR'CHNO_2 \rightarrow RR'C{=}O$), with sodium chlorite under phase-transfer conditions,[784] with tetrapropylammonium perruthenate (TPAP),[785] as well as with other reagents.[786] The zinc-catalyzed reaction of nitroalkanes with a catalytic amount of Bu_4NI gave the corresponding carboxylic acids.[787]

19-22 Oxidation of Primary Alcohols to Carboxylic Acids or Carboxylic Acid Derivatives

$$RCH_2OH \xrightarrow{CrO_3} RCOOH$$

Primary alcohols can be oxidized to carboxylic acids by many strong oxidizing agents, including chromic acid, permanganate,[788] nitric acid,[789] or H_5IO_6/CrO_3.[790] Aliphatic primary alcohols are converted to the carboxylic acid with 30% aqueous H_2O_2, tetrabutylammonium hydrogen sulfate, and a W catalyst with microwave irradiation.[791] Benzylic alcohols are oxidized to benzoic acid derivatives by treatment first with TEMPO[792] (Sec. 5.C.i) and then $NaClO_2$.[793] Oxidation with 5% aqueous NaOCl and a Ni catalyst oxidizes primary alcohols to the corresponding acid.[794] Similar oxidation to the acid occurred with $NaIO_4/RuCl_3$ in aqueous acetonitrile,[795] or 30% aqueous H_2O_2 and a Co salen catalyst.[796] Oxammonium salts and $NaClO_2$ oxidize alcohols to aldehydes or

[780] Knowles, D.A.; Mathews, C.J.; Tomkinson, N.C.O. *Synlett* ***2008***, 2769.
[781] Doyle, M.P.; Siegfried, B. *J. Chem. Soc., Chem. Commun.* ***1976***, 433.
[782] Desjardins, S.; Jacquemot, G.; Canesi, S. *Synlett* ***2012***, *23*, 1497.
[783] Hauser, A.; Bohlmann, R. *Synlett* ***2016***, *27*, 1870.
[784] Ballini, R.; Petrini, M. *Tetrahedron Lett.* ***1989***, *30*, 5329.
[785] Tokunaga, Y.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* ***1997***, 207.
[786] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1227–1228.
[787] Marcé, P.; Lync, J.; Blacker, A.J.; Williams, J.M.J. *Chem. Commun.* ***2016***, *52*, 1013.
[788] See Rankin, K.N.; Liu, Q.; Hendry, J.; Yee, H.; Noureldin, N.A.; Lee, D.G. *Tetrahedron Lett.* ***1998***, *39*, 1095.
[789] See Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 127–132; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 2, Academic Press, NY, ***1988***, pp. 148–165, 391–401. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1646–1650.
[790] Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D.M.; Grabowski, E.J.J.; Reider, P.J. *Tetrahedron Lett.* ***1998***, *39*, 5323.
[791] Bogdal, D.; Lukasiewicz, M. *Synlett* ***2000***, 143.
[792] See DeLuca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* ***2003***, *68*, 4999.
[793] Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D.M.; Grabowski, E.J.J.; Reider, P.J. *J. Org. Chem.* ***1999***, *64*, 2564.
[794] Grill, J.M.; Ogle, J.W.; Miller, S.A. *J. Org. Chem.* ***2006***, *71*, 9291.
[795] Prashad, M.; Lu, Y.; Kim, H.-Y.; Hu, B.; Repič, O.; Blacklock, T.J. *Synth. Commun.* ***1999***, *29*, 2937.
[796] Das, S.; Punniyamurthy, T. *Tetrahedron Lett.* ***2003***, *44*, 6033.

carboxylic acids.[797] Alcohols were oxidized to carboxylic acids by reaction with O_2[798] or air using a catalyst of $Fe(NO_3)_3{\cdot}9H_2O$/TEMPO/KCl;[799] a Ag-catalyzed reaction has also been reported.[800] Primary alcohols were reacted with KOH and a Ru complex $PCy_3{\bullet}HBr_4$ catalyst to give carboxylic acids and dihydrogen.[801] Primary alcohols were oxidized to carboxylic acids by reaction with $NMO{\cdot}H_2O$, which acts as the co-oxidant and as a reagent for aldehyde hydrate stabilization, with TPAP as the catalyst.[802] It is noted that aldehydes reacted with air or *t*-BuOOH in the presence of iron nanoparticles, activated by ethyl acetoacetate, to give the carboxylic acid.[803]

Primary alcohols RCH_2OH can be directly oxidized to acyl fluorides RCOF with cesium fluoroxysulfate.[804]

A mixture of Oxone and NaCl converts alcohols to symmetrical esters.[805] Aliphatic alcohols are converted to a symmetrical ester ($RCH_2OH \rightarrow RCOOCH_2R$) by oxidation with PCC on aluminum without solvent.[806] Hydrogen with a Ru/CO complex converts primary alcohols (ROH) to an ester, RCO_2R.[807] Iodine has been used to convert alcohols to esters.[808] Hydrogen transfer with a Ru catalyst has been used to convert primary alcohols to methyl esters.[809] Oxone in aqueous methanol also converts aryl aldehydes to the corresponding ester.[810] Allylic alcohols are converted to conjugated esters with MnO_2 and NaCN in methanol/acetic acid.[811] Primary alcohols are oxidized to the methyl ester with trichloroisocyanuric acid in methanol.[812] This reagent also converts diols to lactones. The reaction of benzylic alcohols with toluene derivatives and *tert*-butyl hydroperoxide, and a with catalytic amount of Bu_4NI as the catalyst, gave the ester via sequential oxidation of the alcohol to the aldehyde, the carboxylic acid, and then to the benzyl ester.[813] The Pd-catalyzed reaction of primary alcohols with dioxygen gave the ester.[814] The Pd-catalyzed reaction of benzylic alcohols and alcohols with O_2 gave the ester.[815] The aerobic oxidation of benzylic and allylic alcohols used a Ru nanoparticle catalyst.[816] Alcohols reacted with methanol in the presence of O_2, Pd/C as a catalyst, and a catalytic amount of Bi/Te to give the methyl ester.[817] Benzyl alcohol was converted to a methyl ester by reaction with O_2,

[797] Qiu, J.C.; Pradhan, P.P.; Blanck, N.B.; Bobbitt, J.M.; Bailey, W.F. *Org. Lett.* ***2012***, *14*, 350.
[798] See Bandna, Aggarwal, N.; Das, P. *Tetrahedron Lett.* ***2011***, *52*, 4954. For the effect of ionic liquids, see Oda, Y.; Hirano, K.; Satoh, T.; Kuwabata, S.; Miura, M. *Tetrahedron Lett.* ***2011***, *52*, 5392.
[799] Jiang, X.; Zhang, J.; Ma, S. *J. Am. Chem. Soc.* ***2016***, *138*, 8344.
[800] Ghalehshahi, H.G.; Madsen, R. *Chem. Eur. J.* ***2017***, *23*, 11920.
[801] Santilli, C.; Makarov, I.S.; Fristrup, P.; Madsen, R. *J. Org. Chem.* ***2016***, *81*, 9931.
[802] Schmidt, A.-K.C.; Stark, C.B.W. *Org. Lett.* ***2011***, *13*, 4164.
[803] Villano, R.; Acocella, M.R.; Scettri, A. *Tetrahedron Lett.* ***2014***, *55*, 2442.
[804] Stavber, S.; Planinsek, Z.; Zupan, M. *Tetrahedron Lett.* ***1989***, *30*, 6095.
[805] Schulze, A.; Pagona, G.; Giannis, A. *Synth. Commun.* ***2006***, *36*, 1147.
[806] Bhar, S.; Chaudjuri, S.K. *Tetrahedron* ***2003***, *59*, 3493.
[807] Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* ***2005***, *127*, 10840.
[808] Mori, N.; Togo, H. *Tetrahedron* ***2005***, *61*, 5915.
[809] Owston, N.A.; Parker, A.J.; Williams, J.M.J. *Chem. Commun.* ***2008***, 624.
[810] Koo, B.-S.; Kim, E.-H.; Lee, K.-J. *Synth. Commun.* ***2002***, *32*, 2275.
[811] Foot, J.S.; Kanno, H.; Giblin, G.M.P.; Taylor, R.J.K. *Synlett* ***2002***, 1293.
[812] Hiegel, G.A.; Gilley, C.B. *Synth. Commun.* ***2003***, *33*, 2003.
[813] Liu, L.; Yun, L.; Wang, Z.; Fu, X.; Yan, C.-h. *Tetrahedron Lett.* ***2013***, *54*, 5383.
[814] Gowrisankar, S.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* ***2011***, *50*, 5139.
[815] Liu, C.; Wang, J.; Meng, L.; Deng, Y.; Li, Y.; Lei, A. *Angew. Chem. Int. Ed.* ***2011***, *50*, 5144.
[816] Das, P.; Aggarwal, N.; Guha, N.R. *Tetrahedron Lett.* ***2013***, *54*, 2924.
[817] Powell, A.B.; Stahl, S.S. *Org. Lett.* ***2013***, *15*, 5072.

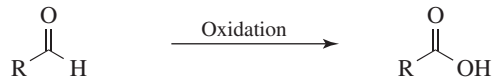
methanol, and a cobalt nanoparticle catalyst,[818] and alcohols reacted with methanol and an iridium catalyst to give the methyl ester. Note that the oxidative esterification of simple ketones by reaction with alcohols and CuBr/Py in open air led to C—C bond cleavage and formation of the corresponding ester.[819]

Lactones can be prepared by oxidizing diols in which at least one OH is primary;[820] addition of a chiral additive, such as sparteine, leads to lactones with high asymmetric induction.[821] The reaction of α,ω-diols with O_2 in the presence of a diruthenium catalyst, a Co catalyst, and a quinone gave the ω-hydroxycarboxylic acid that closed to the corresponding lactone.[822] One hydroxyl unit of a 1,6-diol system was oxidized to the carboxylic acid, which cyclized to the lactone in the presence of Cu/9-azabicyclo[3.3.1]nonan-*N*-oxyl catalyst for symmetrical diols and hindered unsymmetrical diols, and with a Cu/2,2,6,6-tetramethyl-1-piperidinyl-*N*-oxyl catalyst for the oxidation of less-hindered unsymmetrical diols.[823]

2-(3-Hydroxypropyl)aniline was oxidized to an acyl derivative that cyclized to give a lactam when heated with a Rh catalyst.[824] Heating an alcohol and an amine with a hydrotalcite-supported nano-gold heterogeneous catalyst led to the dehydrogenative synthesis of amides.[825] Primary alcohols reacted with ammonia to give the corresponding primary amide upon reaction with manganese oxide-based octahedral molecular sieve.[826] Alcohols reacted with amines in the presence of a Ru or a Rh catalyst to give the amide.[827] Alcohols reacted with amines to give amides using a Ru catalyst and *t*-BuOH/acetone.[828]

OS **I**, 138, 168; **IV**, 499, 677; **V**, 580; **VII**, 406; **IX**, 462; **81**, 195. Also see, OS **III**, 745.

19-23 Oxidation of Aldehydes to Carboxylic Acids, Carboxylic Acid Derivatives, and Nitriles



Esters and amides can be prepared by the oxidation of aldehydes,[829] and carboxylic acids were also prepared by direct oxidation.[830] Oxidation of aldehydes to carboxylic acids is

[818] Su, H.; Zhang, K.-X.; Zhang, B.; Wang, H.-H.; Yu, Q.-Y.; Li, X.-H.; Antonietti, M.; Chen, J.-S. *J. Am. Chem. Soc.* ***2017***, *139*, 811.
[819] Huang, X.; Li, X.; Zou, M.; Song, S.; Tang, C.; Yuan, Y.; Jiao, N. *J. Am. Chem. Soc.* ***2014***, *136*, 14858.
[820] See Ito, M.; Osaku, A.; Shiibashi, A.; Ikariya, T. *Org. Lett.* ***2007***, *9*, 1821. For a list of reagents used to effect this conversion, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1650–1652.
[821] Yanagisawa, Y.; Kashiwagi, Y.; Kurashima, F.; Anzai, J.; Osa, T.; Bobbitt, J.M. *Chem. Lett.* ***1996***, 1043.
[822] Endo, Y.; Bäckvall, J.-E. *Chem. Eur. J.* ***2011***, *17*, 12596.
[823] Xie, X.; Stahl, S.S. *J. Am. Chem. Soc.* ***2015***, *137*, 3767.
[824] Fujita, K.-i.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* ***2004***, *6*, 2785.
[825] Zhu, J.; Zhang, Y.; Shi, F.; Deng, Y. *Tetrahedron Lett.* ***2012***, *53*, 3178.
[826] Yamaguchi, K.; Kobayashi, H.; Oishi, T.; Mizuno, N. *Angew. Chem. Int. Ed.* ***2012***, *51*, 544.
[827] Chen, C.; Hong, S.H. *Org. Biomol. Chem.* ***2011***, *9*, 20.
[828] Watson, A.J.A.; Russell, J.; Wakeham, R.J.; Maxwell, A.C.; Williams, J.M.J. *Tetrahedron* ***2014***, *70*, 3683.
[829] Gaspa, S.; Porcheddu, A.; De Luca, L. *Tetrahedron Lett.* ***2016***, *57*, 3433.
[830] Yu, D.-F.; Xing, P.; Jiang, B. *Tetrahedron* ***2015***, *71*, 4269.

quite common[831] and has been carried out with many oxidizing agents, including permanganate in acid, basic, or neutral solution,[832] chromic acid,[833] and bromine. Silver oxide is a fairly specific oxidizing agent for aldehydes and does not readily attack other groups. *Benedict's solution* and *Fehling's solution* oxidize aldehydes[834] (there is a test for aldehydes that depends on this reaction), but the method is seldom used for preparative purposes and gives very poor results with aromatic aldehydes. α,β-Unsaturated aldehydes can be oxidized by sodium chlorite without disturbing the double bond.[835]

Mechanisms of aldehyde oxidation[836] are not firmly established, but there are at least two main types: a free-radical mechanism and an ionic one. In the free-radical process, the aldehyde hydrogen is abstracted to leave an acyl radical, which obtains OH from the oxidizing agent. In the ionic process, the first step is addition of an alkoxide tetrahedral intermediate in alkaline solution, or a hydroxyl-containing tetrahedral intermediate in acid or neutral solution. For oxidation with acid dichromate the picture seems to be quite complex.[837] Still another possible process has been proposed, in which the chromic acid ester decomposes.[838] The mechanism with permanganate is less well known, but an ionic mechanism has been proposed[839] for neutral and acid permanganate. For alkaline permanganate, a tetrahedral mechanism has been proposed.[840]

Aldehydes are also oxidized to carboxylic acids by atmospheric oxygen, but the actual direct oxidation product in this case is the peroxyacid RCO_3H,[841] which then disproportionates with another molecule of aldehyde to give two molecules of acid (see **14-6**).[842] The air oxidation of aldehydes to carboxylic acids is mediated by a mixture of Pd/C/$NaBH_4$ and KOH.[843] An aldehyde can be converted to the carboxylic acid by treatment with 30% hydrogen peroxide and methyl(trioctyl)ammonium hydrogen sulfate at 90 °C.[844] Aryl aldehydes are similarly oxidized by a mixture of hydrogen peroxide and selenium dioxide (SeO_2).[845]

[831] See Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1988***, pp. 241–263, 423–428; Chinn, L.J. *Selection of Oxidants in Synthesis*, Marcel Dekker, NY, ***1971***, pp. 63–70; Lee, D.G. in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 81–86.

[832] See Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 174–180; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1653–1661; Srivastava, R.G.; Venkataramani, P.S. *Synth. Commun.* ***1988***, *18*, 2193. See also, Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1988***.

[833] See Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*, Springer, NY, ***1984***, pp. 217–225.

[834] See Nigh, W.G. in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 31–34.

[835] Dalcanale, E.; Montanari, F. *J. Org. Chem.* ***1986***, *51*, 567. See also, Bayle, J.P.; Perez, F.; Courtieu, J. *Bull. Soc. Chim. Fr.* ***1990***, 565.

[836] See Rocek, J., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 461–505.

[837] Wiberg, K.B.; Szeimies, G. *J. Am. Chem. Soc.* ***1974***, *96*, 1889. See also, Sen Gupta, S.; Dey, S.; Sen Gupta, K.K. *Tetrahedron* ***1990***, *46*, 2431.

[838] See Rocek, J.; Ng, C. *J. Org. Chem.* ***1973***, *38*, 3348.

[839] See Freeman, F.; Lin, D.K.; Moore, G.R. *J. Org. Chem.* ***1982***, *47*, 56; Jain, A.L.; Banerji, K.K. *J. Chem. Res. (S)* ***1983***, 60.

[840] Freeman, F.; Brant, J.B.; Hester, N.B.; Kamego, A.A.; Kasner, M.L.; McLaughlin, T.G.; Paul, E.W. *J. Org. Chem.* ***1970***, *35*, 982.

[841] See Swern, D. in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, pp. 313–516.

[842] For reviews of the autoxidation of aldehydes, see Vardanyan, I.A.; Nalbandyan, A.B. *Russ. Chem. Rev.* ***1985***, *54*, 532 (gas phase); Sajus, L.; Sérée de Roch, I. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 16, Elsevier, NY, ***1980***, pp. 89–124 (liquid phase); see Larkin, D.R. *J. Org. Chem.* ***1990***, *55*, 1563.

[843] Lim, M.; Yoon, C.M.; An, G.; Rhee, H. *Tetrahedron Lett.* ***2007***, *48*, 3835.

[844] Sato, K.; Hyodo, M.; Takagi, J.; Aoki, M.; Noyori, R. *Tetrahedron Lett.* ***2000***, *41*, 1439.

[845] Wójtowicz, H.; Brzaszcz, M.; Kloc, K.; Mlochowski, J. *Tetrahedron* ***2001***, *57*, 9743.

Polymer-bound hypervalent iodine + TEMPO oxidizes aldehydes to acids.[846] Organocatalysts have been used for the anodic oxidation of aldehydes.[847] *N*-heterocyclic carbenes catalyze oxidation of aldehydes to the corresponding ester.[848] Aryl aldehydes are converted to the corresponding aryl carboxylic ester with hydrogen peroxide and a V_2O_5 catalyst[849] or a titanosilicate[850] in an alcohol solvent. Esterification of aldehydes with alcohols uses an Ir catalyst.[851] The reaction of aldehydes with aqueous alcohols, in the presence of iodine and $NaNO_2$, gives an ester.[852] Organoboronic acids and molecular oxygen convert aldehydes to an ester using a Pd catalyst.[853]

The NHC-mediated reaction of aldehydes with alcohols to give esters, in the presence of DBU, was reported in an undivided microfluidic electrolysis cell (Sec. 7.D).[854] The oxidation of aliphatic aldehydes to the corresponding carboxylic acids by reaction with O_2, and in some cases with a catalytic amount of a Mn catalyst, was reported using a flow reactor (Sec. 7.D).[855] Aryl and conjugated aldehydes reacted with air in the presence of a *N*-heterocyclic carbene catalyst and water in DMF or DMSO to give the corresponding carboxylic acid.[856] A NHC organocatalyst was used for the oxidative esterification of aldehydes by reaction with alcohols and a quinone oxidant (a diphenoquinone derivative).[857] Primary alcohols reacted with O_2 using immobilized Pt nanoparticles on superhydrophobic organic–inorganic hybrid silicas as a catalyst in water.[858] Aldehydes were oxidized to the corresponding carboxylic acid with H_2O_2 using a sulfonic acid resin catalyst.[859]

In the presence of hydrogen peroxide and a vanadium catalyst, aryl aldehydes were oxidized to aryl carboxylic acids.[860] Aliphatic and aromatic aldehydes reacted with alcohols to give the corresponding esters using a palladium catalyst and the addition of acetone, which was reduced to isopropanol.[861] The redox conversion of an α,β-unsaturated aldehyde to a carboxylic acid ester or amide by reaction with an alcohol or ammonia/amine has reported, using a combination of TMSCN and DBU.[862] Aromatic aldehydes were converted to the methyl ester using a polymer-supported bromine chloride resin in methanol in the presence of potassium carbonate.[863] Amides or carboxylic acids were prepared by the *N*-heterocyclic carbene-catalyzed reaction of amines or water with α-unbranched

[846] Tashino, Y.; Togo, H. *Synlett* ***2004***, 2010.
[847] Finney, E.E.; Ogawa, K.A.; Boydston, A.J. *J. Am. Chem. Soc.* ***2012***, *134*, 12374.
[848] Maki, B.E.; Scheidt, K.A. *Org. Lett.* ***2008***, *10*, 4331.
[849] Gopinath, R.; Patel, B.K. *Org. Lett.* ***2000***, *2*, 577.
[850] Chavan, S.P.; Dantale, S.W.; Govande, C.A.; Venkatraman, M.S.; Praveen, C. *Synlett* ***2002***, 267.
[851] Kiyooka, S.-i.; Wada, Y.; Ueno, M.; Yokoyama, T.; Yokoyama, R. *Tetrahedron* ***2007***, *63*, 12695.
[852] Kiran, Y.B.; Ikeda, R.; Sakai, N.; Konakahara, T. *Synthesis* ***2010***, 276.
[853] Qin, C.; Wu, H.; Chen, J.; Liu, M.; Cheng, J.; Su, W.; Ding, J. *Org. Lett.* ***2008***, *10*, 1537. Using boronic acids: see Rosa, J.N.; Reddy, R.S.; Candeias, N.R.; Cal, P.M.S.D.; Gois, P.M.P. *Org. Lett.* ***2010***, *12*, 2686.
[854] Green, R.A.; Pletcher, D.; Leach, S.G.; Brown, R.C.D. *Org. Lett.* ***2015***, *17*, 3290.
[855] Vanoye, L.; Aloui, A.; Pablos, M.; Philippe, R.; Percheron, A.; Favre-Réguillon, A.; de Bellefon, C. *Org. Lett.* ***2013***, *15*, 5978.
[856] Chiang, P.-C.; Bode, J.W. *Org. Lett.* ***2011***, *13*, 2422.
[857] Berry, M.T.; Castrejon, D.; Hein, J.E. *Org. Lett.* ***2014***, *16*, 3676.
[858] Wang, M.; Wang, F.; Ma, J.; Chen, C.; Shi, S.; Xu, J. *Chem. Commun.* ***2013***, *49*, 6623.
[859] Yang, X.; Tang, S.; Lu, T.; Chen, C.; Zhou, L.; Su, Y.; Xu, J. *Synth. Commun.* ***2013***, *43*, 979.
[860] Talukdar, D.; Sharma, K.; Bharadwaj, S.K.; Thakur, A.J. *Synlett* ***2013***, *24*, 963.
[861] Tschaen, B.A.; Schmink, J.R.; Molander, G.A. *Org. Lett.* ***2013***, *15*, 500.
[862] Kaise, H.; Shimokawa, J.; Fukuyama, T. *Org. Lett.* ***2014***, *16*, 727.
[863] Sridhar, A.; Swarnalakshmi, S.; Selvaraj, M. *Synlett* ***2016***, *27*, 1344.

aldehydes via oxidation by NCS.[864] The Cu-catalyzed reaction of aldehydes with hydroxylamine hydrochloride gave the acid upon heating,[865] and a bioglycerol-based carbon catalyst has been used.[866]

The NHC-catalyzed reaction of aldehydes with thiols used phenazine as an oxidant to give the thioester.[867] Photocatalysis using an Fe catalyst converted aldehydes to esters.[868] Organocatalysts were used to convert aldehydes to amides or esters.[869]

Aldehydes reacted with ammonium chloride or amine hydrochloride salts using Cu catalysts and aqueous *tert*-butyl hydroperoxide.[870] Aromatic and aliphatic aldehydes that reacted with trichloroisocyanuric acid were first converted to the corresponding acyl chloride, and subsequent reaction with a variety of alcohols or phenols then gave the corresponding esters.[871] Aldehydes reacted with $TsNBr_2$ and methanol to give the methyl ester.[872] Heating aromatic aldehydes with ammonium$^+$ or pyridinium$^+$ $S_2O_8^-$ salts and alcohols gave aromatic esters.[873] α,β-Unsaturated or aromatic aldehydes reacted with reactive cinnamyl bromides with a *N*-heterocyclic carbene catalyst in the presence of air oxygen or MnO_2 to give the ester.[874] Heating aldehydes with phenols in the presence of air gave the phenyl ester via Pd-catalyzed esterification.[875] Heating aryl aldehydes with benzyl bromide with a Pd catalyst in ethanol gave the corresponding ethyl ester.[876] 1-Butyl-3-methylimidazolium tetrafluoroborate ($BmimBF_4$) has been used in the NHC-catalyzed oxidation with MnO_2 and DBU or $CsCO_3$ to give the corresponding ester.[877] The reaction of aryl aldehydes with methanol and H_2O_2 in the presence of $CaCl_2$ or $MgCl_2$ gave the corresponding methyl benzoate.[878] A nitrile intermediate was formed by reaction of an aldehyde with hydroxylamine hydrochloride in dimethyl sulfoxide (DMSO) at 100 °C, and subsequent reaction with ethanol and sulfuric acid at 130 °C gave the ethyl ester.[879] Aldehydes were converted to thioesters by reaction with thiols, 4-methyl-3-(2,4,6-trimethylphenyl)thiazolium tetrafluoroborate, 4-methyl-3-(2,6-diisopropylphenyl)thiazolium tetrafluoroborate, or DMAP, and by using a graphite anode and a Pt cathode.[880] The iron-catalyzed reaction is also known.[881]

Nitriles were prepared by the reaction of aldehydes with acyl hydroxylamine, with a Bi catalyst, that converted an intermediate aldoxime to the nitriles.[882] Aldehydes reacted

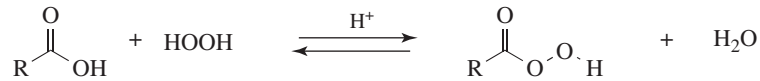
[864] Kuwano, S.; Harada, S.; Oriez, R.; Yamada, K.-i. *Chem. Commun.* ***2012***, *48*, 145. See Delany, E.G.; Fagan, C.-L.; Gundala, S.; Mari, A.; Broja, T.; Zeitler, K.; Connon, S.J. *Chem. Commun.* ***2013***, *49*, 6510.
[865] Ganguly, N.C.; Roy, S.; Mondal, P. *Tetrahedron Lett.* ***2012***, *53*, 1413.
[866] Ramesh, K.; Murthy, S.N.; Karnakar, K.; Reddy, K.H.V.; Nageswar, Y.V.D.; Vijay, M.; Devi, B.L.A.P.; Prasad, R.B.N. *Tetrahedron Lett.* ***2012***, *53*, 2636.
[867] Uno, T.; Inokuma, T.; Takemoto, Y. *Chem. Commun.* ***2012***, *48*, 1901.
[868] Argouarch, G.; Grelaud, G.; Roisnel, T.; Humphrey, M.G.; Paul, F. *Tetrahedron Lett.* ***2012***, *53*, 5015.
[869] Tan, B.; Toda, N.; Barbas III, C.F. *Angew. Chem. Int. Ed.* ***2012***, *51*, 12538.
[870] Ghosh, S.C.; Ngiam, J.S.Y.; Seayad, A.M.; Tuan, D.T.; Chai, C.L.L.; Chen, A. *J. Org. Chem.* ***2012***, *77*, 8007.
[871] Gaspa, S.; Porcheddu, A.; De Luca, L. *Org. Lett.* ***2015***, *17*, 3666.
[872] Rajbongshi, K.K.; Sarma, M.J.; Phukan, P. *Tetrahedron Lett.* ***2014***, *55*, 5358.
[873] Guo, Y.-F.; Mahmood, S.; Xu, B.-H.; Yao, X.-Q.; He, H.-Y.; Zhang, S.-J. *J. Org. Chem.* ***2017***, *82*, 1591.
[874] Maji, B.; Vedachalan, S.; Ge, X.; Cai, S.; Liu, X.-W. *J. Org. Chem.* ***2011***, *76*, 3016.
[875] Zhang, M.; Zhang, S.; Zhang, G.; Chen, F.; Cheng, J. *Tetrahedron Lett.* ***2011***, *52*, 2480.
[876] Heropoulos, G.A.; Villalonga-Barber, C. *Tetrahedron Lett.* ***2011***, *52*, 5219.
[877] Chiarotto, I.; Feroci, M.; Sotgiu, G.; Inesi, A. *Tetrahedron* ***2013***, *69*, 8088.
[878] Feng, J.-B.; Gong, J.-L.; Li, Q.; Wu, X.-F. *Tetrahedron Lett.* ***2014***, *55*, 1657.
[879] Siler, P.J.; Chill, S.T.; Mebane, R.C. *Synth. Commun.* ***2010–2011***, *41*, 1247.
[880] Ogawa, K.A.; Boydston, A.J. *Org. Lett.* ***2014***, *16*, 1928.
[881] Huang, Y.-T.; Lu, S.-Y.; Yi, C.-L.; Lee, C.-F. *J. Org. Chem.* ***2014***, *79*, 4561.
[882] Sridhar, M.; Reddy, M.K.K.; Sairam, V.V.; Raveendra, J.; Godala, K.R.; Narsaiah, C.; Ramanaiah, B.C.; Reddy, C.S. *Tetrahedron Lett.* ***2012***, *53*, 3421.

with aqueous ammonia and molecular iodine, and subsequent reaction with *O*,*O*-diethyl dithiophosphoric acid gave the corresponding primary thioamide.[883] The reaction of aryl aldehydes with *t*-BuOOH and a Cu catalyst in DMSO gave the diaryl anhydride.[884]

A flow process (Sec. 7.D) for a NHC-mediated anodic reaction of aldehydes with DBU and then with amines gave the corresponding amide.[885] Aldehydes reacted with amines and TBHP using a Cu catalyst in water to give the amide.[886] Aryl aldehydes reacted with amines and $NaOCl/Bu_4NHSO_4$ in PEG 400 to give the amide.[887] Tertiary amides were prepared by the reaction of tertiary amines and aldehydes with TBHP and an iron catalyst.[888] The reaction of aldehydes and ketones with hydroxylamine and sodium acetate, followed by reaction of the resulting oxime with *O*,*O*-diethyl dithiophosphoric acid, gave the thioamide.[889] Aryl aldehydes reacted with a secondary amine and TBHP using a zinc catalyst to give the amide.[890] A gold-catalyzed reaction has been reported.[891] Aromatic aldehydes reacted with aliphatic azides in the presence of KO*t*-Bu in DMF to give the amide.[892]

OS **I**, 166; **II**, 302, 315, 538; **III**, 745; **IV**, 302, 493, 499, 919, 972, 974.

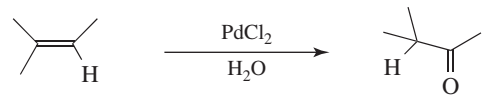
19-24 Oxidation of Carboxylic Acids to Peroxyacids



The oxidation of carboxylic acids with H_2O_2 and an acid catalyst is the best general method for the preparation of peroxyacids.[893] A mixture of $Me_2C(OMe)OOH$ and DCC has also been used.[894] Concentrated sulfuric acid is a common catalyst for aliphatic R. The reaction is in an equilibrium and is driven to the right by removal of water or by the use of excess reagents. For aromatic R, the best catalyst is methanesulfonic acid, which is also used as the solvent.

D. Reactions in Which Oxygen Is Added to the Substrate

19-25 Oxidation of Alkenes to Aldehydes and Ketones



[883] Yadav, A.K.; Srivastava, V.P.; Yadav, L.D.S. *Synth. Commun.* ***2014***, *44*, 408.
[884] Nuree, Y.; Singha, R.; Ghosh, M.; Roy, P.; Ray, J.K. *Tetrahedron Lett.* ***2016***, *57*, 1479.
[885] Green, R.A.; Pletcher, D.; Leach, S.G.; Brown, R.C.D. *Org. Lett.* ***2016***, *18*, 1198.
[886] Lu, S.-Y.; Badsara, S.S.; Wu, Y.-C.; Reddy, D.M.; Lee, C.-F. *Tetrahedron Lett.* ***2016***, *57*, 633.
[887] Liang, J.; Lv, J.; Shang, Z.-c. *Tetrahedron* ***2011***, *67*, 8532.
[888] Li, Y.; Jia, F.; Li, Z. *Chem. Eur. J.* ***2013***, *19*, 82.
[889] Yadav, A.K.; Srivastava, V.P.; Yadav, L.D.S. *Tetrahedron Lett.* ***2012***, *53*, 7113.
[890] Zhang, M.; Wu, X.-F. *Tetrahedron Lett.* ***2013***, *54*, 1059.
[891] Li, G.-L.; Kung, K.K.-Y.; Wong, M.-K. *Chem. Commun.* ***2012***, *48*, 4112.
[892] Kulkarni, S.S.; Hu, X.; Manetsch, R. *Chem. Commun.* ***2013***, *49*, 1193. See Carbone, G.; Burnley, J.; Moss, J.E. *Chem. Commun.* ***2013***, *49*, 2759.
[893] See Swern, D. in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, pp. 313–516. For a review of peroxyacids in organic synthesis, see Kaaur, N.; Kishore, D. *Synth. Commun.* ***2014***, *44*, 721.
[894] Dussault, P.; Sahli, A. *J. Org. Chem.* ***1992***, *57*, 1009.

Monosubstituted and 1,2-disubstituted alkenes can be oxidized to aldehydes and ketones by $PdCl_2$, where the $PdCl_2$ is reduced to Pd.[895] Internal alkenes have been oxidized using a Pd catalyst and TBHP.[896] Similar salts of noble metals also work, but 1,1-disubstituted alkenes generally give poor results. The reaction is used industrially to prepare acetaldehyde from ethylene (the *Wacker process*),[897] but it is also suitable for laboratory preparations. The reagent is expensive, so the reaction is usually carried out with a co-oxidant, often $CuCl_2$, whose function is to reoxidize the Pd to Pd(II). The $CuCl_2$ is reduced to Cu(I), which itself is reoxidized to Cu(II) by air, so that atmospheric oxygen is the only oxidizing agent actually used up. Many other co-oxidants have been tried, among them O_3, O_2,[898] Fe^{3+}, and PbO_2. Terminal alkenes are oxidized to methyl ketones with O_2 and a Pd catalyst[899] and hypervalent iodine has been used.[900] An aldehyde is the principal product only from ethylene, while with other alkenes *Markovnikov's rule* is followed, and ketones are formed predominantly, although anti-Markovnikov reactions have been reported.[901] A catalyst-controlled Wacker-type oxidation, using Pd/Cu catalysts, gave functionalized aldehydes.[902] Palladium and hypervalent iodine co-catalysis allowed the tandem Wacker oxidation–dehydrogenation of terminal alkenes to give linear aryl and alkyl α,β-unsaturated ketones.[903] The Wacker oxidation of homoallylic alcohols has been reported.[904] An aldehyde-selective Wacker oxidation of aryl-substituted alkenes used a palladium catalyst, 1,4-benzoquinone, and *t*-BuOH in air.[905] An Oxone-mediated oxidation of benzo-fused alkenes has been reported.[906] The Ru-catalyzed oxidation of alkenes with TBHP gave the α-diketone.[907] Alkynes were converted to 1,2-diketones using RuO_4, generated *in situ* from $RuCl_3 \cdot xH_2O$, and NaOCl.[908]

[895] See Tsuji, J. *Organic Synthesis with Palladium Compounds*, Springer, NY, ***1980***, pp. 6–12; Tsuji, J. *Synthesis* ***1990***, 739; Heck, R.F. *Palladium Reagents in Organic Syntheses*, Academic Press, NY, ***1985***, pp. 59–80; Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, NY, ***1981***, pp. 189–193, 299–303; Jira, R.; Freiesleben, W. *Organomet. React.* ***1972***, *3*, 1 (pp. 1–44); Hüttel, R. *Synthesis* ***1970***, 225 (see pp. 225–236). See Mann, S.E.; Benhamou, L.; Sheppard, T.D. *Synthesis* ***2015***, *47*, 3079.

[896] DeLuca, R.J.; Edwards, J.L.; Steffens, L.D.; Michel, B.W.; Qiao, X.; Zhu, C.; Cook, S.P.; Sigman, M.S. *J. Org. Chem.* ***2013***, *78*, 1682.

[897] *The Merck Index*, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, ***2006***, p. ONR-98; Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis*, 2nd ed., Wiley-Interscience, New Jersey, ***2005***, pp. 676–677. See Baiju, T.V.; Gravel, E.; Doris, E.; Namboothiri, I.N.N. *Tetrahedron Lett.* ***2016***, *57*, 3993; Liu, B.; Jin, F.; Wang, T.; Yuan, X.; Han, W. *Angew. Chem. Int. Ed.* ***2017***, *56*, 12712. For green processes, see Kulkarni, M.G.; Shaikh, Y.B.; Borhade, A.S.; Chavhan, S.W.; Dhondge, A.P.; Gaikwad, D.D.; Desai, M.P.; Birhade, D.R.; Dhatrak, N.R. *Tetrahedron Lett.* ***2013***, *54*, 2293; Zhang, G.; Xie, X.; Wang, Y.; Wen, X.; Zhao, Y.; Ding, C. *Org. Biomol. Chem.* ***2013***, *11*, 2947.

[898] Wang, Y.-F.; Gao, Y.-R.; Mao, S.; Zhang, Y.-L.; Guo, D.-D.; Yan, Z.-L.; Guo, S.-H.; Wang, Y.-Q. *Org. Lett.* ***2014***, *16*, 1610.

[899] See Cornell, C.N.; Sigman, M.S. *Org. Lett.* ***2006***, *8*, 4117.

[900] Chaudhari, D.A.; Fernandes, R.A. *J. Org. Chem.* ***2016***, *81*, 2113.

[901] Kim, K.E.; Li, J.; Grubbs, R.H.; Stoltz, B.M. *J. Am. Chem. Soc.* ***2016***, *138*, 13179. For a review, see Dong, J.J.; Browne, W.R.; Feringa, B.L. *Angew. Chem. Int. Ed.* ***2015***, *54*, 734.

[902] Wickens, Z.K.; Skakuj, K.; Morandi, B.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2014***, *136*, 890.

[903] Bigi, M.A.; White, M.C. *J. Am. Chem. Soc.* ***2013***, *135*, 7831.

[904] McCombs, J.R.; Michel, B.W.; Sigman, M.S. *J. Org. Chem.* ***2011***, *76*, 3609. See Bethi, V.; Fernandes, R.A. *J. Org. Chem.* ***2016***, *81*, 8577.

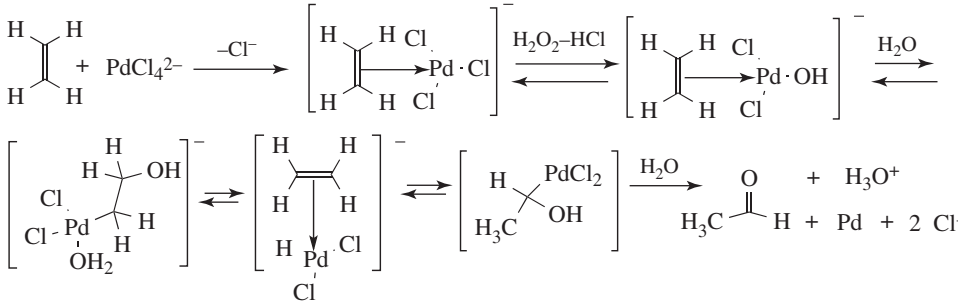
[905] See Wickens, Z.K.; Morandi, B.; Grubbs, R.H. *Angew. Chem. Int. Ed.* ***2013***, *52*, 11257.

[906] Phatake, R.S.; Ramana, C.V. *Tetrahedron Lett.* ***2015***, *56*, 3868.

[907] Chen, S.; Liu, Z.; Shi, E.; Chen, L.; Wei, W.; Li, H.; Cheng, Y.; Wan, X. *Org. Lett.* ***2011***, *13*, 2274. Also see Jia, H.-P.; Dreyer, D.R.; Bielawski, C.W. *Tetrahedron* ***2011***, *67*, 4431.

[908] Miao, Y.; Dupé, A.; Bruneau, C.; Fischmeister, C. *Eur. J. Org. Chem.* ***2014***, 5071.

The generally accepted mechanism shown below involves π complexes of Pd.[909] This mechanism accounts for the fact, established by deuterium labeling, that the four hydrogen atoms of the acetaldehyde all come from the original ethylene and none from the solvent.



Similar reactions have been carried out with other oxidizing agents. An example involving migration of an alkyl group instead of hydrogen is oxidation of $Me_2C{=}CMe_2$ with peroxytrifluoroacetic acid/boron trifluoride to give Me_3COMe (pinacolone).[910] This reaction consists of epoxidation (**15-50**) followed by pinacol rearrangement of the epoxide (**18-2**). A migration is also involved in the conversion of $ArCH{=}CHCH_3$ to $ArCH(CH_3)CHO$ by treatment with I_2/Ag_2O in aqueous dioxane.[911] Other reagents have been used, for example $Pb(OAc)_4/F_3CCO_2H$,[912] or H_2O_2 and a Pd catalyst for the conversion $PhCH{=}CH_2 \rightarrow PhCH_2CHO$.[913] Terminal alkenes react with ceric ammonium nitrate in methanol to give α-methoxy ketones.[914]

Alkenes have also been converted to more highly oxidized products. Examples of these reactions are: (i) treatment with $KMnO_4$ in aqueous acetone containing acetic acid gives α-hydroxy ketones;[915] (ii) 1,2-disubstituted and trisubstituted alkenes give α-chloro ketones when oxidized with chromyl chloride in acetone ($RCH{=}CR^1R^2 \rightarrow RCOCClR^1R^2$);[916] (iii) α-iodo ketones can be prepared by treating alkenes with bis(*sym*-collidine)iodine(I) tetrafluoroborate;[917] and (iv) potassium permanganate in acetic anhydride oxidizes large-ring cycloalkenes to 1,2-diketones.[918]

Enol ethers are oxidized to carboxylic esters ($RCH{=}CHOR' \rightarrow RCH_2COOR'$) with pyridinium chlorochromate (PCC)[919] and enamines are oxidized to α-amino ketones with

[909] See Keith, J.A.; Nielsen, R.J.; Oxgaard, J.; Goddard III, W.A. *J. Am. Chem. Soc.* ***2007***, *129*, 12342; Michel, B.W.; Steffens, L.D.; Sigman, M.S. *J. Am. Chem. Soc.* ***2011***, *133*, 8317; Ye, X.; Liu, G.; Popp, B.V.; Stahl, S.S. *J. Org. Chem.* ***2011***, *76*, 1031.

[910] Hart, H.; Lerner, L.R. *J. Org. Chem.* ***1967***, *32*, 2669.

[911] Kikuchi, H.; Kogure, K.; Toyoda, M. *Chem. Lett.* ***1984***, 341.

[912] Lethbridge, A.; Norman, R.O.C.; Thomas, C.B. *J. Chem. Soc., Perkin Trans. 1* ***1973***, 35.

[913] Roussel, M.; Mimoun, H. *J. Org. Chem.* ***1980***, *45*, 5387.

[914] Nair, V.; Nair, L.G.; Panicker, S.B.; Sheeba, V.; Augustine, A. *Chem. Lett.* ***2000***, 584.

[915] Srinivasan, N.S.; Lee, D.G. *Synthesis* ***1979***, 520. See also, Baskaran, S.; Das, J.; Chandrasekaran, S. *J. Org. Chem.* ***1989***, *54*, 5182.

[916] Sharpless, K.B.; Teranishi, A.Y. *J. Org. Chem.* ***1973***, *38*, 185. See also, Lee, J.G.; Ha, D.S. *Tetrahedron Lett.* ***1989***, *30*, 193.

[917] Evans, R.D.; Schauble, J.H. *Synthesis* ***1986***, 727.

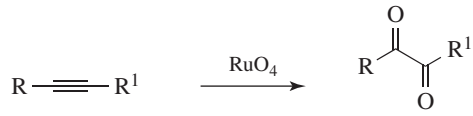
[918] Jensen, H.P.; Sharpless, K.B. *J. Org. Chem.* ***1974***, *39*, 2314.

[919] Piancatelli, G.; Scettri, A.; D'Auria, M. *Tetrahedron Lett.* ***1977***, 3483. See Baskaran, S.; Islam, I.; Raghavan, M.; Chandrasekaran, S. *Chem. Lett.* ***1987***, 1175.

N-sulfonyloxaziridines.[920] Polysubstituted enamines ($R^1R^4C{=}CR^2NR_2{}^3$, $R^4 \neq H$) do not give these products, but lose the amino group to give α-hydroxy ketones, $R^1R^4C(OH)COR^2$.[920] Carboxylic acids can be prepared from terminal alkynes by conversion of the alkyne to its phenylthio ether ($RC{\equiv}CSPh$) and treatment of this with $HgSO_4$ in $HOAc/H_2SO_4$.[921] Aza-Wacker reactions are known.[922]

OS **VI**, 1028; **VII**, 137; **VIII**, 208.

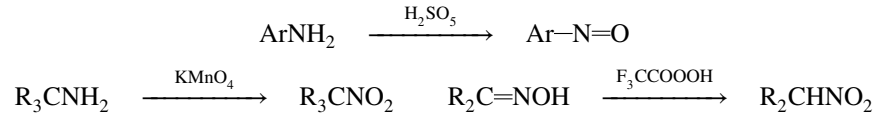
19-26 The Oxidation of Alkynes to α-Diketones



Internal alkynes have been oxidized[923] to α-diketones[924] by several oxidizing agents,[925] including neutral $KMnO_4$,[926] bis(trifluoroacetoxy)iodobenzene,[927] $NaIO_4/RuO_2$,[928] $MeReO_3/H_2O_2$,[929] or oxygen and a mixture of Pd and Cu catalysts.[930] A Ru complex with a small amount of trifluoroacetic acid converts internal alkynes to the α-diketone.[931] The Ru-catalyzed oxidation of alkynes using Oxone and a catalytic amount of TEMPO gave 1,2-diketones.[932] The Pd/C-catalyzed and pyridine *N*-oxide-mediated oxidation of diarylalkynes gave the 1,2-diketone derivative.[933] Ozone generally oxidizes triple-bond compounds to carboxylic acids (**19-9**), but α-diketones are sometimes obtained.[934] Selenium dioxide (SeO_2) with a small amount of H_2SO_4 oxidizes alkynes to α-diketones as well as arylacetylenes to α-keto acids ($ArC{\equiv}CH \rightarrow ArCOCO_2H$).[935] A mixture of formic acid, methanesulfonic acid, and DMSO with an HBr catalyst converts alkynes to α-diketones.[936]

[920] Davis, F.A.; Sheppard, A.C. *Tetrahedron Lett.* ***1988***, *29*, 4365.
[921] Abrams, S.R. *Can. J. Chem.* ***1983***, *61*, 2423.
[922] Hu, H.; Tian, J.; Liu, Y.; Liu, Y.; Shi, F.; Wang, X.; Kan, Y.; Wang, C. *J. Org. Chem.* ***2015***, *80*, 2842; Elliott, L.D.; Wrigglesworth, J.W.; Cox, B.; Lloyd-Jones, G.C.; Booker-Milburn, K.I. *Org. Lett.* ***2011***, *13*, 728; Yang, G.; Zhang, W. *Org. Lett.* ***2012***, *14*, 268; Yang, R.; Yu, J.-T.; Sun, S.; Zheng, Q.; Cheng, J. *Tetrahedron Lett.* ***2017***, *58*, 445.
[923] See Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Vol. 1, Academic Press, NY, ***1985***, pp. 153–162, 332–338; Simándi, L.I. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, Supplement C, pt. 1, Wiley, NY, ***1983***, pp. 513–570.
[924] For a review, see Yuan, L.-Z.; Hamze, A.; Alami, M.; Provot, O. *Synthesis* ***2017***, *49*, 504.
[925] See Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, p. 92.
[926] See Tatlock, J.H. *J. Org. Chem.* ***1995***, *60*, 6221.
[927] Vasil'eva, V.P.; Khalfina, I.L.; Karpitskaya, L.G.; Merkushev, E.B. *J. Org. Chem. USSR* ***1987***, *23*, 1967.
[928] See Al-Rashid, Z.F.; Johnson, W.L.; Hsung, R.P.; Wei, Y.; Yao, P.-Y.; Liu, R.; Zhao, K. *J. Org. Chem.* ***2008***, *73*, 8780.
[929] Zhu, Z.; Espenson, J.H. *J. Org. Chem.* ***1995***, *60*, 7728.
[930] Ren, W.; Xia, Y.; Ji, S.-J.; Zhang, Y.; Wan, X.; Zhao, J. *Org. Lett.* ***2009***, *11*, 1841.
[931] Che, C.-M.; Yu, W.-Y.; Chan, P.-M.; Cheng, W.-C.; Peng, S.-M.; Lau, K.-C.; Li, W.-K. *J. Am. Chem. Soc.* ***2000***, *122*, 11380.
[932] Xu, Y.; Wan, X. *Tetrahedron Lett.* ***2013***, *54*, 642.
[933] Sawama, Y.; Takubo, M.; Mori, S.; Monguchi, Y.; Sajiki, H. *Eur. J. Org. Chem.* ***2011***, 3361.
[934] Chu, J.H.; Chen, Y.-J.; Wu, M.-J. *Synthesis* ***2009***, 2115.
[935] Sonoda, N.; Yamamoto, Y.; Murai, S.; Tsutsumi, S. *Chem. Lett.* ***1972***, 229.
[936] Wan, Z.; Jones, C.D.; Mitchell, D.; Pu, J.Y.; Zhang, T.Y. *J. Org. Chem.* ***2006***, *71*, 826.

19-27 Oxidation of Amines and Other Nitrogen Compounds



Primary aromatic amines can be oxidized[937] to nitroso compounds. Most often the conversion is accomplished by *Caro's acid* (H_2SO_5) or with H_2O_2 in HOAc.[938] The mechanism with H_2SO_5 has been postulated to involve attack of the amine on the electrophilic oxygen of $^-O_3S—O—OH$ (the OH unit).[939] Other reagents used for this oxidation are H_2O_2 with a Ti complex,[940] HOF generated *in situ*,[941] and Na_2WO_4/H_2O_2.[942] Hydroxylamines have been oxidized to oximes, using Cu/air,[943] In/TEMPO,[944] or TEMPO.[945] Hydroxylamines, which are probably intermediates in most cases, can sometimes be isolated, but under the reaction conditions they are generally oxidized to the nitroso compounds. Primary aliphatic amines can be oxidized in this manner, but the nitroso compound is stable only if there is no α hydrogen. If there is an α hydrogen, the compound tautomerizes to the oxime.[946] *N*-Nitroso compounds, known as nitrosamines, have also been prepared. The reaction of secondary or tertiary amines with *o*-iodoxybenzoic acid, a catalytic amount of TBAF, and nitromethane gave aliphatic or aromatic *N*,*N*-disubstituted nitrosamines.[947]

Secondary amines (R_2NH) are oxidized to hydroxylamines (R_2NHOH), which are resistant to further oxidation by reaction with dimethyldioxirane[948] or by reaction with benzoyl peroxide and Na_2HPO_4.[949] Oxone on silica also oxidizes secondary alcohols to the hydroxylamine.[950] Hydroxylamines are formed when secondary amines react with the enzyme cyclohexanone monooxygenase.[951] Carbamates, such as *N*-Boc amines, are converted to the *N*-hydroxy compound with *bis*(trifluoromethyl)dioxirane.[952] Dialkylamines are oxidized to the *N*-nitroso compound with N_2O_2 on poly(vinylpyrrolidinone).[953]

OS **III**, 334; **VIII**, 93; **80**, 207.

[937] Rosenblatt, D.H.; Burrows, E.P. in Patai, S. *The Chemistry of Functional Groups*, Supplement F, pt. 2, Wiley, NY, ***1982***, pp. 1085–1149; Challis, B.C.; Butler, A.R. in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 320–338; Hedayatullah, M. *Bull. Soc. Chim. Fr.* ***1972***, 2957.
[938] Holmes, R.R.; Bayer, R.P. *J. Am. Chem. Soc.* ***1960***, *82*, 3454.
[939] Gragerov, I.P.; Levit, A.F. *J. Gen. Chem. USSR* ***1960***, *30*, 3690.
[940] Dewkar, G.K.; Nikalje, M.D.; Ali, I.S.; Paraskar, A.S.; Jagtap, H.S.; Sadalai, A. *Angew. Chem. Int. Ed.* ***2001***, *40*, 405.
[941] Dirk, S.M.; Mickelson, E.T.; Henderson, J.C.; Tour, J.M. *Org. Lett.* ***2002***, *2*, 3405.
[942] Corey, E.J.; Gross, A.W. *Org. Synth. 65*, 166.
[943] Frazier, C.P.; Bugarin, A.; Engelking, J.R.; de Alaniz, J.R. *Org. Lett.* ***2012***, *14*, 3620.
[944] Yu, J.; Cao, X.; Lu, M. *Tetrahedron Lett.* ***2014***, *55*, 5751.
[945] Wertz, S.; Studer, A. *Helv. Chim. Acta* ***2012***, *95*, 1758.
[946] See Kahr, K.; Berther, C. *Chem. Ber.* ***1960***, *93*, 132.
[947] Potturi, H.K.; Gurung, R.K.; Hou, Y. *J. Org. Chem.* ***2012***, *77*, 626.
[948] Murray, R.W.; Singh, M. *Synth. Commun.* ***1989***, *19*, 3509. See Wittman, M.D.; Halcomb, R.L.; Danishefsky, S.J. *J. Org. Chem.* ***1990***, *55*, 1981.
[949] Biloski, A.J.; Ganem, B. *Synthesis* ***1983***, 537.
[950] Fields, J.D.; Kropp, P.J. *J. Org. Chem.* ***2000***, *65*, 5937.
[951] Colonna, S.; Pironti, V.; Carrea, G.; Pasta, P.; Zambianchi, F. *Tetrahedron* ***2004***, *60*, 569.
[952] Detomaso, A.; Curci, R. *Tetrahedron Lett.* ***2001***, *42*, 755.
[953] Iranpoor, N.; Firouzabadi, H.; Pourali, A.R. *Synthesis* ***2003***, 1591.

Tertiary alkyl primary amines can be oxidized to nitro compounds in excellent yields with $KMnO_4$.[954] All classes of primary amine (including primary, secondary, and tertiary alkyl as well as aryl) are oxidized to nitro compounds in high yields with dimethyldioxirane.[955] Other reagents that oxidize various types of primary amines to nitro compounds are dry ozone,[956] peroxyacids,[957] $MeReO_3/H_2O_2$,[958] Oxone,[959] and sodium perborate.[960] An aqueous solution of fluorine oxidizes amino esters to α-nitro esters.[961]

Dimethyldioxirane in wet acetone oxidizes isocyanates to nitro compounds ($RNCO \rightarrow RNO_2$).[962] Oximes can be oxidized to nitro compounds with peroxytrifluoroacetic acid, or with sodium perborate,[963] among other ways.[954] Secondary hydroxylamines are also oxidized to nitrones with MnO_2 in dichloromethane.[964] Primary and secondary alkyl azides have been converted to nitro compounds by treatment with Ph_3P followed by ozone.[965] Aromatic nitroso compounds are easily oxidized to nitro compounds by many oxidizing agents.[966]

Secondary amines were oxidized to nitrones using a Mo catalyst.[967] Tertiary and secondary amines were oxidized to their corresponding *N*-oxides and nitrones, respectively, by reaction with trichloroacetonitrile–hydrogen peroxide.[968] An Ir-catalyzed reaction of *N*-hydroxyamides with $(Me_2HSi)_2O$ gave functionalized nitrones.[969] Magnetically separable tungstophosphoric acid-supported silica-encapsulated γ-Fe_2O_3 nanoparticles have been used for the oxidation of amines to nitrones.[970] Primary amines were oxidized to oximes using O_2 and 1,1-diphenyl-2-picrylhydrazyl, with WO_3/Al_2O_3 as catalysts.[971] The mcpba-mediated conversion of aliphatic amines to oximes was reported.[972]

Primary azides were oxidized to nitriles using aqueous TBHP and a catalytic amount of KI.[973]

OS **III**, 334; **V**, 367, 845; **VI**, 803; **81**, 204.

[954] Larson, H.O. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Vol. 1, Wiley, NY, ***1969***, pp. 306–310. See also, Barnes, M.W.; Patterson, J.M. *J. Org. Chem.* ***1976***, *41*, 733. For reviews, see Butler, R.N. *Chem. Rev.* ***1984***, *84*, 249; Boyer, J.H. *Chem. Rev.* ***1980***, *80*, 495.
[955] Murray, R.W.; Rajadhyaksha, S.N.; Mohan, L. *J. Org. Chem.* ***1989***, *54*, 5783. See also, Zabrowski, D.L.; Moorman, A.E.; Beck Jr., K.R. *Tetrahedron Lett.* ***1988***, *29*, 4501.
[956] See Keinan, E.; Mazur, Y. *J. Org. Chem.* ***1977***, *42*, 844.
[957] See Liu, J.; Li, J.; Ren, J.; Zeng, B.-B. *Tetrahedron Lett.* ***2014***, *55*, 1581.
[958] See Cardona, F.; Soldaini, G.; Goti, A. *Synlett* ***2004***, 1553.
[959] Webb, K.S.; Seneviratne, V. *Tetrahedron Lett.* ***1995***, *36*, 2377.
[960] McKillop, A.; Tarbin, J.A. *Tetrahedron* ***1987***, *43*, 1753.
[961] Harel, T.; Rozen, S. *J. Org. Chem.* ***2007***, *72*, 6500.
[962] Eaton, P.E.; Wicks, G.E. *J. Org. Chem.* ***1988***, *53*, 5353.
[963] Olah, G.A.; Ramaiah, P.; Lee, G.K.; Prakash, G.K.S. *Synlett* ***1992***, 337.
[964] Cicchi, S.; Marradi, M.; Goti, A.; Brandi, A. *Tetrahedron Lett.* ***2001***, *42*, 6503.
[965] Corey, E.J.; Samuelsson, B.; Luzzio, F.A. *J. Am. Chem. Soc.* ***1984***, *106*, 3682.
[966] See Boyer, J.H. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Vol. 1, Wiley, NY, ***1969***, pp. 264–265.
[967] Abrantes, M.; Gonçalves, I.S.; Pillinger, M.; Vurchio, C.; Cordero, F.M.; Brandi, A. *Tetrahedron Lett.* ***2011***, *52*, 7079.
[968] Nikbakht, F.; Heydari, A. *Tetrahedron Lett.* ***2014***, *55*, 2513.
[969] Katahara, S.; Kobayashi, S.; Fujita, K.; Matsumoto, T.; Sato, T.; Chida, N. *J. Am. Chem. Soc.* ***2016***, *138*, 5246.
[970] Nikbakht, F.; Heydari, A.; Saberi, D.; Azizi, K. *Tetrahedron Lett.* ***2013***, *54*, 6520.
[971] Suzuki, K.; Watanabe, T.; Murahashi, S.-i. *J. Org. Chem.* ***2013***, *78*, 2301.
[972] Patil, V.V.; Gayakwad, E.M.; Shankarling, G.S. *J. Org. Chem.* ***2016***, *81*, 781.
[973] Lamani, M.; Devadig, P.; Prabhu, K.R. *Org. Biomol. Chem.* ***2012***, *10*, 2753.

19-28 Oxidation of Tertiary Amines to Amine Oxides

$$R_3N \xrightarrow{H_2O_2} R_3\overset{+}{N}{-}O^-$$

Tertiary amines can be converted to amine oxides by oxidation. Hydrogen peroxide is often used, but peroxyacids are also important reagents for this purpose. Pyridine and its derivatives are oxidized by peroxyacids[974] rather than hydrogen peroxide. Note, however, that urea/H_2O_2 in formic acid does indeed oxidize pyridine.[975] Oxidation with *Caro's acid* has been shown to proceed via attack of the amine on the electrophilic oxygen of $^-O_3S{-}O{-}OH$ (the OH unit).[976] This mechanism is the same as that in the previous section; the products differ only because tertiary amine oxides cannot be further oxidized. The mechanism with other peroxyacids is probably the same. A green procedure for oxidation of tertiary amines has been developed, using a Mg/Al complex with aqueous hydrogen peroxide.[977] Nitrones can be prepared using a ball-mill.[978]

An alternative oxidation using O_2 and a $RuCl_3$ catalyst converted pyridine to pyridine *N*-oxide.[979] Bromamine-T and $RuCl_3$ in aqueous acetonitrile also oxidizes pyridine to the *N*-oxide.[980] Tertiary amines are oxidized to the *N*-oxide with O_2 and Fe_2O_3 in the presence of an aliphatic aldehyde.[981] Oxygen and a Co/Schiff base complex also oxidizes tertiary amines, including pyridine.[982] Bifunctional organocatalysts have been used for the enantioselective synthesis of axially chiral isoquinoline *N*-oxides.[983] Isoxazoline *N*-oxides have been prepared by reaction with hypervalent iodine compounds.[984]

Analogous to the oxidation of tertiary amines, tertiary phosphines are oxidized to phosphine oxides ($R_3P{=}O$). Triphenylphosphine is converted to triphenylphosphine oxide with N_2O at 100 °C, for example. Triphenylphosphine is also oxidized with PhIO on Montmorillonite K-10.[985] *tert*-Butylhydroperoxide oxidizes $Ph_3P{\rightarrow}BH_3$ to $Ph_3P{=}O$.[986] *P*-Stereogenic phosphine oxides have been prepared.[987] 1,1-Diethoxyalkylphosphinates reacted with bromine and an alcohol or an amine to give phosphonates or phosphonamides.[988] Tertiary phosphines reacted with Selectfluor in aqueous acetonitrile to give tertiary phosphine oxides, phosphinates, and phosphonates.[989]

OS **IV**, 612, 704, 828; **VI**, 342, 501; **VIII**, 87.

[974] Albini, A.; Pietra, S. *Heterocyclic N-Oxides*, CRC Press, Boca Raton, FL, ***1991***, pp. 31–41; Katritzky, A.R.; Lagowski, J.M. *Chemistry of the Heterocyclic N-Oxides*, Academic Press, NY, ***1971***, pp. 21–72, 539–542.
[975] Balicki, R.; Golinski, J. *Synth. Commun.* ***2000***, *30*, 1529.
[976] Ogata, Y.; Tabushi, I. *Bull. Chem. Soc. Jpn.* ***1958***, *31*, 969.
[977] Choudary, B.M.; Bharathi, B.; Reddy, Ch.V.; Kantam, M.L.; Raghavan, K.V. *Chem. Commun.* ***2001***, 1736.
[978] Colacino, E.; Nun, P.; Maria Colacino, F.; Martinez, J.; Lamaty, F. *Tetrahedron* ***2008***, *64*, 5569.
[979] Jain, S.L.; Sain, B. *Chem. Commun.* ***2002***, 1040.
[980] Sharma, V.B.; Jain, S.L.; Sain, B. *Tetrahedron Lett.* ***2004***, *45*, 4281.
[981] Wang, F.; Zhang, H.; Song, G.; Lu, X. *Synth. Commun.* ***1999***, *29*, 11.
[982] Jain, S.L.; Sain, B. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1265.
[983] Miyaji, R.; Asano, K.; Matsubara, S. *J. Am. Chem. Soc.* ***2015***, *137*, 6766.
[984] Raihan, M.J.; Kavala, V.; Habib, P.M.; Guan, Q.-Z.; Kuo, C.-W.; Yao, C.-F. *J. Org. Chem.* ***2011***, *76*, 424.
[985] Mielniczak, G.; Lopusinski, A. *Synlett* ***2001***, 505.
[986] Uziel, J.; Darcel, C.; Moulin, D.; Bauduin, C.; Juge, S. *Tetrahedron: Asymmetry* ***2001***, *12*, 1441.
[987] Bergin, E.; O'Connor, C.T.; Robinson, S.B.; McGarrigle, E.M.; O'Mahony, C.P.; Gilheany, D.G. *J. Am. Chem. Soc.* ***2007***, *129*, 9566.
[988] Yao, Q.; Yuan, C. *J. Org. Chem.* ***2012***, *77*, 10985.
[989] Chen, Q.; Zeng, J.; Yan, X.; Huang, Y.; Du, Z.; Zhang, K.; Wen, C. *Tetrahedron Lett.* ***2016***, *57*, 3379.

19-29 Oxidation of Thiols and Other Sulfur Compounds to Sulfonic Acid Derivatives

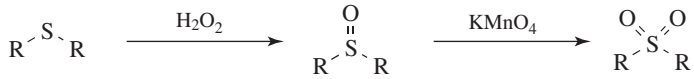
$$RSH \xrightarrow{HNO_3} RSO_3H$$

Thiols, sulfoxides, sulfones, disulfides,[990] and other sulfur compounds can be oxidized to sulfonic acids with various oxidizing agents, but for synthetic purposes the reaction is most important for thiols.[991] Among oxidizing agents used are boiling nitric acid, barium permanganate, and dimethyl dioxirane.[992] Autoxidation (oxidation by atmospheric oxygen) can be accomplished in basic solution.[993] Oxidation of thiols with chlorine and water gives sulfonyl chlorides directly.[994] Thiols can also be oxidized to disulfides (**19-33**).

In another oxidation reaction, primary alkyl aryl sulfones were oxidized to the corresponding carboxylic acids via double deprotonation by reaction with a base, followed by subsequent exposure to atmospheric oxygen.[995]

OS **II**, 471; **III**, 226. Also see, OS **V**, 1070.

19-30 Oxidation of Thioethers to Sulfoxides and Sulfones



Thioethers can be oxidized to sulfoxides[996] by 1 equivalent of 30% H_2O_2 or by many other oxidizing agents,[997] including H_2O_2 and Sc,[998] $MeReO_3$,[999] Ti,[1000] Cu,[1001] Zn,[1002] sulfamic acids,[1003] 2,2,2-trifluoroacetophenone,[1004] cyanuric chloride/urea,[1005] diselenide/

[990] See Savige, W.E.; Maclaren, J.A. in Kharasch, N.; Meyers, C.Y. *Organic Sulfur Compounds*, Vol. 2; pp. 367–402, Pergamon, NY, ***1966***.

[991] See Capozzi, G.; Modena, G. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 785–839; Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 217–239.

[992] Gu, D.; Harpp, D.N. *Tetrahedron Lett.* ***1993***, *34*, 67. See Ballistreri, F.P.; Tomaselli, G.A.; Toscano, R.M. *Tetrahedron Lett.* ***2008***, *49*, 3291.

[993] Wallace, T.J.; Schriesheim, A. *Tetrahedron* ***1965***, *21*, 2271.

[994] See Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 202–214.

[995] Bonaparte, A.C.; Betush, M.P.; Panseri, B.M.; Mastarone, D.J.; Murphy, R.K.; Murphree, S.S. *Org. Lett.* ***2011***, *13*, 1447.

[996] Yamamoto, T.; Dai, J.; Jacobsen, N.E.; Ammam, M.; Hall, G.B.; Mozziconacci, O.; Schöneich, C.; Wilson, G.S.; Glass, R.S. *Org. Lett.* ***2016***, *18*, 3522.

[997] See Hudlicky, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 252–263; Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 233–378 (pp. 235–255); Madesclaire, M. *Tetrahedron* ***1986***, *42*, 5459; Drabowicz, J.; Mikolajczyk, M. *Org. Prep. Proced. Int.* ***1982***, *14*, 45; Holland, H.L. *Chem. Rev.* ***1988***, *88*, 473.

[998] Matteucci, M.; Bhalay, G.; Bradley, M. *Org. Lett.* ***2003***, *5*, 235.

[999] See Choi, S.; Yang, J.-D.; Ji, M.; Choi, H.; Kee, M.; Ahn, K.-H.; Byeon, S.-H.; Baik, W.; Koo, S. *J. Org. Chem.* ***2001***, *66*, 8192.

[1000] See Kon, Y.; Yokoi, T.; Yoshioka, M.; Tanaka, S.; Uesaka, Y.; Mochizuki, T.; Sato, K.; Tatsumi, T. *Tetrahedron* ***2014***, *70*, 7584.

[1001] Gogoi, P.; Kalita, M.; Bhattacharjee, T.; Barman, P. *Tetrahedron Lett.* ***2014***, *55*, 1028.

[1002] Wu, X.-F. *Tetrahedron Lett.* ***2012***, *53*, 4328.

[1003] Jafari, H.; Rostami, A.; Ahmad-Jangi, F.; Chorbani-Choghamarani, A. *Synth. Commun.* ***2012***, *42*, 3150.

[1004] Voutyritsa, E.; Triandafillidi, I.; Kokotos, C.G. *Synthesis* ***2017***, *49*, 917.

[1005] Jeon, H.B.; Kim, K.T.; Kim, S.H. *Tetrahedron Lett.* ***2014***, *55*, 3905.

urea,[1006] Cr,[1007] or V as catalyst.[1008] Other catalysts include $NaIO_4$,[1009] HIO_3/wet SiO_2,[1010] dioxiranes,[1011] graphite oxide,[1012] O_2 and a ceric ammonium nitrate catalyst,[1013] $H_5IO_6/FeCl_3$,[1014] Au/Mn,[1015] thiourea dioxide,[1016] Ag/*t*-BuOOH,[1017] aminotetrazoles/H_2O,[1018] Bi/*t*-BuOOH,[1019] calcium hypobromite,[1020] flavin/O_2,[1021] polymer-anchored Cu,[1022] pyridinium bromide perbromide/*tert*-butyl nitrite/air,[1023] peroxotungten complex,[1024] hypervalent iodine compounds,[1025] cetyltrimethylammonium periodate,[1026] and peroxyacids.[1027] Sulfides were oxidized to sulfoxides using a bifunctional ionic liquid, [pmim] IO_4.[1028] Immobilized taurine and homotaurine in aqueous media were used to oxidize sulfides to sulfoxides.[1029] A vitamin B2 organocatalyst has been used.[1030] Sulfides reacted with 1.1 equivalents of $PhI(OAc)_2$ and a TsOH catalyst to give the sulfoxide in aqueous solution, whereas sulfones were formed by treatment with 2.1 equivalents of $PhI(OAc)_2$.[1031]

When the oxidizing agent is a peroxide, the mechanism[1032] of oxidation to the sulfoxide is similar to that of **19-28**, and the sulfide sulfur attacks the electrophilic O of R′OOH to give R_2S^+—OH, which loses R′OH to give the sulfoxide.[1033] The second oxidation to the sulfone, which is normally slower than the first (which is why sulfoxides are so easily isolable), has the same mechanism in neutral or acid solution, but in basic solution it has been shown that the conjugate base of the peroxy compound ($R'OO^-$) also attacks the SO group as a nucleophile, and loss of $R'O^-$ leads to the sulfone.[1034] It is possible to oxidize

[1006] Bulman Page, P.C.; Buckley, B.R.; Elliott, C.; Chan, Y.; Dreyfus, N.; Marken, F. *Synlett* ***2016***, *27*, 80.
[1007] Afrasiabi, R.; Farsani, M.R.; Yadollahi, B. *Tetrahedron Lett.* ***2014***, *55*, 3923.
[1008] Hussain, S.; Talukdar, D.; Bharadwaj, S.K.; Chaudhuri, M.K. *Tetrahedron Lett.* ***2012***, *53*, 6512.
[1009] See Varma, R.S.; Saini, R.K.; Meshram, H.M. *Tetrahedron Lett.* ***1997***, *38*, 6525.
[1010] Lakouraj, M.M.; Tajbakhsh, M.; Shirini, F.; Asady Tamami, M.V. *Synth. Commun.* ***2005***, *35*, 775.
[1011] Colonna, S.; Gaggero, N. *Tetrahedron Lett.* ***1989***, *30*, 6233. For the mechanism, see González-Núñez, M.E.; Mello, R.; Royo, J.; Ríos, J.V.; Asensio, G. *J. Am. Chem. Soc.* ***2002***, *124*, 9154.
[1012] Dreyer, D.R.; Jia, H.-P.; Todd, A.D.; Geng, J.; Bielawshi, C.W. *Org. Biomol. Chem.* ***2011***, *9*, 7292.
[1013] See Ali, M.H.; Kriedelbaugh, D.; Wencewicz, T. *Synthesis* ***2007***, 3507.
[1014] Kim, S.S.; Nehru, K.; Kim, S.S.; Kim, D.W.; Jung, H.C. *Synthesis* ***2002***, 2484.
[1015] Taketoshi, A.; Concepción, P.; García, H.; Corma, A.; Haruta, M. *Bull. Chem. Soc. Jpn.* ***2013***, *86*, 1412.
[1016] Kumar, S.; Verma, S.; Jain, S.L.; Sain, B. *Tetrahedron Lett.* ***2011***, *52*, 3393.
[1017] Das, R.; Chakraborty, D. *Synthesis* ***2011***, *43*, 277.
[1018] Secci, F.; Arca, M.; Frongia, A.; Piras, P.P. *New J. Chem.* ***2014***, 3622.
[1019] Malik, P.; Chakraborty, D. *Tetrahedron Lett.* ***2012***, *53*, 5652.
[1020] Pace, V.; Castoldi, L.; Holzer, W. *Tetrahedron Lett.* ***2012***, *53*, 967.
[1021] See Imada, Y.; Kitagawa, T.; Iwata, S.; Komiya, N.; Naota, T. *Tetrahedron* ***2014***, *70*, 495.
[1022] Islam, S.M.; Roy, A.S.; Mondal, P.; Tuhina, K.; Mobarak, M.; Mondal, J. *Tetrahedron Lett.* ***2012***, *53*, 127.
[1023] Zhang, H.; Wang, G. *Tetrahedron Lett.* ***2014***, *55*, 56.
[1024] Das, S.P.; Boruah, J.J.; Chetry, H.; Islam, N.S. *Tetrahedron Lett.* ***2012***, *53*, 1163.
[1025] See Koposov, A.Y.; Zhdankin, V.V. *Synthesis* ***2005***, 22.
[1026] Chaudhari, U.V.; Doata, P.T. *Org. Prep. Proceed. Int.* ***2012***, *44*, 381.
[1027] See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, p. 16.
[1028] Ahammed, S.; Kundu, D.; Siddiqui, M.N.; Ranu, B.C. *Tetrahedron Lett.* ***2015***, *56*, 335.
[1029] Shen, H.-M.; Zhou, W.-J.; Wu, H.-K.; Yu, W.-B.; Ai, N.; Ji, H.-B.; Shi, H.-X.; She, Y.-B. *Tetrahedron Lett.* ***2015***, *56*, 4494.
[1030] Imada, Y.; Tonomura, I.; Komiya, N.; Naota, T. *Synlett* ***2013***, *24*, 1679; Imada, Y.; Takagishi, M.; Komiya, N.; Naota, T. *Synth. Commun.* ***2013***, *43*, 3064.
[1031] Yu, B.; Guo, C.-X.; Zhong, C.-L.; Diao, Z.-F.; He, L.-N. *Tetrahedron Lett.* ***2014***, *55*, 1818.
[1032] See Agarwal, A.; Bhatt, P.; Banerji, K.K. *J. Phys. Org. Chem.* ***1990***, *3*, 174; Lee, D.G.; Chen, T. *J. Org. Chem.* ***1991***, *56*, 5346.
[1033] Modena, G.; Todesco, P.E. *J. Chem. Soc.* ***1962***, 4920, and references cited therein.
[1034] Curci, R.; Di Furia, F.; Modena, G. *J. Chem. Soc., Perkin Trans. 2* ***1978***, 603 and references cited therein. See also, Akasaka, T.; Ando, W. *J. Chem. Soc., Chem. Commun.* ***1983***, 1203.

a thioether to a sulfoxide in the presence of an alcohol moiety using MnO_2/HCl.[1035] *N*-Sulfonyloxaziridines can be used to oxidize sulfides to sulfoxides.[1036]

Selenides (R_2Se) can be oxidized to selenoxides and selenones.[1037]

Sulfoxides can be further oxidized to sulfones by another equivalent of H_2O_2, $KMnO_4$, sodium perborate, or a number of other agents. If enough oxidizing agent is present, thioethers can be directly converted to sulfones without isolation of the sulfoxides.[1038] Thioethers can be oxidized directly to the sulfone by treatment with H_2O_2[1039] and a Fe,[1040] Zr,[1041] Ta,[1042] V,[1043] Au,[1044] Mo,[1045] or urea catalyst.[1046] In addition, TPAP,[1047] a flavin/ionic liquid catalyst,[1048] or peroxy monosulfate and a Mn catalyst[1049] can be used. These reactions give high yields, and many functional groups do not interfere.[1050] There are some reagents that oxidize sulfoxides in preference to sulfides, for example, $NaMnO_4$.[1051]

As with tertiary amines (**19-28**), racemic thioethers can be kinetically resolved by oxidation to sulfoxides with an optically active reagent, and this has often been done.[1052] In addition, the use of chiral additives in conjunction with various oxidizing agents leads to chiral nonracemic sulfoxides with good-to-excellent enantioselectivity.[1053] Asymmetric oxidation using bacterial monooxygenases is known,[1054] and horseradish peroxidase gives modest enantioselectivity.[1055] Chiral sulfur reagents are also known.[1056] Oxidation to give chiral sulfoxides with good enantioselectivity has been reported using confined chiral Brønsted acids,[1057] Mn,[1058] Ti,[1059] Ru/mcpba,[1060] Fe/porphyrin/

[1035] Gabbi, C.; Ghelfi, F.; Grandi, R. *Synth. Commun.* ***1997***, *27*, 2857.
[1036] See Jennings, W.B.; O'Shea, J.H.; Schweppe, A. *Tetrahedron Lett.* ***2001***, *42*, 101.
[1037] See Reich, H.J. in Trahanovsky, W.S. *Oxidations in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 7–13; Kobayashi, M.; Ohkubo, H.; Shimizu, T. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 503.
[1038] See Schank, K. in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 165–231 (pp. 205–213).
[1039] Kaczorowska, K.; Kolarska, Z.; Mitka, K.; Kowalski, P. *Tetrahedron* ***2005***, *61*, 8315. See Velusamy, S.; Kumar, A.V.; Saini, R.; Punniyamurthy, T. *Tetrahedron Lett.* ***2005***, *46*, 3819.
[1040] Margues, A.; Marin, M.; Ruasse, M.-F. *J. Org. Chem.* ***2001***, *66*, 7588.
[1041] Bahrami, K. *Tetrahedron Lett.* ***2006***, *47*, 2009.
[1042] Kirihara, M.; Yamamoto, J.; Noguchi, T.; Hirai, Y. *Tetrahedron Lett.* ***2009***, *50*, 1180.
[1043] Trivedi, R.; Lalitha, P. *Synth. Commun.* ***2006***, *36*, 3777.
[1044] Yuan, Y.; Bian, Y. *Tetrahedron Lett.* ***2007***, *48*, 8518.
[1045] See Gamelas, C.A.; Lourenço, T.; da Costa, A.P.; Simplício, A.L.; Royo, B.; Romão, C.C. *Tetrahedron Lett.* ***2008***, *49*, 4708.
[1046] Balicki, R. *Synth. Commun.* ***1999***, *29*, 2235.
[1047] Guertin, K.R.; Kende, A.S. *Tetrahedron Lett.* ***1993***, *34*, 5369.
[1048] Lindén, A.A.; Johansson, M.; Hermanns, N.; Bäckvall, J.-E. *J. Org. Chem.* ***2006***, *71*, 3849.
[1049] Iranpoor, N.; Mohajer, D.; Rezaeifard, A.-R. *Tetrahedron Lett.* ***2004***, *45*, 3811.
[1050] See Venier, C.G.; Barager III, H.J. *Org. Prep. Proced. Int.* ***1974***, *6*, 77 (pp. 85–86).
[1051] See Henbest, H.B.; Khan, S.A. *Chem. Commun.* ***1968***, 1036.
[1052] For reviews, see Kagan, H.B.; Rebiere, F. *Synlett* ***1990***, 643; Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. *Org. Prep. Proceed. Int.* ***1982***, *14*, 45 (see p. 288).
[1053] See Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* ***2007***, *129*, 8940; del Río, R.E.; Wang, B.; Achab, S.; Bohé, L. *Org. Lett.* ***2007***, *9*, 2265; Yamaguchi, T.; Matsumoto, K.; Saito, B.; Katsuki, T. *Angew. Chem. Int. Ed.* ***2007***, *46*, 4729; Matsumoto, K.; Yamaguchi, T.; Katsuki, T. *Chem. Commun.* ***2008***, 1704; Jurok, R.; Cibulka, R.; Dvořáková, H.; Hampl, F.; Hodačová, J. *Eur. J. Org. Chem.* ***2010***, 5217.
[1054] See Colonna, S.; Gaggero, N.; Pasta, P.; Ottolina, G. *Chem. Commun.* ***1996***, 2303.
[1055] Ozaki, S.-i.; Watanabe, S.; Hayasaka, S.; Konuma, M. *Chem. Commun.* ***2001***, 1654.
[1056] Mikolajczyk, M.; Drabowicz, J.; Kielbasinski, P. *Chiral Sulfur Reagents*, CRC Press, Boca Raton, FL, ***1997***.
[1057] Liao, S.; Čorić, I.; Wang, Q.; List, B. *J. Am. Chem. Soc.* ***2012***, *134*, 10765.
[1058] Dai, W.; Li, J.; Chen, B.; Li, G.; Lv, Y.; Wang, L.; Gao, S. *Org. Lett.* ***2013***, *15*, 5658.
[1059] Capozzi, M.A.M.; Centrone, C.; Fracchiolla, G.; Naso, F.; Cardellicchio, C. *Eur. J. Org. Chem.* ***2011***, 4327; Bryliakov, K.P.; Talsi, E.P. *Eur. J. Org. Chem.* ***2011***, 4693.
[1060] Li, Z.-Z.; Yao, S.-Y.; Wu, J.-J.; Ye, B.-H. *Chem. Commun.* ***2014***, *50*, 5644.

H_2O_2,[1061] Ti,[1062] or a Cu catalyst.[1063] Chiral sulfoxides were prepared by the asymmetric alkylation of sulfenate salts with alkyl halides using a chiral phase-transfer catalyst.[1064] Alkyl disulfides give oxidation of one sulfur to give a RS—S(=O)R compound with good enantioselectivity when using aqueous hydrogen peroxide, a catalytic amount of a V catalyst, and a chiral Schiff base ligand.[1065]

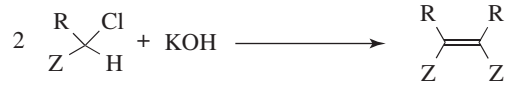
Sulfides were oxidized to the corresponding sulfine by reaction with cyanuric chloride and H_2O_2.[1066]

Selenides were oxidized to selenones by reaction with HOF/MeCN.[1067]

OS **V**, 791; **VI**, 403, 404, 482; **VII**, 453, 491; **VIII**, 464, 543; **IX**, 63; **80**, 190. Also see, OS **V**, 723; **VI**, 23.

E. Oxidative Coupling

19-31 Coupling Involving Carbanions



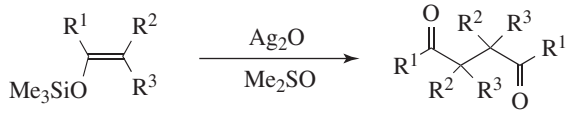
Alkyl halides with an electron-withdrawing group on the halogen-bearing carbon can be dimerized to alkenes by treatment with bases. The Z group may be nitro, aryl, and so on. It is likely that in most cases the mechanism[1068] involves nucleophilic substitution followed by elimination.[1069] α,α-Dibromotoluenes ($ArCHBr_2$) give tolanes ArC≡CAr by debromination of the intermediates ArCBr=CBrAr.[1070] In a related reaction, diarylmethane dihalides (Ar_2CX_2) have been dimerized to tetraaryl alkenes ($Ar_2C{=}CAr_2$) with Cu,[1071] and with iron(II) oxalate dihydrate.[1072]

A somewhat different type of coupling is observed when salts of β-keto esters, arylacetonitriles ($ArCH_2CN$), and other compounds of the form ZCH_2Z' are treated with an oxidizing agent, such as iodine[1073] or Cu(II) salts.[1074] Arylmethanesulfonyl chlorides ($ArCH_2SO_2Cl$) couple to give ArCH=CHAr when treated with Et_3N.[1075]

OS **II**, 273; **IV**, 372, 869, 914; **VIII**, 298. Also see, OS **I**, 46; **IV**, 877.

[1061] Le Maux, P.; Simonneaux, G. *Chem. Commun.* ***2011***, *47*, 6957.
[1062] Gogoi, P.; Kotipalli, T.; Indukuri, K.; Bondalapati, S.; Saha, P.; Saikia, A.K. *Tetrahedron Lett.* ***2012***, *53*, 2726.
[1063] See O'Mahony, G.E.; Eccles, K.S.; Morrison, R.E.; Ford, A.; Lawrence, S.E.; Maguire, A.R. *Tetrahedron* ***2013***, *69*, 10168.
[1064] Gelat, F.; Jayashankaran, J.; Lohier, J.-F.; Gaumont, A.-C.; Perrio, S. *Org. Lett.* ***2011***, *13*, 3170.
[1065] Blum, S.A.; Bergman, R.G.; Ellman, J.A. *J. Org. Chem.* ***2003***, *68*, 150.
[1066] Bahrami, K.; Khodaei, M.M.; Sohrabnezhad, S. *Tetrahedron Lett.* ***2011***, *52*, 6420.
[1067] Potash, S.; Rozen, S. *Eur. J. Org. Chem.* ***2013***, 5574.
[1068] See Saunders Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 548–554.
[1069] See Reisdorf, D.; Normant, H. *Organomet. Chem. Synth.* ***1972***, *1*, 375; Hanna, S.B.; Wideman, L.G. *Chem. Ind. (London)* ***1968***, 486; Bethell, D.; Bird, R. *J. Chem. Soc., Perkin Trans. 2* ***1977***, 1856.
[1070] Vernigor, E.M.; Shalaev, V.K.; Luk'yanets, E.A. *J. Org. Chem. USSR* ***1981***, *17*, 317.
[1071] Buckles, R.E.; Matlack, G.M. *Org. Synth.* ***IV***, 914.
[1072] Khurana, J.M.; Maikap, G.C.; Mehta, S. *Synthesis* ***1990***, 731.
[1073] See Aurell, M.J.; Gil, S.; Tortajada, A.; Mestres, R. *Synthesis* ***1990***, 317.
[1074] Rathke, M.W.; Lindert, A. *J. Am. Chem. Soc.* ***1971***, *93*, 4605; Baudin, J.; Julia, M.; Rolando, C.; Verpeaux, J. *Bull. Soc. Chim. Fr.* ***1987***, 493.
[1075] Nakayama, J.; Tanuma, M.; Honda, Y.; Hoshino, M. *Tetrahedron Lett.* ***1984***, *25*, 4553.

19-32 Dimerization of Silyl Enol Ethers or of Lithium Enolates

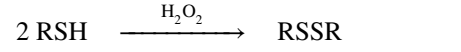


Silyl enol ethers can be dimerized to symmetrical 1,4-diketones by treatment with Ag_2O in DMSO or certain other polar aprotic solvents.[1076] The reaction has been performed with R^2, R^3 = hydrogen or alkyl, although best yields are obtained when $R^2 = R^3 = H$. In certain cases, unsymmetrical 1,4-diketones have been prepared by using a mixture of two silyl enol ethers. Other reagents that have been used to achieve either symmetrical or cross-coupled products are iodosobenzene/BF_3-OEt_2,[1077] ceric ammonium nitrate,[1078] and lead tetraacetate.[1079] If R^1 = OR (in which case the substrate is a ketene silyl acetal), dimerization with $TiCl_4$ leads to a dialkyl succinate (R^1 = OR; above).[1080]

In a similar reaction, lithium enolates, RC(OLi)=CH_2, were dimerized to 1,4-diketones ($RCOCH_2CH_2COR$) with $CuCl_2$, $FeCl_3$, or copper(II) triflate, in a nonprotic solvent.[1081] The V-induced intermolecular cross-coupling of boron enolates and silyl enolates gave unsymmetrical 1,4-diones via an electrophilic carbonyl α-radical species.[1082]

OS **VIII**, 467.

19-33 Oxidation of Thiols to Disulfides



Thiols are easily oxidized to disulfides.[1083] Hydrogen peroxide is the most common reagent,[1084] but many oxidizing agents give the reaction, among them Br_2 on hydrated silica,[1085] SmI_2,[1086] PPh_3/Rh,[1087] a Pd catalyst,[1088] cupric nitrate,[1089] I_2/DMSO,[1090] diaryl tellurides,[1091] O_2 with nanoporous Co,[1092] Se/ionic liquid,[1093] cetyltrimethylammonium

[1076] Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* ***1975***, *97*, 649.
[1077] Moriarty, R.; Prakash, O.; Duncan, M.P. *J. Chem. Soc., Perkin Trans. 1* ***1987***, 559.
[1078] Baciocchi, E.; Casu, A.; Ruzziconi, R. *Tetrahedron Lett.* ***1989***, *30*, 3707.
[1079] Moriarty, R.M.; Penmasta, R.; Prakash, I. *Tetrahedron Lett.* ***1987***, *28*, 873.
[1080] Inaba, S.; Ojima, I. *Tetrahedron Lett.* ***1977***, 2009. See also, Totten, G.E.; Wenke, G.; Rhodes, Y.E. *Synth. Commun.* ***1985***, *15*, 291, 301.
[1081] Frazier Jr., R.H.; Harlow, R.L. *J. Org. Chem.* ***1980***, *45*, 5408.
[1082] Amaya, T.; Maegawa, Y.; Masuda, T.; Osafune, Y.; Hirao, T. *J. Am. Chem. Soc.* ***2015***, *137*, 10072.
[1083] See Capozzi, G.; Modena, G. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 785–839; Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***.
[1084] See, however, Evans, B.J.; Doi, J.T.; Musker, W.K. *J. Org. Chem.* ***1990***, *55*, 2337.
[1085] Ali, M.H.; McDermott, M. *Tetrahedron Lett.* ***2002***, *43*, 6271.
[1086] Zhan, Z.-P.; Lang, K.; Liu, F.; Hu, L.-m. *Synth. Commun.* ***2004***, *34*, 3203.
[1087] Tanaka, K.; Ajiki, K. *Tetrahedron Lett.* ***2004***, *45*, 25.
[1088] Dutta, P.K.; Majumder, A.; Dutta, S.; Dhar, B.B.; Munshi, P.; Sen, S. *Tetrahedron Lett.* ***2017***, *58*, 527.
[1089] Soleiman-Beigi, M.; Taherinia, Z. *Monatsh. Chem.* ***2014***, *145*, 1151.
[1090] Bettanin, L.; Saba, S.; Galetto, F.Z.; Mike, G.A.; Rafique, J.; Braga, A.L. *Tetrahedron. Lett.* ***2017***, *58*, 4713.
[1091] Oba, M.; Tanaka, K.; Nishiyama, K.; Ando, W. *J. Org. Chem.* ***2011***, *76*, 4173.
[1092] Chauhan, D.; Kumar, P.; Joshi, C.; Labhsetwar, N.; Ganguly, S.K.; Jain, S.L. *New J. Chem.* ***2015***, 6193.
[1093] Thurow, S.; Pereira, V.A.; Martinez, D.M.; Alves, D.; Perin, G.; Jacob, R.G.; Lenardão, E.J. *Tetrahedron Lett.* ***2011***, *52*, 640.

dichromate,[1094] and NO. Hydrogen peroxide (30%) in hexafluoropropan-2-ol converts thiols to disulfides,[1095] and solvent-free reactions on MnO_2,[1096] PCC,[1097] or SO_2Cl_2[1098] are also effective. Even oxygen in the air oxidizes thiols on standing, if a small amount of base is present. The reaction is reversible, and the interconversion between cysteine and cystine is an important one in biochemistry. The mechanism has been studied for several oxidizing agents and varies with the agent.[1099]

Unsymmetrical disulfides can be prepared[1100] by treatment of a thiol RSH with diethyl azodicarboxylate (EtOOCN=NCOOEt) to give an adduct, to which another thiol R′SH is then added, producing the disulfide RSSR′.[1101]

The oxidation of thiols to the corresponding disulfide used HBr or HI with dimethyl sulfoxide.[1102] The oxidative coupling of two different thiols with trichloroisocyanuric acid gave the unsymmetrical disulfide.[1103] Thiols were converted to the corresponding homodisulfides by reaction with O_2 and H_2O/Et_2NH.[1104] Unsymmetrical sulfides were prepared by the cross-coupling reaction of aryl/het-aryl/benzyl halides with sulfonyl hydrazides as thiol surrogates by reaction with [DBU][HOAc] and CuI with microwave irradiation.[1105] A mixture of thiols reacted with DDQ to give the corresponding unsymmetrical disulfide.[1106] Aryl iodides reacted with elemental tellurium in the presence of KOH to give the diaryl telluride.[1107] Aryl or alkyl halides reacted with potassium 5-methyl-1,3,4-oxadiazole-2-thiolate in the presence of a Ni catalyst to give symmetrical aryl or alkyl disulfides.[1108] Symmetrical dibenzyl diselenides or disulfides were prepared by reaction of a benzyl alcohol with $NaBH_2Se_3$ or $NaBH_2S_3$ as the selenium-transfer or the sulfur-transfer reagent.[1109]

OS **III**, 86, 116.

19.B.ii. Reductions[1110]

The reactions in this section are classified into groups depending on the type of bond change involved. These groups are (i) attack at carbon (C=C, C≡C, C—O, and C=O), (ii) attack at noncarbonyl multiple bonds to heteroatoms, (iii) reactions in which a heteroatom is removed from the substrate, (iv) reduction with cleavage, (v) reductive coupling, and (vi) reactions in which an organic substrate is both oxidized and reduced. Most of the reagents in this section are metal hydrides, metals with an acid or a protic solvent, hydrogen gas with

[1094] Patel, S.; Mishra, B.K. *Tetrahedron Lett.* ***2004***, *45*, 1371. See also, Tajbakhsh, M.; Hosseinzadeh, R.; Shakoori, A. *Tetrahedron Lett.* ***2004***, *45*, 1889.
[1095] Kesavan, V.; Bonnet-Delpon, D.; Bégué, J.-P. *Synthesis* ***2000***, 223.
[1096] Firouzabadi, H.; Abbassi, M.; Karimi, B. *Synth. Commun.* ***1999***, *129*, 2527.
[1097] Salehi, P.; Farrokhi, A.; Gholizadeh, M. *Synth. Commun.* ***2001***, *31*, 2777.
[1098] Leino, R.; Lönnqvist, J.-E. *Tetrahedron Lett.* ***2004***, *45*, 8489.
[1099] Tarbell, D.S. in Kharasch, N. *Organic Sulfur Compounds*, Pergamon, Elmsford, NY, ***1961***, pp. 97–102.
[1100] Mukaiyama, T.; Takahashi, K. *Tetrahedron Lett.* ***1968***, 5907.
[1101] Also see Boustany, K.S.; Sullivan, A.B. *Tetrahedron Lett.* ***1970***, 3547; Oae, S.; Fukushima, D.; Kim, Y.H. *J. Chem. Soc., Chem. Commun.* ***1977***, 407.
[1102] Natarajan, P.; Sharma, H.; Kaur, M.; Sharma, P. *Tetrahedron Lett.* ***2015***, *56*, 5578.
[1103] Yang, F.; Wang, W.; Li, K.; Zhao, W.; Dong, X. *Tetrahedron Lett.* ***2017***, *58*, 218.
[1104] Abace, M.S.; Mojtahedi, M.; Navidipoor, S. *Synth. Commun.* ***2010–2011***, *41*, 170.
[1105] Singh, N.; Singh, R.; Raghuvanshi, D.S.; Singh, K.N. *Org. Lett.* ***2013***, *15*, 5874.
[1106] Vandavasi, J.K.; Hu, W.-P.; Chen, C.-Y.; Wang, J.-J. *Tetrahedron* ***2011***, *67*, 8895.
[1107] Zhang, S.; Karra, K.; Koe, A.; Jin, J. *Tetrahedron Lett.* ***2013***, *54*, 2452.
[1108] Soleiman-Beigi, M.; Mohammadi, F. *Synlett* ***2015***, *26*, 911.
[1109] Panduranga, V.; Prabhu, G.; Basavaprabhu; Panguluri, N.R.; Sureshbabu, V.V. *Synthesis* ***2016***, *48*, 1711.
[1110] See Willemsen, J.S.; van Hest, J.C.M.; Rutjes, F.P.J.T. *Chem. Commun.* ***2013***, *49*, 3143.

a catalyst, etc. Other reducing agents are available, and will be introduced in the appropriate section. It is noted that plants can be used as reducing agents.[1111]

A. Selectivity[1112]

It is often necessary to reduce one group in a molecule without affecting another reducible group (this is called chemoselectivity), and reducing agents are available that will do this. The most common broad-spectrum reducing agents are the metal hydrides[1113] or hydrogen (with a catalyst).[1114] Many different metal hydride systems and hydrogenation catalysts have been investigated in order to find conditions under which a given group will be reduced chemoselectively. The ease of reduction for various functional groups towards catalytic hydrogenation is acyl halides > alkyl nitro compounds > alkynes > aldehydes > alkenes > ketones > benzylic ethers > nitriles > esters > amides.[1115] A list of the reactivity of various functional groups with $LiAlH_4$ or with BH_3 has been reported.[1115] Table 19.2 shows which groups can be reduced by catalytic hydrogenation or by various metal hydrides.[1116] Of course, the tables cannot be exact, because the nature of R and the reaction conditions obviously affect reactivity. Nevertheless, the tables do give a fairly good indication of which reagents reduce which groups.[1117] $LiAlH_4$ is very powerful and unselective reagent.[1118] Other metal hydrides are generally used when chemoselectivity is required. As will be seen in **19-40**, less reactive (and more selective) reagents have been prepared by replacing some of the hydrogen atoms of $LiAlH_4$ with alkoxy groups.[1119] Most of the metal hydrides are nucleophilic reagents and attack the carbon atom of a carbon-hetero single or multiple bond. However, BH_3[1120,1121] and AlH_3[1122] are electrophiles (Lewis acids) and attack the heteroatom. This accounts for the different patterns of selectivity.

[1111] Bruni, R.; Fantin, G.; Medici, A.; Pedrini, P.; Sacchetti, G. *Tetrahedron Lett.* ***2002***, *43*, 3377.

[1112] See Hudlicky, M. *Reductions in Organic Chemistry*, Wiley, NY, ***1984***; Augustine, R.L. *Reduction*, Marcel Dekker, NY, ***1968***.

[1113] See Brown, H.C.; Krishnamurthy, S. *Tetrahedron* ***1979***, *35*, 567; Walker, E.R.H. *Chem. Soc. Rev.* ***1976***, *5*, 23; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 209–251; Rerick, M.N. in Augustine, R.L. *Reduction*, Marcel Dekker, NY, ***1968***.

[1114] See Rylander, P.N. *Aldrichimica Acta* ***1979***, *12*, 53. See also, Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***.

[1115] See House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, p. 9. Tables 19.2 and 19.3 are from Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 213 and 232, respectively.

[1116] The first 10 columns are from Brown, H.C.; Krishnamurthy, S. *Tetrahedron* ***1979***, *35*, 567, p. 604. The column on $(i\text{-Bu})_2AlH$ is from Yoon, N.M.; Gyoung, Y.S. *J. Org. Chem.* ***1985***, *50*, 2443; the column on $NaAlEt_2H_2$ is from Stinson, S.R. *Chem. Eng. News* ***Nov. 3***, ***1980***, *58*, No. 44, 19; and the column on $LiBEt_3H$ is from Brown, H.C.; Kim, S.C.; Krishnamurthy, S. *J. Org. Chem.* ***1980***, *45*, 1. Also see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, p. 129; Hajós, A. *Complex Hydrides*, Elsevier, NY, ***1979***, pp. 16–17; Hudlicky, M. *Reductions in Organic Chemistry*, Wiley, NY, ***1984***, pp. 177–200.

[1117] See also the table in Hudlicky, M. *J. Chem. Educ.* ***1977***, *54*, 100.

[1118] See Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 101–194.

[1119] See Málek, J. *J. Org. Chem.* ***1988***, *36*, 249; ***1985***, *34*, 1.

[1120] See Brown, H.C.; Heim, P.; Yoon, N.M. *J. Am. Chem. Soc.* ***1970***, *92*, 1637; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 319–371. For reviews of reductions with BH_3, see Wade, R.C. *J. Mol. Catal.* ***1983***, *18*, 273 (BH_3 and a catalyst); Lane, C.F. *Chem. Rev.* ***1976***, *76*, 773; *Aldrichimica Acta* ***1977***, *10*, 41; Brown, H.C.; Krishnamurthy, S. *Aldrichimica Acta* ***1979***, *12*, 3. For reviews of reduction with borane derivatives, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 125–164; Pelter, A. *Chem. Ind. (London)* ***1976***, 888.

[1121] Reacts with solvent, reduced in aprotic solvents.

[1122] Reduced to an aldehyde (**19-48**).

TABLE 19.2 Reactivity of various functional groups with some metal hydrides and toward catalytic hydrogenation[1116]

	Reaction[a]	A	B	C	D[b]	E[c]	F[d]	G	H	I	J[e]	K[f]	L	M	N
19-39	$RCHO \rightarrow RCH_2OH$	+	+	+	+	+	+	+	+	+	+	+	+	+	+
19-39	$RCOR \rightarrow RCHOHR$	+	+	+	+	+	+	+	+	+	+	+	+	+	+
19-67	$RCOCl \rightarrow RCHO$, $RCOCl \rightarrow RCH_2OH$	+[g]	+	+	−	−	+	+	+	+	+	+	+	+	+
19-67	Lactone → Diol	−	+	+	+	+	+	±	+	+	+	+	+	+	+
19-39	Epoxide → Alcohol	−	+	+	+	±	±	±	+	+	+	+	+	+	+
19-42	$RCO_2R' \rightarrow RCH_2OH + R'OH$	−	+	+	±	−	±	±	+	+	+	+	+	+	+
19-41	$RCO_2H \rightarrow RCH_2OH$	−	−	+	+	−	±	−	+	+	+	−	+	+	−
19-41	$RCO_2^- \rightarrow RCH_2OH$	−	−	+	−	−	−	−	+	+	+	−	−		−
19-68 **19-45**	$RCONR_2' \rightarrow RCH_2NR_2'$, $RCONR_2' \rightarrow RCHO$	−	−	−	−	+	+	+	−	+	+	+	+	+	+
19-47	$RC{\equiv}N \rightarrow RCH_2NH_2$	−	−	−	+	−	±	−	+	+	+	±	+[h]	+	+
19-34	$RCH{=}CHR \rightarrow RCH_2CH_2R$	−	−	−	+	+	+	−	−	−	−	+	−	−	+
19-57	$RX + LiAlH_4 \rightarrow RH$														
19-63	$ROSO_2R' + LiAlH_4 \rightarrow RH$														
19-39	 + $LiAlH_4$ ⟶														

A = $NaBH_4$ in EtOH, **B** = $NaBH_4$ + LiCl in diglyme, **C** = $NaBH_4$ + $AlCl_3$ in diglyme, **D** = BH_3/THF, **E** = bis-3-methyl-2-butylborane (disiamylborane) in THF, **F** = 9-BBN, **G** = $LiAlH(Ot\text{-}Bu)_3$ in THF, **H** = $LiAlH(OMe)_3$ in THF, **I** = $LiAlH_4$ in ether, **J** = AlH_3 in THF, **K** = $LiBEt_3H$, **L** = $(i\text{-}Bu)_2AlH$ [DIBALH], **M** = $NaAl(OCH_2CH_2OMe)_2H_2$, **N** = catalytic hydrogenation.

[a] ±indicates a borderline case; [b] [1116]; [c] [1123]; [d] [1124]; [e] [1125]; [f] [1126]; [g] [1127]; [h] reduced to RCHO; [i] [1128].

Reprinted with permission from Brown, H.C.; Krishnamurthy, S. *Tetrahedron* ***1979****, 35*, 567, p. 604, copyright 1979, with permission from Elsevier Science; reprinted with permission from Yoon, N.M.; Gyoung, Y.S. *J. Org. Chem.* ***1985****, 50*, 2443, copyright 1985, American Chemical Society; reprinted with permission from Brown, H.C.; Kim, S.C.; Krishnamurthy, S. *J. Org. Chem.* ***1980****, 45,* 1, copyright 1980, American Chemical Society.

[1123] Brown, H.C.; Bigley, D.B.; Arora, S.K.; Yoon, N.M. *J. Am. Chem. Soc.* ***1970***, *92*, 7161. For reductions with thexylborane, see Brown, H.C.; Heim, P.; Yoon, N.M. *J. Org. Chem.* ***1972***, *37*, 2942.

[1124] Brown, H.C.; Krishnamurthy, S.; Yoon, N.M. *J. Org. Chem.* ***1976***, *41*, 1778.

[1125] See Yoon, N.M.; Brown, H.C. *J. Am. Chem. Soc.* ***1968***, *90*, 2927.

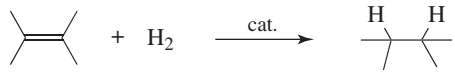
[1126] Brown, H.C.; Kim, S.C.; Krishnamurthy, S. *J. Org. Chem.* ***1980***, *45*, 1. See Brown, H.C.; Singaram, B.; Singaram, S. *J. Organomet. Chem.* ***1982***, *239*, 43.

[1127] See Brown, H.C.; Heim, P.; Yoon, N.M. *J. Am. Chem. Soc.* ***1970***, *92*, 1637; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 319–371. Also see Wade, R.C. *J. Mol. Catal.,* ***1983***, *18*, 273; Lane, C.F. *Chem. Rev.* ***1976***, *76*, 773; *Aldrichimica Acta* ***1977***, *10*, 41; Brown, H.C.; Krishnamurthy, S. *Aldrichimica Acta* ***1979***, *12*, 3; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 125–164; Pelter, A. *Chem. Ind. (London)* ***1976***, 888.

[1128] Reduced to a hydroxylamine (**19-46**).

B. Attack at Carbon (C=C, C≡C, C–O, and C=O)

19-34 Hydrogenation of Double and Triple Bonds[1129]



Most carbon-carbon double bonds, whether substituted by electron-donating or electron-withdrawing substituents, can be catalytically hydrogenated, usually in quantitative or near-quantitative yields.[1130] However, a transition metal catalyst is required to break apart H_2 into metal-bound hydrogen atoms before reaction can occur with the alkene. Almost all known alkenes added hydrogen at temperatures between 0 and 275 °C.[1131] Hydrogenation is generally under thermodynamic control and steric effects play an important role.[1132] The catalysts used can be divided into two broad classes:

1. Catalysts insoluble in the reaction medium (*heterogeneous catalysts*). Among the most effective are Raney nickel,[1133] Pd-on-charcoal,[1134] Co,[1135] Pt metal[1136] or its oxide, Rh, and Ru. The facet-dependent catalysis in the hydrogenation of alkenes was examined using shape-controlled Pd nanocrystals.[1137] It is noted that heterogeneous catalysts are usually poisoned by small amounts of sulfur, which is often found in rubber stoppers, or by thiols and sulfides.[1138]
2. Catalysts soluble in the reaction medium (*homogeneous catalysts*).[1139] Heterocycles such as pyrroles were hydrogenated to chiral 1-pyrrolines using a Pd catalyst and $EtSO_3H$.[1140] An important example is *Wilkinson's*

[1129] See Mitsui, S.; Kasahara, A. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 175–214. Also see, Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 364–389.

[1130] See Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***; *Catalytic Hydrogenation in Organic Synthesis*, Academic Press, NY, ***1979***; Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis*, Wiley, NY, ***1978***; *Practical Catalytic Hydrogenation*, Wiley, NY, ***1971***; Augustine, R.L. *Catalytic Hydrogenation*, Marcel Dekker, NY, ***1965***; Parker, D. in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 979–1047.

[1131] For calculations for heat of hydrogenation of small ring compounds, see Wiberg, K.B. *J. Org. Chem.* ***2012***, *77*, 10393.

[1132] Iwasaki, K.; Wan, K.K.; Oppedisano, A.; Crossley, S.W.M.; Shenvi, R.A. *J. Am. Chem. Soc.* ***2014***, *136*, 1300.

[1133] Pizey, J.S. *Synthetic Reagents*, Vol. 2, Wiley, NY, ***1974***, pp. 175–311; Pojer, P.M. *Chem. Ind. (London)* ***1986***, 177.

[1134] See Chandrasekhar, S.; Narsihmulu, Ch.; Chandrashekar, G.; Shyamsunder, T. *Tetrahedron Lett.* ***2004***, *45*, 2421.

[1135] Friedfeld, M.R.; Shevlin, M.; Margulieux, G.W.; Campeau, L.-C.; Chirik, P.J. *J. Am. Chem. Soc.* ***2016***, *138*, 3314; Zhang, G.; Scott, B.L.; Hanson, S.K. *Angew. Chem. Int. Ed.* ***2012***, *51*, 12102.

[1136] Takahashi, M.; Imaoka, T.; Hongo, Y.; Yamamoto, K. *Angew. Chem. Int. Ed.* ***2013***, *52*, 7419.

[1137] Zhao, X.; Zhao, Y.; Fu, G.; Zheng, N. *Chem. Commun.* ***2015***, *51*, 12016. Also see Mäsing, F.; Nüsse, H.; Klingauf, J.; Studer, A. *Org. Lett.* ***2017***, *19*, 2658.

[1138] Barbier, J.; Lamy-Pitara, E.; Marecot, P.; Boitiaux, J.P.; Cosyns, J.; Verna, F. *Adv. Catal.* ***1990***, *37*, 279–318.

[1139] James, B.R. *Homogeneous Hydrogenation*, Wiley, NY, ***1973***; Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA, ***1987***, pp. 523–564; Birch, A.J.; Williamson, D.H. *Org. React.* ***1976***, *24*, 1; James, B.R. *Adv. Organomet. Chem.* ***1979***, *17*, 319; Harmon, R.E.; Gupta, S.K.; Brown, D.J. *Chem. Rev.* ***1973***, *73*, 21; Rylander, P.N. *Organic Syntheses with Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 60–76.

[1140] Wang, D.-S.; Ye, Z.-S.; Chen, Q.-A.; Zhou, Y.-G.; Yu, C.-B.; Fan, H.-J.; Duan, Y. *J. Am. Chem. Soc.* ***2011***, *133*, 8866.

catalyst[1141] [chlorotris(triphenylphosphine)rhodium, $RhCl(Ph_3P)_3$],[1142] which is tolerant of many functional groups in the same molecule.[1143] Even unsaturated aldehydes can be reduced to saturated aldehydes,[1144] although in this case decarbonylation (**14-26**) is sometimes a side reaction. While homogenous catalysts are generally tolerant of many functional groups, some are susceptible to catalytic reduction. However, it is usually possible to find conditions under which double bonds can be reduced selectively.[1145] Using soluble homogeneous catalysts,[1146] unfunctionalized alkenes are hydrogenated with good selectivity using various metal catalysts. Modification of the catalyst includes a polymer-bound Ru catalyst[1147] and a polymer-incarcerated Pd catalyst.[1148] A nanoparticulate Pd catalyst in an ionic liquid has been used for the hydrogenation of alkenes.[1149]

Homogeneous catalysts[1150] have the advantages of better catalyst reproducibility and better selectivity. Homogeneous catalysts are also less susceptible to catalyst poisoning.[1151] It is noted that heterogeneous catalysts are usually easier to separate from a reaction mixture. Apart from Wilkinson's catalyst, chlorotris(triphenylphosphine)hydridoruthenium(II), $(Ph_3P)_3RuClH$,[1152] is an important homogeneous catalyst that is specific for terminal double bonds. Other double bonds are hydrogenated slowly or not at all.

Hydrogenations are carried out at room temperature and just above atmospheric pressure, in most cases, but some double bonds are more resistant and require higher temperatures and pressures. The poor reactivity is usually a function of increasing substitution and is presumably caused by steric factors since both alkene and hydrogen gas must bind to the catalyst (see below). Trisubstituted double bonds require, say, 25 °C and 100 atm, while tetrasubstituted double bonds may require 275 °C and 1000 atm. Among the double bonds most difficult to hydrogenate or which cannot be hydrogenated at all are those common to two rings. Hydrogenations, even at about atmospheric pressure, are often performed in a special hydrogenator, but this is not always necessary. Indeed, placing a hydrogen-filled balloon over the reaction flask is common for small-scale hydrogenations that do not require heat or pressure. It has been shown that the pressure of the reaction can influence enantioselectivity in asymmetric catalytic hydrogenations.[1153]

[1141] See Jardine, F.H. *Prog. Inorg. Chem.* ***1981***, *28*, 63–202.
[1142] See van Bekkum, H.; van Rantwijk, F.; van de Putte, T. *Tetrahedron Lett.* ***1969***, 1.
[1143] Harmon, R.E.; Parsons, J.L.; Cooke, D.W.; Gupta, S.K.; Schoolenberg, J. *J. Org. Chem.* ***1969***, *34*, 3684. See also, Mohrig, J.R.; Dabora, S.L.; Foster, T.F.; Schultz, S.C. *J. Org. Chem.* ***1984***, *49*, 5179.
[1144] Jardine, F.H.; Wilkinson, G. *J. Chem. Soc. C* ***1967***, 270.
[1145] See Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 59–120. Also see, Hudlicky, M. *Reductions in Organic Chemistry*, Ellis Horwood Ltd., Chichester, ***1984***.
[1146] Eisenstein, O.; Crabtree, R.H. *New J. Chem.* ***2013***, 21.
[1147] Taylor, R.A.; Santora, B.P.; Gagné, M.R. *Org. Lett.* ***2000***, *2*, 1781.
[1148] Okamoto, K.; Akiyama, R.; Kobayashi, S. *J. Org. Chem.* ***2004***, *69*, 2871. See also, Bremeyer, N.; Ley, S.V.; Ramarao, C.; Shirley, I.M.; Smith, S.C. *Synlett* ***2002***, 1843.
[1149] Huang, J.; Jiang, T.; Han, B.; Gao, H.; Chang, Y.; Zhao, G.; Wu, W. *Chem. Commun.* ***2003***, 1654.
[1150] Bennie, L.S.; Fraser, C.J.; Irvine, S.; Kerr, W.J.; Andersson, S.; Nisson, G.N. *Chem. Commun.* ***2011***, *47*, 11653.
[1151] Birch, A.J.; Walker, K.A.M. *Tetrahedron Lett.* ***1967***, 1935.
[1152] Hallman, P.S.; McGarvey, B.R.; Wilkinson, G. *J. Chem. Soc. A* ***1968***, 3143; Jardine, F.H.; McQuillin, F.J. *Tetrahedron Lett.* ***1968***, 5189.
[1153] Sun, Y.; Landau, R.N.; Wang, J.; LeBlond, C.; Blackmond, D.G. *J. Am. Chem. Soc.* ***1996***, *118*, 1348.

Ligand development[1154] has been an important area of research that impacts homogeneous catalysts, especially enantioselective reactions,[1155] and ligands are used with many transition metals, including Ir,[1156] Co,[1157] Ni,[1158] Rh,[1159] Ru,[1160] Os,[1161] Au,[1162] Pd,[1163] or Zr.[1164] The chiral transition metal catalyst (Rh and Ru are probably the most common) is usually prepared with suitable chiral ligands[1165] prior to addition to the reaction. Alternatively, an achiral catalyst such as *Wilkinson's catalyst* is simply added along with a chiral ligand. With monophosphine chiral ligands,[1166] the phosphorus may be chiral but pyramidal inversion at elevated temperatures (Sec. 4.C) limits the utility of such ligands. Examples are R-camp, which is cyclohexyl(2-methoxyphenyl)(methyl)phosphane,[1167] and dipamp, which is 1,2-bis((2-methoxyphenyl)(phenyl)phosphaneyl)ethane.[1168] The alternative is to prepare phosphines that contain a chiral carbon, as in ((2*S*,3*S*)-butane-2,3-diyl)bis(diphenylphosphane) (known as Chiraphos),[1169] but there are many variations of chiral bis(phosphine) ligands.[1170] Chiral poisoning has been used as a strategy for asymmetric catalysis.[1171] Ionic liquids have been used for catalytic hydrogenation.[1172]

[1154] Pàmies, O.; Diéguez, M.; Andersson, P.G. *Chem. Rev.* ***2014***, *114*, 2130; Lindqvist, M.; Borre, K.; Axenov, K.; Kótai, B.; Nieger, M.; Leskelä, M.; Pápai, I.; Repo, T. *J. Am. Chem. Soc.* ***2015***, *137*, 4038; Vallianatou, K.A.; Frank, D.J.; Antonopoulou, G.; Georgakopoulos, S.; Siapi, E.; Zervou, M.; Kostas, I.D. *Tetrahedron Lett.* ***2013***, *54*, 397; Schumacher, A.; Bernasconi, M.; Pfaltz, A. *Angew. Chem. Int. Ed.* ***2013***, *52*, 7422; Chen, Z.; Guan, Z.; Li, M.; Yang, Q.; Li, C. *Angew. Chem. Int. Ed.* ***2011***, *50*, 4913; Passays, J.; Ayad, T.; Ratovelomanana-Vidal, V.; Gaumont, A.-C.; Jubault, P.; Leclerc, E. *Tetrahedron: Asymmetry* ***2011***, *22*, 562; Zhao, Y.; Huang, H.; Shao, J.; Xia, C. *Tetrahedron: Asymmetry* ***2011***, *22*, 769.

[1155] Cui, X.; Burgess, K. *Chem. Rev.* ***2005***, *105*, 3272; Woodmansee, D.H.; Pfaltz, A. *Chem. Commun.* ***2011***, *47*, 7912.

[1156] Roseblade, S.J.; Pfaltz, A. *Acc. Chem. Res.* ***2007***, *40*, 1402; Mazuela, J.; Norrby, P.-O.; Andersson, P.G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* ***2011***, *133*, 13634; Chen, L.-A.; Xu, W.; Huang, B.; Ma, J.; Wang, L.; Xi, J.; Harms, K.; Gong, L.; Meggers, E. *J. Am. Chem. Soc.* ***2013***, *135*, 10598; Rageot, D.; Woodmansee, D.H.; Pugin, B.; Pfaltz, A. *Angew. Chem. Int. Ed.* ***2011***, *50*, 9598.

[1157] Zhang, G.; Vasudevan, K.V.; Scott, B.L.; Hanson, S.K. *J. Am. Chem. Soc.* ***2013***, *135*, 8668; Friedfeld, M.R.; Margulieux, G.W.; Schaefer, B.A.; Chirik, P.J. *J. Am. Chem. Soc.* ***2014***, *136*, 13178.

[1158] Cammarota, R.C.; Lu, C.C. *J. Am. Chem. Soc.* ***2015***, *137*, 12486; Yuan, Q.; Liu, D.; Zhang, W. *Org. Lett.* ***2017***, *19*, 1144; Mokhov, V.M.; Popov, Yu.V.; Nebykov, D.N. *Russ. J. Org. Chem.* ***2016***, *52*, 319.

[1159] Kita, Y.; Hida, S.; Higashihara, K.; Jena, H.S.; Higashida, K.; Mashima, K. *Angew. Chem. Int. Ed.* ***2016***, *55*, 8299.

[1160] Pranckevicius, C.; Fan, L.; Stephan, D.W. *J. Am. Chem. Soc.* ***2015***, *137*, 5582.

[1161] Chelucci, G.; Baldino, S.; Baratta, W. *Acc. Chem. Res.* ***2015***, *48*, 363.

[1162] Comas-Vives, A.; Ujaque, G. *J. Am. Chem. Soc.* ***2013***, *135*, 1295.

[1163] Callis, N.M.; Thiery, E.; Le Bras, J.; Muzart, J. *Tetrahedron Lett.* ***2007***, *48*, 8128. See Brunel, J.M. *Tetrahedron* ***2007***, *63*, 3899.

[1164] Troutman, M.V.; Appella, D.H.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1999***, *121*, 4916.

[1165] Tang, W.; Qu, B.; Capacci, A.G.; Rodriguez, S.; Wei, X.; Haddad, N.; Narayanan, B.; Ma, S.; Grinberg, N.; Yee, N.K.; Krishnamurthy, D.; Chris, H.; Senanayake, C.H. *Org. Lett.* ***2010***, *12*, 176; Zhang, X.; Huang, K.; Hou, G.; Cao, B.; Zhang, X. *Angew. Chem. Int. Ed.* ***2010***, *49*, 6421; Diguez, M.; Mazuela, J.; Pmies, O.; Verendel, J.J.; Andersson, P.G. *J. Am. Chem. Soc.* ***2008***, *130*, 7208; Chen, W.; Roberts, S.M.; Whittall, J. *Tetrahedron Lett.* ***2006***, *47*, 4263; McIntosh, A.I.; Watson, D.J.; Burton, J.W.; Lambert, R.M. *J. Am. Chem. Soc.* ***2006***, *128*, 7329.

[1166] See Jerphagnon, T.; Renaud, J.-L.; Bruneau, C. *Tetrahedron: Asymmetry* ***2004***, *15*, 2101.

[1167] Knowles, W.S.; Sabacky, M.J.; Vineyard, B.D. *Adv. Chem. Ser.* ***1974***, *132*, 274.

[1168] Brown, J.M.; Chaloner, P.A. *J. Am. Chem. Soc.* ***1980***, *102*, 3040.

[1169] See Chan, A.S.C.; Halpern, J. *J. Am. Chem. Soc.* ***1980***, *102*, 838; Chua, P.S.; Roberts, N.K.; Bosnich, B.; Okrasinski, S.J.; Halpern, J. *J. Chem. Soc., Chem. Commun.* ***1981***, 1278.

[1170] See Tang, W.; Zhang, X. *Chem. Rev.* ***2003***, *103*, 3029.

[1171] Faller, J.W.; Parr, J. *J. Am. Chem. Soc.* ***1993***, *115*, 804.

[1172] Ferlin, N.; Courty, M.; Gatard, S.; Spulak, M.; Quilty, B.; Beadham, I.; Ghavre, M.; Haiß, A.; Kümmerer, K.; Gathergood, N.; Bouquillon, S. *Tetrahedron* ***2013***, *69*, 6150; Jin, X.; Xu, X.-f.; Zhao, K. *Tetrahedron: Asymmetry* ***2012***, *23*, 1058; Giershoff, T.N.; Welther, A.; Kessler, M.T.; Prechtl, M.H.G.; von Wangelin, A.J. *Chem. Commun.* ***2014***, *50*, 2261.

The influence of organic solvents on the bioreduction of alkenes was studied using ene-reductases.[1173] A biocatalytic hydrogenation has been reported using continuous flow conditions (Sec. 7.D).[1174] There is a biocompatible alkene hydrogenation which uses hydrogen gas produced directly by microbial metabolism for the hydrogen of alkenes as well as other substrates.[1175] The frustrated Lewis acid-catalyzed hydrogenation of alkenes has been reported.[1176]

Triple bonds can be reduced, either by catalytic hydrogenation or by the other methods mentioned in the following two sections. The comparative reactivity of triple and double bonds depends on the catalyst. *With most catalysts (e.g., Pd), triple bonds are hydrogenated more easily*, and therefore it is usually possible to add just 1 equivalent of hydrogen and reduce a triple bond to a double bond or to reduce a triple bond without affecting a double bond present in the same molecule.[1177] A particularly good catalyst for this purpose is the *Lindlar catalyst* ($Pd/CaCO_2/PbO$),[1178] which gives rather clean *syn* addition, and a (*Z*)-alkene. An alternative catalyst used for selective hydrogenation to (*Z*)-alkenes is Pd on barium sulfate ($BaSO_4$), poisoned with quinoline[1179] (sometimes called the *Rosenmund catalyst*). Palladium-on-calcium carbonate in polyethylene glycol (PEG) has also been used as a recyclable catalyst system.[1180] Other (*Z*)-selective hydrogenation catalysts have been developed,[1181] including those based on Au,[1182] Ni,[1183] Ru,[1184] Co,[1185] Pd,[1186] Cu,[1187] or Nb,[1188] although transition metal catalysis of the semihydrogenation of terminal alkynes is known, including using an Au[1189] or a Pd[1190] catalyst. Semihydrogenation with (*E*)-selectivity is known using heterobimetallic

[1173] Yanto, Y.; Winkler, C.K.; Lohr, S.; Hall, M.; Faber, K.; Bommarius, A.S. *Org. Lett.* ***2011***, *13*, 2540.

[1174] Zor, C.; Reve, H.A.; Quinsn, J.; Thompson, L.A.; Lonsdale, T.H.; Dillon, F.; Grobert, N.; Vincent, K.A. *Chem. Commun.* ***2017***, *54*, 9839.

[1175] Sirasani, G.; Tong, L.; Balskus, E.P. *Angew. Chem. Int. Ed.* ***2014***, *53*, 7785.

[1176] Greb, L.; Oña-Burgos, P.; Schirmer, B.; Grimme, S.; Stephan, D.W.; Paradies, J. *Angew. Chem. Int. Ed.* ***2012***, *51*, 10164; Paradies, J. *Synlett* ***2013***, *24*, 777. See Feng, X.; Du, H. *Tetrahedron Lett.* ***2014***, *55*, 6959.

[1177] See Hutchins, R.O.; Hutchins, M.G.K. in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, Supplement C, pt. 1, Wiley, NY, ***1983***, pp. 571–601; Marvell, E.N.; Li, T. *Synthesis* ***1973***, 457; Gutmann, H.; Lindlar, H. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 355–363. See Whittaker, A.M.; Lalic, G. *Org. Lett.* ***2013***, *15*, 1112; Kusy, R.; Grela, K. *Org. Lett.* ***2016***, *18*, 6196.

[1178] Lindlar, H.; Dubuis, R. *Org. Synth.* ***V***, 880. See also, Rajaram, J.; Narula, A.P.S.; Chawla, H.P.S.; Dev, S. *Tetrahedron* ***1983***, *39*, 2315; McEwen, A.B.; Guttieri, M.J.; Maier, W.F.; Laine, R.M.; Shvo, Y. *J. Org. Chem.* ***1983***, *48*, 4436. See Niu, W.; Gao, Y.; Zhang, W.; Yan, N.; Lu, X. *Angew. Chem. Int. Ed.* ***2015***, *54*, 8271.

[1179] Cram, D.J.; Allinger, N.L. *J. Am. Chem. Soc.* ***1956***, *78*, 2518; Rosenmund, K.W. *Ber.* ***1918***, *51*, 585; Mosettig, E.; Mozingo, R. *Org. React.* ***1948***, *4*, 362.

[1180] Chandrasekhar, S.; Narsihmulu, Ch.; Chandrashekar, G.; Shyamsunder, T. *Tetrahedron Lett.* ***2004***, *45*, 2421.

[1181] See Mohamed, Y.M.A.; Hansen, T.V. *Tetrahedron* ***2013***, *69*, 3872; Pape, F.; Teichert, J.F. *Synthesis* ***2017***, *49*, 240; Konnerth, H.; Prechtl, M.H.G. *Chem. Commun.* ***2016***, *52*, 9129.

[1182] Yan, M.; Jin, T.; Ishikawa, Y.; Minato, T.; Fujita, T.; Chen, L.-Y.; Bao, M.; Asao, N.; Chen, M.-W.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2012***, *134*, 17536; Mitsudome, T.; Yamamoto, M.; Maeno, Z.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *J. Am. Chem. Soc.* ***2015***, *137*, 13452.

[1183] Richmond, E.; Moran, J. *J. Org. Chem.* ***2015***, *80*, 6922.

[1184] Kusy, R.; Grela, K. *Org. Lett.* ***2016***, *18*, 6196.

[1185] Chen, C.; Huang, Y.; Zhang, Z.; Dong, X.-Q.; Zhang, X. *Chem. Commun.* ***2017***, *53*, 4612.

[1186] Nishibayashi, R.; Kurahashi, T.; Matsubara, S. *Synlett* ***2014***, *25*, 1287.

[1187] Semba, K.; Kameyama, R.; Nakao, Y. *Synlett* ***2015***, *26*, 318.

[1188] Gianetti, T.L.; Tomson, N.C.; Arnold, J.; Bergman, R.G. *J. Am. Chem. Soc.* ***2011***, *133*, 14904.

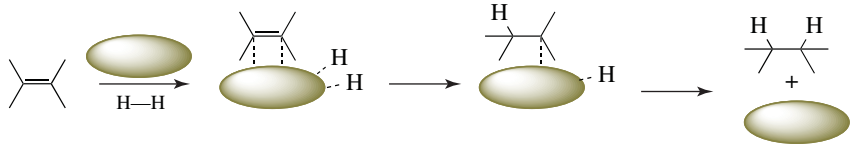
[1189] Li, G.; Jin, R. *J. Am. Chem. Soc.* ***2014***, *136*, 11347.

[1190] For a magnetically recoverable Pd-on-maagnetite catalyst, see da Silva, F.P.; Rossi, L.M. *Tetrahedron* ***2014***, *70*, 3314.

catalysts,[1191] Fe,[1192] or Ru/AgOTf.[1193] The transition metal-free (*E*)-selective semihydrogenation has been reported using $Na_2S{\bullet}9H_2O$.

Conjugated dienes can add hydrogen by 1,2 or 1,4 addition. Selective 1,4 addition can be achieved by hydrogenation in the presence of CO, with bis(cyclopentadienyl)chromium as catalyst.[1194] With allenes[1195] catalytic hydrogenation usually reduces both double bonds.

The mechanism of the heterogeneous catalytic hydrogenation of double bonds is not thoroughly understood.[1196] Because the metal catalyst is insoluble in the reaction medium, kinetic data, although easy to obtain (measurement of decreasing hydrogen pressure), are difficult to interpret and there are the difficulties caused by hydrogen exchange. The currently accepted mechanism for the common two-phase reaction was originally proposed in 1934.[1197] According to this proposal, the alkene is adsorbed onto the surface of the metal. The nature of the actual bonding is unknown,[1198] despite many attempts to elucidate it.[1199] In the 1934 work, the metallic site was indicated by an asterisk, but here  is used. For steric reasons it is apparent that adsorption of the alkene takes place with its less-hindered side attached to the catalyst surface, probably as an η^2 complex (Sec. 3.C.i). The fact that addition of hydrogen is generally also from the less-hindered side indicates that the hydrogen too is probably adsorbed on the catalyst surface before hydrogen reacts with the alkene. It has been shown that Pt catalyzes homolytic cleavage of hydrogen molecules,[1200] and cleavage of H—H is likely common to the other metal catalysts. The H_2 molecule is probably adsorbed on (coordinated to) the metal catalyst, and then cleavage occurs to give η^1-coordinated hydrogen atoms (Sec. 3.C.i).



Note that this model suggest a single metal particle for coordination of the alkene and the hydrogen atoms, but the hydrogen atoms and the alkene could be coordinated to different metal particles.[1201] In the second step, one of the adsorbed (η^1-coordinated) hydrogen atoms becomes attached to a carbon atom, creating in effect, an alkyl radical (which is still bound to the catalyst although only by one bond, probably η^1 coordination). Transfer of a hydrogen atom to carbon opens a site on the metal catalyst for coordination to additional

[1191] Karunananda, M.K.; Mankad, N.P. *J. Am. Chem. Soc.* ***2015***, *137*, 14598. Also see Fu, S.; Chen, N.-Y.; Liu, X.; Shao, Z.; Luo, S.-P.; Liu, Q. *J. Am. Chem. Soc.* ***2016***, *138*, 8588.

[1192] Srimani, D.; Diskin-Posner, Y.; Ben-David, Y.; Milstein, D. *Angew. Chem. Int. Ed.* ***2013***, *52*, 14131.

[1193] Michaelides, I.N.; Dixon, D.J. *Angew. Chem. Int. Ed.* ***2013***, *52*, 806.

[1194] Miyake, A.; Kondo, H. *Angew. Chem. Int. Ed.* ***1968***, *7*, 631. For other methods, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 403–404.

[1195] See Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 57–61.

[1196] See Webb, G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 20; Elsevier, NY, ***1978***, pp. 1–121; Clarke, J.K.A.; Rooney, J.J. *Adv. Catal.* ***1976***, *25*, 125–183.

[1197] Horiuti, I.; Polanyi, M. *Trans. Faraday Soc.* ***1934***, *30*, 1164.

[1198] See Burwell Jr., R.L.; Schrage, K. *J. Am. Chem. Soc.* ***1965***, *87*, 5234.

[1199] See Bautista, F.M.; Campelo, J.M.; Garcia, A.; Guardeño, R.; Luna, D.; Marinas, J.M. *J. Chem. Soc., Perkin Trans. 2*, ***1989***, 493.

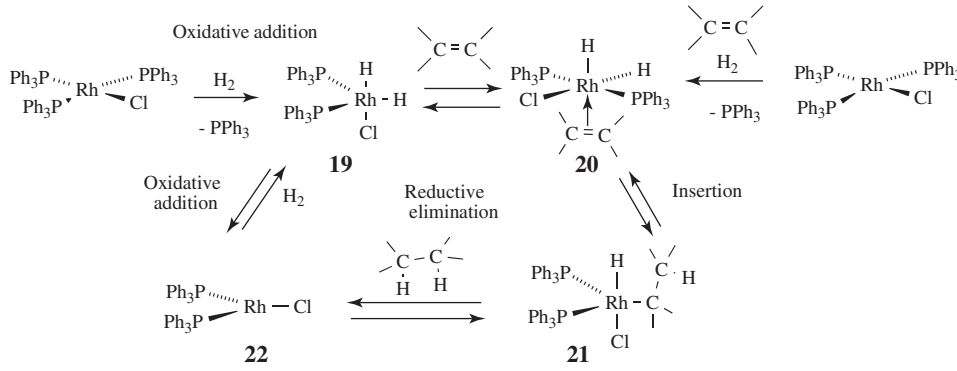
[1200] Krasna, A.I. *J. Am. Chem. Soc.* ***1961***, *83*, 289.

[1201] See Schlögl, R.; Noack, K.; Zbinden, H.; Reller, A. *Helv. Chim. Acta* ***1987***, *70*, 627.

hydrogen atoms. Finally, another hydrogen atom (not necessarily the one originally connected to the first hydrogen) combines with the radical to give the reaction product, freed from the catalyst surface, and the metal catalyst is now available for coordination of additional hydrogen atoms and/or alkenes. All the various side reactions, including hydrogen exchange and isomerism, can be explained by this type of process.[1202]

It is noted that a different mechanism has been proposed,[1203] and there are questions that the mechanistic cartoon shown does not answer,[1204] among them the nature of the ⬭, the nature of the bonding, and the differences caused by the differing nature of each catalyst.[1204] An important problem with any study of heterogeneous catalysis is that it occurs at the surface, and there are different exposures of the metal to the medium and reactants. Maier suggested the presence of *terrace*-, *step*-, and *kink*-type atoms on the surface of a heterogeneous catalyst. These terms refer to different atom types, characterized by the number of nearest neighbors,[1204] which effectively correspond to different coordination states of that metal.[1205] A terrace-type atom typically has eight or nine neighbors and corresponds to a geometry for a ML_5 particle. The step-type of atom usually has seven neighbors and can be correlated with the geometry for a ML_4 particle. Finally, the kink-type atom has six neighbors and corresponds to geometry for the ML_3 particle. Depending on how much of the metal is "buried" in the heterogeneous metal particle, only one, two or three sites are available for binding to the alkene and H_2.[1206] In general, as the particle size increases, the relative concentration of terrace atoms will increase, whereas small particle size favors the kink-type of surface atoms.

The mechanism of homogeneous hydrogenation varies with the metal[1207] but can be illustrated by the reaction of $RhCl(Ph_3P)_3$ (*Wilkinson's catalyst*)[1208] with hydrogen to form a metal hydride $(PPh_3)_2RhH_2Cl$ (**19**).[1209]



[1202] Smith, G.V.; Burwell Jr., R.L. *J. Am. Chem. Soc.* ***1962***, *84*, 925.

[1203] A different mechanism has been proposed by Zaera, F.; Somorjai, G.A. *J. Am. Chem. Soc.* ***1984***, *106*, 2288, but there is evidence against it: Beebe Jr., T.P.; Yates Jr., J.T. *J. Am. Chem. Soc.* ***1986***, *108*, 663. See also, Thomson, S.J.; Webb, G. *J. Chem. Soc., Chem. Commun.* ***1976***, 526.

[1204] See Maier, W.F. *Angew. Chem. Int. Ed.* ***1989***, *28*, 135.

[1205] Maier, W.F. in Rylander, P.N.; Greenfield, H.; Augustine, R.L. *Catalysis of Organic Reactions*, Marcel Dekker, NY, ***1988***, pp 211–231 (see p 220).

[1206] See Maier, W.F. *Angew. Chem. Int. Ed.* ***1989***, *28*, 135.

[1207] See Crabtree, R.H. *Organometallic Chemistry of the Transition Metals*, Wiley, NY, ***1988***, pp. 190–200; Jardine, F.H. in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 1049–1071.

[1208] Koga, N.; Daniel, C.; Han, J.; Fu, X.Y.; Morokuma, K. *J. Am. Chem. Soc.* ***1987***, *109*, 3455.

[1209] Tolman, C.A.; Meakin, P.Z.; Lindner, D.L.; Jesson, J.P. *J. Am. Chem. Soc.* ***1974***, *96*, 2762.

Replacement of a triphenylphosphine ligand with two atoms of hydrogen constitutes an oxidative addition. After coordination of the alkene to form **20**, transfer of hydrogen to carbon is an insertion process, presumably generating **21**, and a second insertion liberates the hydrogenated compound, and Rh species **22**, which adds hydrogen by oxidative addition to give **19**. In a different study of Pd-catalyzed hydrogenations, a palladium hydride species was detected.[1210] Alternatively, replacement of triphenylphosphine can lead to **20**, with two hydrogen atoms and a η^2 alkene complex. If a mixture of H_2 and D_2 is used, the product contains only dideuterated and nondeuterated compounds; no monodeuterated products are found, indicating that (unlike the case of heterogeneous catalysis) H_2 or D_2 has been added to one alkene molecule and that no exchange takes place.[1208] Although conversion of **20** to the products takes place in two steps,[1211] the addition of H_2 to the double bond is *syn*, although bond rotation in **21** can lead to stereochemical mixtures.

Catalytic hydrogenation of double or triple bonds (involve binding of both a π bond and hydrogen to the metal, whether heterogeneous or homogeneous) has been shown to be mostly *syn*, with the hydrogen atoms incorporated from the less-hindered side of the molecule.[1212] The *selectivity depends in large part of how well the reactive intermediates are bound to the metal, and isomerization of the double bond is possible*. Catalytic hydrogenation of alkynes is nearly always stereoselective, giving the *cis*-alkene (usually at least 80%), even when it is thermodynamically less stable, but this observation depends on the metal catalyst used. One factor that complicates the study of the stereochemistry of heterogeneous catalytic hydrogenation is that exchange of hydrogen atoms takes place, as can be shown by hydrogenation with deuterium.[1213] Thus deuterogenation of ethylene produced all the possible deuterated ethenes and ethanes (even C_2H_6), as well as HD.[1214] With but-2-ene, it was found that double-bond migration, *cis*/*trans* isomerization, and even exchange of hydrogen with groups not on the double bond, could occur. For example, $C_4H_2D_8$ and C_4HD_9 were detected on treatment of *cis*-but-2-ene with deuterium and a catalyst.[1215] Indeed, *alkanes* have been found to exchange with deuterium over a catalyst,[1216] for example, $CH_4 + CD_4 \rightarrow CHD_3 + CH_3D$ in the gas phase, with a catalyst. These problems make it difficult to investigate the stereochemistry of heterogeneous catalytic hydrogenation.

Reductions of double and triple bonds are found at OS **I**, 101, 311; **II**, 191, 491; **III**, 385, 794; **IV**, 298, 304, 408; **V**, 16, 96, 277; **VI**, 68, 459; **VII**, 226, 287; **VIII**, 420. 609; **IX**, 169, 533.

Catalysts and apparatus for hydrogenation are found at OS **I**, 61, 463; **II**, 142; **III**, 176, 181, 685; **V**, 880; **VI**, 1007.

19-35 Other Reductions of Double and Triple Bonds

[1210] López-Serrano, J.; Duckett, S.B.; Lledós, A. *J. Am. Chem. Soc.* ***2006***, *128*, 9596.

[1211] Smith, G.V.; Shuford, R.J. *Tetrahedron Lett.* ***1970***, 525; Atkinson, J.G.; Luke, M.O. *Can. J. Chem.* ***1970***, *48*, 3580.

[1212] See Brown, J.M. *Angew. Chem. Int. Ed.* ***1987***, *26*, 190.

[1213] See Gudkov, B.S. *Russ. Chem. Rev.* ***1986***, *55*, 259.

[1214] Turkevich, J.; Schissler, D.O.; Irsa, P. *J. Phys. Chem.* ***1951***, *55*, 1078.

[1215] Wilson, J.N.; Otvos, J.W.; Stevenson, D.P.; Wagner, C.D. *Ind. Eng. Chem.* ***1953***, *45*, 1480.

[1216] See Gudkov, B.S.; Balandin, A.A. *Russ. Chem. Rev.* ***1966***, *35*, 756. For an intramolecular exchange, see Lebrilla, C.B.; Maier, W.F. *Tetrahedron Lett.* ***1983***, *24*, 1119. See also, Poretti, M.; Gäumann, T. *Helv. Chim. Acta* ***1985***, *68*, 1160.

Although catalytic hydrogenation is the method most often used, double or triple bonds can also be reduced by other reagents. These reagents include sodium in ethanol, sodium and *tert*-butyl alcohol in HMPA,[1217] lithium in aliphatic amines[1218] (see also, **19-36**), zinc and acids, and $(EtO)_3SiH/Pd(OAc)_2$.[1219] When double bonds are reduced by lithium in ammonia or amines, the mechanism is similar to that of the *Birch reduction* (**19-36**).[1220] Note that sodium in liquid ammonia does not reduce ordinary double bonds,[1221] although it does reduce alkynes, allenes, conjugated dienes,[1222] and aromatic rings (**19-36**). Zinc metal catalyzes the reduction of alkenes in water in the presence of a Rh complex.[1223] Trialkylsilanes (R_3SiH) in conjunction with an acid will reduce double bonds.[1224] The reduction with trifluoroacetic acid and Et_3SiH has an ionic mechanism, with H^+ coming in from the acid and "H^-" from the silane,[1225] so the reaction can be applied only to those alkenes which when protonated can form a tertiary carbocation or one stabilized in some other way, for example, by a OR substitution.[1226]

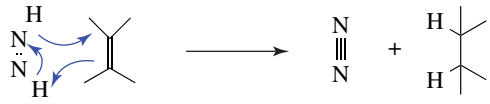
Reduction of an alkyne to an alkene can be done by heating with In metal in aqueous ethanol.[1227] Alkynes are reduced with palladium acetate and sodium ethoxide. In methanol the product is the alkane, whereas in THF the product is the *cis*-alkene.[1228] Triethylamine reduces alkynes in the presence of a Pd catalyst.[1229] Samarium iodide in water and a triamine additive led to reduction of alkenes.[1230]

Another hydrogenation method is called *transfer hydrogenation*.[1231] In this method the hydrogen atom comes from another organic molecule, which is oxidized. A transition metal catalyst, heterogeneous or homogeneous, is frequently employed. Nickel nanoparticles reduce alkenes by transfer hydrogenation using propan-2-ol.[1232] Transfer hydrogenation of alkenes with strongly electron-withdrawing groups on one side of the double bond occurs by reaction with ammonia borane under mild conditions without using a catalyst.[1233] The Ru-catalyzed transfer hydrogenation of 1,6-diynes occurs via alcohol activation.[1234] The Fe-catalyzed transfer hydrogenation of terminal alkynes has been reported.[1235]

[1217] Whitesides, G.M.; Ehmann, W.J. *J. Org. Chem.* ***1970***, *35*, 3565.
[1218] Benkeser, R.A.; Schroll, G.; Sauve, D.M. *J. Am. Chem. Soc.* ***1955***, *77*, 3378.
[1219] Tour, J.M.; Pendalwar, S.L. *Tetrahedron Lett.* ***1990***, *31*, 4719.
[1220] See Toromanoff, E. *Bull. Soc. Chim. Fr.* ***1987***, 893–901; Russell, G.A. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, ***1989***, pp. 471–512.
[1221] For exceptions: see Butler, D.N. *Synth. Commun.* ***1977***, *7*, 441, and references cited therein.
[1222] See Caine, D. *Org. React.* ***1976***, *23*, 1–258.
[1223] Sato, T.; Watanabe, S.; Kiuchi, H.; Oi, S.; Inoue, Y. *Tetrahedron Lett.* ***2006***, *47*, 7703.
[1224] Masuno, M.N.; Molinski, T.F. *Tetrahedron Lett.* ***2001***, *42*, 8263; Kursanov, D.N.; Parnes, Z.N.; Kalinkin, M.I.; Loim, N.M. *Ionic Hydrogenation and Related Reactions*, Harwood Academic Publishers, Chur, Switzerland, ***1985***.
[1225] See Blake, P.G.; Vayjooee, M.H.B. *J. Chem. Soc., Perkin Trans. 2*, ***1976***, 1533.
[1226] Parnes, Z.N.; Bolestova, G.I.; Kursanov, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1972***, *21*, 1927.
[1227] Ranu, B.C.; Dutta, J.; Guchhait, S.K. *J. Org. Chem.* ***2001***, *66*, 5624.
[1228] Wei, L.-L.; Wei, L.-M.; Pan, W.-B.; Leou, S.-P.; Wu, M.-J. *Tetrahedron Lett.* ***2003***, *44*, 1979.
[1229] Luo, F.; Pan, C.; Wang, W.; Ye, Z.; Cheng, J. *Tetrahedron* ***2010***, *66*, 1399. See Han, J.W.; Hayashi, T. *Tetrahedron: Asymmetry* ***2010***, *21*, 2193.
[1230] Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* ***2003***, *44*, 2661.
[1231] Johnstone, R.A.W.; Wilby, A.H.; Entwistle, I.D. *Chem. Rev.* ***1985***, *85*, 129; Brieger, G.; Nestrick, T.J. *Chem. Rev.* ***1974***, *74*, 567; Wang, D.; Astruc, D. *Chem. Rev.* ***2015***, *115*, 6621.
[1232] Alonso, F.; Riente, P.; Yus, M. *Acc. Chem. Res.* ***2011***, *44*, 379.
[1233] Yang, X.; Fox, T.; Berke, H. *Chem. Commun.* ***2011***, *47*, 2053.
[1234] Yamashita, K.; Nagasima, Y.; Yamamoto, Y.; Nishiyama, H. *Chem. Commun.* ***2011***, *47*, 11552.
[1235] Wienhöfer, G.; Westerhaus, F.Z.; Jagadeesh, R.V.; Junge, K.; Junge, H.; Beller, M. *Chem. Commun.* ***2012***, *48*, 4827.

Asymmetric transfer hydrogenation in propan-2-ol with 2 equivalents of KOH per Ru atom by using a Ru catalyst is reported for the hydrogenation of alkene moieties.[1236]

Diimide NH=NH is a reducing agent for simple alkenes, and is formed *in situ* from N_2H_4 from the reaction of a mixture of hydrazine and hydroxylamine.[1237] The rate of this reaction has been studied.[1238] Diimide has been generated from hydrazine with synthetic flavin catalysts.[1239] Diimide has been generated using flow techniques (Sec. 7.D).[1240] Although both the *syn* and *anti* forms of diimide are produced, only the *syn* form reduces the double bond,[1241] at least in part by a cyclic mechanism shown.[1242]



The addition is stereospecifically *syn*[1243] and, like catalytic hydrogenation, generally takes place from the less-hindered side of a double bond, although not much discrimination in this respect is observed where the difference in bulk effects is small.[1244] Diimide reductions are most successful with symmetrical multiple bonds (C=C, C≡C, N=N) and are not useful for those that are inherently polar (C≡N, C=N, C=O, etc.). Diimide is not stable enough for isolation at ordinary temperatures, although it has been prepared[1245] as a yellow solid at −196 °C.

Hydrazine has been used for the hydrogenation of alkenes.[1246] The hydrogenation of alkenes using aqueous hydrazine and quinidine nitrate has been reported.[1247] The reaction of alkenes and hydrazine under photolytic conditions and air gave the hydrogenation product.[1248] Enantioselective reduction of certain alkenes has also been achieved by reduction with baker's yeast.[1249] A complex of lumiflavin with 2,6-bis(acylamino)pyridine that bears a 3,4,5-trialkoxybenzyl ether dendron unit was an efficient organocatalyst for the aerobic reduction of styrene to ethylbenzene.[1250]

An indirect method[1251] of double-bond reduction involves formation of an alkylborane from an alkene, followed by hydrolysis of the borane (**15-11**). Trialkylboranes can

[1236] Wu, R.; Beauchamps, M.G.; Laquidara, J.M.; Sowa Jr., J.R. *Angew. Chem. Int. Ed.* ***2012***, *51*, 2106.
[1237] See Pasto, D.J.; Taylor, R.T. *Org. React.* ***1991***, *40*, 91; Hünig, S.; Müller, H.R.; Thier, W. *Angew. Chem. Int. Ed.* ***1965***, *4*, 271.
[1238] Nelson, D.J.; Henley, R.L.; Yao, Z.; Smith, T.D. *Tetrahedron Lett.* ***1993***, *34*, 5835.
[1239] Imada, Y.; Iida, H.; Kitagawa, T.; Naota, T. *Chem. Eur. J.* ***2011***, *17*, 5908.
[1240] Pieber, B.; Martinez, S.T.; Cantillo, D.; Kappe, C.O. *Angew. Chem. Int. Ed.* ***2013***, *52*, 10241.
[1241] Aylward, F.; Sawistowska, M.H. *J. Chem. Soc.* ***1964***, 1435.
[1242] Willis, C.; Back, R.A.; Parsons, J.A.; Purdon, J.G. *J. Am. Chem. Soc.* ***1977***, *99*, 4451.
[1243] Corey, E.J.; Pasto, D.J.; Mock, W.L. *J. Am. Chem. Soc.* ***1961***, *83*, 2957.
[1244] van Tamelen, E.E.; Timmons, R.J. *J. Am. Chem. Soc.* ***1962***, *84*, 1067.
[1245] Wiberg, N.; Fischer, G.; Bachhuber, H. *Angew. Chem. Int. Ed.* ***1977***, *16*, 780. See also, Craig, N.C.; Kliewer, M.A.; Shih, N.C. *J. Am. Chem. Soc.* ***1979***, *101*, 2480.
[1246] Chen, H.; Wang, J.; Hong, X.; Zhou, H.-B.; Dong, C. *Can. J. Chem.* ***2012***, *90*, 758.
[1247] Lamani, M.; Siddappa, R.S.; Prabhu, K.R. *Chem. Commun.* ***2012***, *48*, 6583.
[1248] Leow, D.; Chen, Y.-H.; Hung, T.-H.; Su, Y.; Lin, Y.-Z. *Eur. J. Org. Chem.* ***2014***, 7347.
[1249] See Ferraboschi, P.; Reza-Elahi, S.; Verza, E.; Santaniello, E. *Tetrahedron: Asymmetry* ***1999***, *10*, 2639. For reviews of baker's yeast, see Csuk, R.; Glänzer, B.I. *Chem. Rev.* ***1991***, *91*, 49; Servi, S. *Synthesis* ***1990***, 1.
[1250] Imada, Y.; Kugimiya, Y.; Iwata, S.; Komiya, N.; Naota, T. *Tetrahedron* ***2013***, *69*, 8572.
[1251] See Zweifel, G. *Intra-Sci. Chem. Rep.* ***1973***, *7(2)*, 181–189.

be hydrolyzed by heating to reflux with carboxylic acids,[1252] while monoalkylboranes (RBH_2) can be hydrolyzed with base.[1253] Triple bonds can be similarly reduced to *cis*-alkenes.[1254] Further reduction is also possible.[1255] Reduction of alkenes occurs with *tert*-butylamine•borane complex in methanol with 10% Pd/C.[1256]

Metallic hydrides, such as lithium aluminum hydride and sodium borohydride, without additives, do not typically reduce carbon-carbon double bonds. There are special cases where the double bond is polar, as in 1,1-diarylethenes[1257] and in enamines,[1258] where reduction can occur. Note that both $LiAlH_4$ and $NaBH_4$, as well as NaH, reduce ordinary alkenes and alkynes when complexed with transition metal salts such as $FeCl_2$ or $CoBr_2$.[1259] Transition metals such as Pd[1260] and Ru[1261] catalyze the reduction of alkenes using $NaBH_4$. The Ni-catalyzed semihydrogenation of alkynes in the presence of $NaBH_4$ showed good selectivity for the (*Z*)-alkene.[1262]

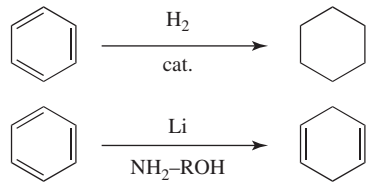
Triple bonds can also be selectively reduced to double bonds with diisobutylaluminum hydride (Dibal-H),[1263] with activated zinc (see **12-37**),[1264] or (internal triple bonds only) with alkali metals (Na, Li) in liquid ammonia or a low molecular weight amine.[1265] Terminal alkynes are not reduced by the Na/NH_3 procedure because they are converted to acetylide ions under these conditions. A terminal alkyne was reduced with lithium naphthalenide and $NiCl_2$[1266] and simple alkenes could be reduced.[1267] It is noted that the reaction with Dibal-H usually gives the *cis* alkene (**19-34**). Most of the other methods of triple-bond reduction lead to the more thermodynamically stable *trans* alkene. However, hydrolysis of boranes or reductions with activated zinc, hydrazine, or NH_2OSO_3H give the *cis* products.

Reduction of just one double bond of an allene, to give an alkene, has been accomplished by treatment with Na/NH_3[1268] or with Dibal-H,[1269] and by hydrogenation with $RhCl(PPh_3)_3$ as catalyst.[1270]

Reductions of double and triple bonds are found at OS **III**, 586, 742; **IV**, 136, 302, 887; **V**, 281, 993; **VII**, 524; **80**, 120.

[1252] Brown, H.C.; Murray, K.J. *Tetrahedron* ***1986***, *42*, 5497; Kabalka, G.W.; Newton Jr., R.J.; Jacobus, J. *J. Org. Chem.* ***1979***, *44*, 4185.
[1253] Weinheimer, A.J.; Marisco, W.E. *J. Org. Chem.* ***1962***, *27*, 1926.
[1254] Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1959***, *81*, 1512.
[1255] Lee, S.H.; Park, Y.J.; Yoon, C.M. *Tetrahedron Lett.* ***2000***, *41*, 887.
[1256] Couturier, M.; Andresen, B.M.; Tucker, J.L.; Dubé, P.; Brenek, S.J.; Negri, J.J. *Tetrahedron Lett.* ***2001***, *42*, 2763.
[1257] See Granoth, I.; Segall, Y.; Leader, H.; Alkabets, R. *J. Org. Chem.* ***1976***, *41*, 3682.
[1258] Gribble, G.W.; Nutaitis, C.F. *Org. Prep. Proced. Int.* ***1985***, *17*, 317; Nilsson, A.; Carlson, R. *Acta Chem. Scand. Sect. B* ***1985***, *39*, 187.
[1259] See Osby, J.O.; Heinzman, S.W.; Ganem, B. *J. Am. Chem. Soc.* ***1986***, *108*, 67.
[1260] Tran, A.T.; Huynh, V.A.; Friz, E.M.; Whitney, S.K.; Cordes, D.B. *Tetrahedron Lett.* ***2009***, *50*, 1817.
[1261] Adair, G.R.A.; Kapoor, K.K.; Scolan, A.L.B.; Williams, J.M.J. *Tetrahedron Lett.* ***2006***, *47*, 8943.
[1262] Wen, X.; Shi, X.; Qiao, X.; Wu, Z.; Bai, G. *Chem. Commun.* ***2017***, *53*, 5372.
[1263] Ulan, J.G.; Maier, W.F.; Smith, D.A. *J. Org. Chem.* ***1987***, *52*, 3132.
[1264] Chou, W.; Clark, D.L.; White, J.B. *Tetrahedron Lett.* ***1991***, *32*, 299. See Kaufman, D.; Johnson, E.; Mosher, M.D. *Tetrahedron Lett.* ***2005***, *46*, 5613.
[1265] Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 405–410.
[1266] Alonso, F.; Yus, M. *Tetrahedron Lett.* ***1997***, *38*, 149.
[1267] Alonso, F.; Yus, M. *Tetrahedron Lett.* ***1996***, *37*, 6925.
[1268] Vaidyanathaswamy, R.; Joshi, G.C.; Devaprabhakara, D. *Tetrahedron Lett.* ***1971***, 2075.
[1269] Montury, M.; Goré, J. *Tetrahedron Lett.* ***1980***, *21*, 51.
[1270] Bhagwat, M.M.; Devaprabhakara, D. *Tetrahedron Lett.* ***1972***, 1391.

19-36 Reduction of Aromatic Rings



Aromatic rings can be reduced by catalytic hydrogenation,[1271] but higher temperatures (100–200 °C) are required than for double bonds in alkenes.[1272] Although the reaction is usually carried out with heterogeneous catalysts, homogeneous catalysts have also been used; conditions are much milder with these.[1273] Hydrogenations using phase-transfer catalysts often proceed under mild conditions.[1274] Hydrogenation in ionic liquids is known,[1275] as is hydrogenation in supercritical ethane containing water.[1276] Phenols may be reduced to cyclohexanones, presumably through the enol. A computational study of the mechanism of hydrogenation of aromatic compounds has been reported, and it was shown that the barrier for uncatalyzed 1,4-hydrogenation is substantially lower than that for 1,2-hydrogenation, despite similar reaction enthalpies.[1277]

It is usually impossible to stop the reduction of benzene rings after only one or two bonds have been reduced, since alkenes are more easily reduced than aromatic rings.[1278] Thus, 1 molar equivalent of benzene, treated with 1 molar equivalent of hydrogen, gives no cyclohexadiene or cyclohexene, but one-third equivalent of cyclohexane and two-thirds equivalent of recovered benzene.[1279] This mixture is not true for all aromatic systems. With anthracene, for example, it is easy to stop after only the 9,10-bond has been reduced (Sec. 2.I.i). The catalytic asymmetric hydrogenation of naphthalenes[1280] and other polycyclic aromatic hydrocarbons has been reported.[1281] Hydrogenation of phenol derivatives can lead to conjugated cyclohexenones.[1282] Hydrogenation of toluene in an ionic liquid using a Ru catalyst gave methylcyclohexane.[1283]

[1271] See Karakhanov, E.A.; Dedov, A.G.; Loktev, A.S. *Russ. Chem. Rev.* ***1985***, *54*, 171. See Zhuo, C.-X.; Zheng, C.; You, S.-L. *Acc. Chem. Res.* ***2014***, *47*, 2558.
[1272] See Timmer, K.; Thewissen, D.H.M.W.; Meinema, H.A.; Bulten, E.J. *Recl. Trav. Chim. Pays-Bas* ***1990***, *109*, 87.
[1273] Muetterties, E.L.; Bleeke, J.R. *Acc. Chem. Res.* ***1979***, *12*, 324. See also, Tsukinoki, T.; Kanda, T.; Liu, G.-B.; Tsuzuki, H.; Tashiro, M. *Tetrahedron Lett.* ***2000***, *41*, 5865.
[1274] Januszkiewicz, K.R.; Alper, H. *Organometallics* ***1983***, *2*, 1055.
[1275] Dyson, P.J.; Ellis, D.J.; Parker, D.G.; Welton, T. *Chem. Commun.* ***1999***, 25. Rh nanoparticles are used as a catalyst: Mu, X.-d.; Meng, J.-q.; Li, Z.-C.; Kou, Y. *J. Am. Chem. Soc.* ***2005***, *127*, 9694.
[1276] Bonilla, R.J.; James, B.R.; Jessop, P.G. *Chem. Commun.* ***2000***, 941.
[1277] Zhong, G.; Chan, B.; Radom, L. *J. Am. Chem. Soc.* ***2007***, *129*, 924.
[1278] See Harman, W.D.; Taube, H. *J. Am. Chem. Soc.* ***1988***, *110*, 7906.
[1279] See Schwab, F.; Lucas, M.; Claus, P. *Angew. Chem. Int. Ed.* ***2011***, *50*, 10453.
[1280] Kuwano, R.; Morioka, R.; Kashiwabara, M.; Kameyama, N. *Angew. Chem. Int. Ed.* ***2012***, *51*, 4136.
[1281] Segawa, Y.; Stephan, D.W. *Chem. Commun.* ***2012***, *48*, 11963.
[1282] Higashijima, M.; Nishimura, S. *Bull. Chem. Soc. Jpn.* ***1992***, *65*, 824.
[1283] Boxwell, C.J.; Dyson, P.J.; Ellis, D.J.; Welton, T. *J. Am. Chem. Soc.* ***2002***, *124*, 9334.

Heterocyclic compounds are often reduced by hydrogenation.[1284] The catalytic asymmetric hydrogenation of several heterocycles[1285] has been reported, including *N*-Boc-imidazoles and oxazoles,[1286] thiophenes and benzothiophenes,[1287] furans,[1288] benzofurans,[1289] pyridines,[1290] pyrimidines,[1291] indoles,[1292] isoquinolines,[1293] and quinolines.[1294] Furan gives THF, pyrroles[1295] give pyrrolidines, and pyridines[1296] give piperidines. The nitrogen-containing ring of quinolines is reduced by hydrogenation using iodine and an Ir catalyst.[1297] Catalytic hydrogenation of the five-membered ring in indole derivatives using a chiral Rh catalyst gave hydroindoles with excellent enantioselectivity.[1298]

When aromatic rings are reduced by Li (or K or Na) in liquid ammonia (such reductions are known as *dissolving metal reductions*), it is usually in the presence of an alcohol (often ethyl, isopropyl, or *tert*-butyl alcohol), 1,4-Addition of hydrogen takes place and nonconjugated cyclohexadienes are produced.[1299] This reaction is called the *Birch reduction*.[1300] Heterocycles, such as pyrroles,[1301] furans,[1302] pyridines,[1303] and indolones[1304] can be reduced using Birch reduction. Ammonia obtained commercially often has iron salts as impurities that lower the yield in the Birch reduction. Therefore it is often necessary to distill the ammonia.

When substituted aromatic compounds are subjected to the Birch reduction, electron-donating groups such as alkyl or alkoxyl decrease the rate of the reaction and are

[1284] Zhou, Y.-G. *Acc. Chem. Res.* ***2007***, *40*, 1357; Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* ***2012***, *112*, 2557.

[1285] For *N*-heterocycles, see Chakraborty, S.; Brennessel, W.W.; Jones, W.D. *J. Am. Chem. Soc.* ***2014***, *136*, 8564; Zurro, M.; Asmus, S.; Beckendorf, S.; Mück-Lichtenfeld, C.; Mancheño, O.G. *J. Am. Chem. Soc.* ***2014***, *136*, 13999; Adam, R.; Cabrero-Antonino, J.R.; Spannenberg, A.; Junge, K.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed.* ***2017***, *56*, 3216.

[1286] Kuwano, R.; Kameyama, N.; Ikeda, R. *J. Am. Chem. Soc.* ***2011***, *133*, 7312.

[1287] Tang, D.-T.D.; Collins, K.D.; Glorius, F. *J. Am. Chem. Soc.* ***2013***, *135*, 7450.

[1288] Wysocki, J.; Ortega, N.; Glorius, F. *Angew. Chem. Int. Ed.* ***2014***, *53*, 8751. Also see Nguyen, S.T.; Ding, X.; Peet, N.P. *Synthesis* ***2013***, *45*, 1904.

[1289] Ortega, N.; Urban, S.; Beiring, B.; Glorius, F. *Angew. Chem. Int. Ed.* ***2012***, *51*, 1710.

[1290] See Zhou, Q.; Zhang, L.; Meng, W.; Feng, X.; Yang, J.; Du, H. *Org. Lett.* ***2016***, *18*, 5189.

[1291] Kuwano, R.; Hashiguchi, Y.; Ikeda, R.; Ishizuka, K. *Angew. Chem. Int. Ed.* ***2015***, *54*, 2393.

[1292] Duan, Y.; Li, L.; Chen, M.-W.; Yu, C.-B.; Fan, H.-J.; Zhou, Y.-G. *J. Am. Chem. Soc.* ***2014***, *136*, 7688; Touge, T.; Arai, T. *J. Am. Chem. Soc.* ***2016***, *138*, 11299.

[1293] Zhao, D.; Glorius, F. *Angew. Chem. Int. Ed.* ***2013***, *52*, 9616.

[1294] Yan, M.; Jin, T.; Chen, Q.; Ho, H.E.; Fujita, T.; Chen, L.-Y.; Bao, M.; Chen, M.-W.; Asao, N.; Yamamoto, Y. *Org. Lett.* ***2013***, *15*, 1484; Zhang, Z.; Du, H. *Org. Lett.* ***2015***, *17*, 6266.

[1295] Kuwano, R.; Kashiwabara, M.; Ohsumi, M.; Kusano, H. *J. Am. Chem. Soc.* ***2008***, *130*, 808.

[1296] Piras, L.; Genesio, E.; Ghiron, C.; Taddei, M. *Synlett* ***2008***, 1125.

[1297] Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* ***2003***, *125*, 10536.

[1298] Kuwano, R.; Kaneda, K.; Ito, T.; Sato, K.; Kurokawa, T.; Ito, Y. *Org. Lett.* ***2004***, *6*, 2213. See Kim, J.T.; Gevorgyan, V. *J. Org. Chem.* ***2005***, *70*, 2054.

[1299] See Brandsma, L.; van Soolingen, J.; Andringa, H. *Synth. Commun.* ***1990***, *20*, 2165. Also see, Weitz, I.S.; Rabinovitz, M. *J. Chem. Soc., Perkin Trans. 1*, ***1993***, 117.

[1300] Akhrem, A.A.; Reshotova, I.G.; Titov, Yu.A. *Birch Reduction of Aromatic Compounds*, Plenum, NY, ***1972***; Birch, A.J. *Pure Appl. Chem.* ***1996***, *68*, 553; Zimmerman, H.E. *Acc. Chem. Res.* ***2012***, *45*, 164; Rabideau, P.W. *Tetrahedron* ***1989***, *45*, 1579; Birch, A.J.; Subba Rao, G. *Adv. Org. Chem.* ***1972***, *8*, 1; Kaiser, E.M. *Synthesis* ***1972***, 391.

[1301] Donohoe, T.J.; House, D. *J. Org. Chem.* ***2002***, *67*, 5015.

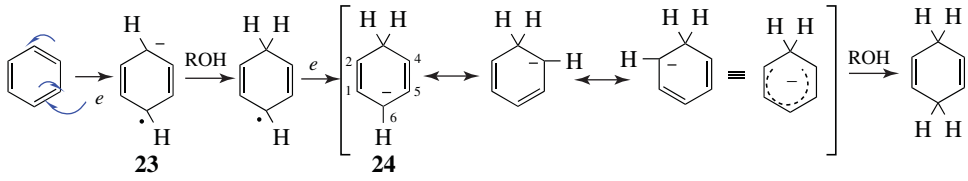
[1302] Kinoshita, T.; Ichinari, D.; Sinya, J. *J. Heterocycl. Chem.* ***1996***, *33*, 1313.

[1303] Donohoe, T.J.; McRiner, A.J.; Helliwell, M.; Sheldrake, P. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1435.

[1304] Guo, Z.; Schultz, A.G. *J. Org. Chem.* ***2001***, *66*, 2154.

generally found on the nonreduced positions of the product. For example, anisole gives 1-methoxy-1,4-cyclohexadiene, not 3-methoxy-1,4-cyclohexadiene. On the other hand, electron-withdrawing groups, such as COOH or $CONH_2$, increase the reaction rate and are found on the reduced positions of the product.[1305] The regioselectivity of the reaction has been examined.[1306] The mechanism involves solvated electrons,[1307] which are transferred from the metal to the solvent, and hence to the ring.[1308]

The sodium becomes oxidized to Na^+ and creates a radical ion (**23**).[1309] There is a great deal of evidence from esr spectra for these species.[1310] The radical ion accepts a proton from the alcohol to give a radical, which is reduced to a carbanion by another sodium atom. Finally, **24** accepts another proton. Thus the function of the alcohol is to supply protons, since with most substrates ammonia is not acidic enough for this purpose. In the absence of the alcohol, products arising from dimerization of **23** are frequently obtained. There is evidence,[1311] at least with some substrates such as biphenyl, that the radical ion corresponding to **23** is converted to the carbanion corresponding to **24** by a different pathway, in which the order of the steps is reversed: first a second electron is gained to give a dianion,[1308] which then acquires a proton, producing the intermediate such as **24**. Ordinary alkenes are usually unaffected by Birch reduction conditions, so double bonds may be present in the molecule if they are not conjugated with the ring. However, phenylated alkenes, internal alkynes (**15-12**),[1312] and conjugated alkenes (with C=C or C=O) are reduced under these conditions.



Note that **23** is a resonance hybrid; that is, two additional canonical forms can be written. The question therefore arises: Why does the carbanion pick up a proton at the 6 position to give the 1,4-diene? Why not at the 2 position to give the 1,3-diene?[1313] An answer to this question has been proposed by Hine, who suggested that this case is an illustration of the operation of the *principle of least motion*.[1314] According to this principle, "those elementary reactions will be favored that involve the least

[1305] See Zimmerman, H.E.; Wang, P.A. *J. Am. Chem. Soc.* ***1990***, *112*, 1280; Rabideau, P.W.; Karrick, G.L. *Tetrahedron Lett.* ***1987***, *28*, 2481.
[1306] Zimmerman, H.E.; Wang, P.A. *J. Am. Chem. Soc.* ***1993***, *115*, 2205.
[1307] For reviews of solvated electrons and related topics, see Dye, J.L. *Prog. Inorg. Chem.* ***1984***, *32*, 327–441; Alpatova, N.M.; Krishtalik, L.I.; Pleskov, Y.V. *Top. Curr. Chem.* ***1987***, *138*, 149–219.
[1308] Birch, A.J.; Nasipuri, D. *Tetrahedron* ***1959***, *6*, 148.
[1309] See Holy, N.L. *Chem. Rev.* ***1974***, *74*, 243.
[1310] See Jones, M.T. in Kaiser, E.T.; Kevan, L. *Radical Ions*, Wiley, NY, ***1968***, pp. 245–274; Bowers, K.W. *Adv. Magn. Reson.*, ***1965***, *1*, 317; Carrington, A. *Q. Rev. Chem. Soc.* ***1963***, *17*, 67.
[1311] Rabideau, P.W.; Peters, N.K.; Huser, D.L. *J. Org. Chem.* ***1981***, *46*, 1593.
[1312] Brandsma, L.; Nieuwenhuizen, W.F.; Zwikker, J.W.; Mäeorg, U. *Eur. J. Org. Chem.* ***1999***, 775.
[1313] See Rabideau, P.W.; Huser, D.L. *J. Org. Chem.* ***1983***, *48*, 4266.
[1314] Hine, J. *J. Org. Chem.* ***1966***, *31*, 1236; Hine, J. *Adv. Phys. Org. Chem.* ***1977***, *15*, 1. See also, Jochum, C.; Gasteiger, J.; Ugi, I. *Angew. Chem. Int. Ed.* ***1980***, *19*, 495.

change in atomic position and electronic configuration."[1313] Note that the ^{13}C NMR spectrum of **24** shows that the 6 position has a somewhat greater electron density than the 2 position, which presumably would make the former more attractive to a proton.[1315]

Reduction of aromatic rings with Li[1316] or Ca[1317] in amines (instead of ammonia: called *Benkeser reduction*) proceeds further and cyclohexenes are obtained. It is thus possible to reduce a benzene ring, by proper choice of reagent, so that one, two, or all three double bonds are reduced.[1318]

Transition metals and metal compounds can reduce aromatic rings in the proper medium. Indium metal reduces the pyridine ring in quinoline in aqueous ethanol solution[1319] as well as the C=C unit in the five-membered ring of indole derivatives.[1320] Samarium iodide (SmI_2) reduces pyridine in aqueous THF[1321] and phenol in MeOH/KOH.[1322] Ammonium formate and a Pd/C catalyst reduces pyridine *N*-oxide to piperidine in methanol.[1323] The nitrogen-containing ring of quinolines is reduced with an Ir catalyst in isopropyl alcohol.[1324] The reduction of phenol to cyclohexanone over a Pd/C catalyst and $HCOONa/H_2O$ has been reported.[1325]

OS **I**, 99, 499; **II**, 566; **III**, 278, 742; **IV**, 313, 887, 903; **V**, 398, 400, 467, 591, 670, 743, 989; **VI**, 371, 395, 461, 731, 852, 856, 996; **VII**, 249.

19-37 Reduction Of Conjugated Double or Triple Bonds

Reduction of only the C=C bond of conjugated C=C–C=O and C=C–C≡N systems[1326] has been achieved by many reducing agents,[1327] including catalytic hydrogenation[1328] with

[1315] Bates, R.B.; Brenner, S.; Cole, C.M.; Davidson, E.W.; Forsythe, G.D.; McCombs, D.A.; Roth, A.S. *J. Am. Chem. Soc.* ***1973***, *95*, 926.
[1316] Benkeser, R.A.; Agnihotri, R.K.; Burrous, M.L.; Kaiser, E.M.; Mallan, J.M.; Ryan, P.W. *J. Org. Chem.* ***1964***, *29*, 1313; Kwart, H.; Conley, R.A. *J. Org. Chem.* ***1973***, *38*, 2011.
[1317] Benkeser, R.A.; Belmonte, F.G.; Kang, J. *J. Org. Chem.* ***1983***, *48*, 2796. See also, Benkeser, R.A.; Laugal, J.A.; Rappa, A. *Tetrahedron Lett.* ***1984***, *25*, 2089.
[1318] See Keay, J.G. *Adv. Heterocycl. Chem.* ***1986***, *39*, 1.
[1319] Moody, C.J.; Pitts, M.R. *Synlett* ***1998***, 1029.
[1320] Pitts, M.R.; Harrison, J.R.; Moody, C.J. *J. Chem. Soc., Perkin Trans. 1*, ***2001***, 955.
[1321] Kamochi, Y.; Kudo, T. *Heterocycles* ***1993***, *36*, 2383.
[1322] Kamochi, Y.; Kudo, T. *Tetrahedron Lett.* ***1994***, *35*, 4169.
[1323] Zacharie, B.; Moreau, N.; Dockendorff, C. *J. Org. Chem.* ***2001***, *66*, 5264.
[1324] Fujita, K.; Kitatsuji, C.; Furukawa, S.; Yamaguchi, R. *Tetrahedron Lett.* ***2004***, *45*, 3215.
[1325] Cheng, H.; Liu, R.; Wang, Q.; Wu, C.; Yu, Y.; Zhao, F. *New J. Chem.* ***2012***, 1085.
[1326] See Keinan, E.; Greenspoon, N. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, ***1989***, pp. 923–1022; Augustine, R.L. *Adv. Catal.* ***1976***, *25*, 56.
[1327] See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 13–27.
[1328] For a discussion of the development of catalysts, see Maurer, F.; Huch, V.; Ullrich, A.; Kazmaier, U. *J. Org. Chem.* ***2012***, *77*, 5139.

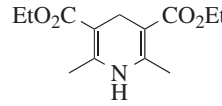
a Rh,[1329] Ru,[1330] Pd,[1331] Au,[1332] Ni,[1333] or Ir[1334] catalyst, and with Raney nickel alone.[1335] Reagents such as SmI_2[1336] and catecholborane[1337] are effective. Formic acid with a Pd catalyst reduced conjugated carboxylic acids.[1338] A zinc/titanocene protocol has been developed for conjugate reductions.[1339] Both $NaBH_4$ in MeOH/THF[1340] and $NaCNBH_3$ on a zeolite[1341] reduce α,β-unsaturated nitro compounds to nitroalkanes.

In certain cases[1342] metallic hydride reagents may selectively reduce double bonds that are in conjugation with C═O bonds,[1343] although the C═O bonds are also reduced in many cases, as in the conversion of cyclopentenone to cyclopentanol.[1344] The reagent $NaBH_4$ has a greater tendency than $LiAlH_4$ to effect this double reduction, although even with $NaBH_4$ the product of 1,2-reduction (of the C═O bond) is usually formed in larger amount than the doubly reduced product. The $NaBH_4$/acetic acid and Pd-catalyzed conditions gave selective 1,4-conjugate reduction of conjugated compounds.[1345] Mixed hydride reducing agents such as $NaBH_4/BiCl_3$,[1346] $NaBH_4/InCl_3$,[1347] and $NaBH_4/Er(OTf)_3$[1348] have been used. The $InCl_3/NaBH_4$ reagent was used to convert conjugated diene ketones (C═C─C═C─C═O) selectively to the nonconjugated alkenyl ketone (C═C─CH_2CH_2─C═O).[1349]

Transfer hydrogenation can be applied to the reduction of conjugated alkenes, including conjugated nitroalkenes.[1350] Reduction of the C═C unit of conjugated aldehydes is

[1329] Li, M.; Kong, D.; Zi, G.; Hou, G. *J. Org. Chem.* ***2017***, *82*, 680.
[1330] Wang, C.-J.; Tao, H.; Zhang, X. *Tetrahedron Lett.* ***2006***, *47*, 1901. Also see Li, W.; Wu, X.-F. *Eur. J. Org. Chem.* ***2015***, 331.
[1331] Nagano, H.; Yokota, M.; Iwazaki, Y. *Tetrahedron Lett.* ***2004***, *45*, 3035.
[1332] Takale, B.S.; Wang, S.; Zhang, X.; Feng, X.; Yu, X.; Jin, T.; Bao, M.; Yamamoto, Y. *Chem. Commun.* ***2014***, *50*, 14401.
[1333] Shevlin, M.; Friedfeld, M.R.; Sheng, H.; Pierson, N.A.; Hoyt, J.M.; Campeau, L.-C.; Chirik, P.J. *J. Am. Chem. Soc.* ***2016***, *138*, 3562.
[1334] Liu, Y.; Gridnev, I.D.; Zhang, W. *Angew. Chem. Int. Ed.* ***2014***, *53*, 1901; Liu, X.; Han, Z.; Wang, Z.; Ding, K. *Angew. Chem. Int. Ed.* ***2014***, *53*, 1978; Li, J.-Q.; Quan, X.; Andersson, P.G. *Chem. Eur. J.* ***2012***, *18*, 10609.
[1335] Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R.; Meneses, R. *Synlett* ***1999***, 1663; Wang, H.; Lian, H.; Chen, J.; Pan, Y.; Shi, Y. *Synth. Commun.* ***1999***, *29*, 129.
[1336] Cabrera, A.; Alper, H. *Tetrahedron Lett.* ***1992***, *33*, 5007. See also, Tarnopolsky, A.; Hoz, S. *J. Am. Chem. Soc.* ***2007***, *129*, 3402.
[1337] Evans, D.A.; Fu, G.C. *J. Org. Chem.* ***1990***, *55*, 5678.
[1338] Arterburn, J.B.; Pannala, M.; Gonzlez, A.M.; Chamberlin, R.M. *Tetrahedron Lett.* ***2000***, *41*, 7847.
[1339] Kosal, A.D.; Ashfeld, B.L. *Org. Lett.* ***2010***, *12*, 44.
[1340] Varma, R.S.; Kabalka, G.W. *Synth. Commun.* ***1985***, *15*, 151.
[1341] Gupta, A.; Haque, A.; Vankar, Y.D. *Chem. Commun.* ***1996***, 1653.
[1342] See Meyer, G.R. *J. Chem. Educ.* ***1981***, *58*, 628.
[1343] For a discussion of hydride affinity with respect to hydride reducing agents, see Zhu, X.-Q.; Zhang, M.; Liu, Q.-Y.; Wang, X.-X.; Zhang, J.-Y.; Cheng, J.-P. *Angew. Chem. Int. Ed.* ***2006***, *45*, 3954; Vianello, R.; Peran, N.; Maksić, Z.B. *Eur. J. Org. Chem.* ***2007***, 5296.
[1344] Brown, H.C.; Hess, H.M. *J. Org. Chem.* ***1969***, *34*, 2206. For other methods of reducing both double bonds, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 1096.
[1345] Russo, A.T.; Amezcua, K.L.; Huynh, V.A.; Rousslang, Z.M.; Cordes, D.B. *Tetrahedron Lett.* ***2011***, *52*, 6823.
[1346] Ren, P.-D.; Pan, S.-F.; Dong, T.-W.; Wu, S.-H. *Synth. Commun.* ***1995***, *25*, 3395.
[1347] Ranu, B.C.; Samanta, S. *Tetrahedron Lett.* ***2002***, *43*, 7405.
[1348] Nardi, M.; Sindona, G.; Costanzo, P.; Oliverio, M.; Procopio, A. *Tetrahedron* ***2015***, *71*, 1132.
[1349] Ranu, B.C.; Samanta, S. *J. Org. Chem.* ***2003***, *68*, 7130.
[1350] Xiang, J.; Sun, E.-X.; Lian, C.-X.; Yuan, W.-C.; Zhu, J.; Wang, Q.; Deng, J. *Tetrahedron* ***2012***, *68*, 4609.

accomplished with an imidazolidinone catalyst[1351] or an amino ester[1352] in the presence of a *Hantzsch ester* such as **25**.



25

Catalysts used for transfer hydrogenation include Pd,[1353] Ni,[1354] and Ti.[1355] A Hantzsch amido dihydropyridine has been used for transfer hydrogenation of conjugated ketones.[1356] Chiral dihydrobenzo[1,4]oxazines have been used as catalysts.[1357] *S*-Benzyl isothiouronium chloride has been used as a recoverable organocatalyst.[1358] Palladium/carbon with microwave heating is used for the transfer hydrogenation of conjugated carboxylic acids, using 1,4-cyclohexadiene as the hydrogen-transfer agent.[1359] Solvent-free transfer hydrogenation is possible using a Ru complex, with formic acid or water[1360] as the hydrogen donor.[1361]

Silanes reduce the C=C unit in conjugated systems in the presence of Cu species.[1362] An asymmetric CuH-catalyzed hydrosilation reaction is known.[1363] Phenylsilane ($PhSiH_3$) and a Ni,[1364] CuCl,[1365] Mn,[1366] or Mo[1367] catalyst have been used for hydrosilation reactions. Poly(methylhydrosiloxane) with a chiral Cu catalyst gave conjugate reduction of conjugated esters to give the saturated derivative with high enantioselectivity.[1368] A β-bromo conjugated lactone was reduced to the β-bromolactone with modest enantioselectivity using an excess of Ph_3SiH and a CuCl catalyst with a chiral ligand.[1369] Tributyltin hydride, in the presence of $MgBr_2 \bullet OEt_2$, gave 1,4-reduction of conjugated esters.[1370] Bulky tertiary amines in the presence of trichlorosilyl triflate reduced α,β-unsaturated ketones to give the corresponding saturated ketones.[1371] The enantioselective hydrogenation of β,β-disubstituted

[1351] See Tuttle, J.B.; Ouellet, S.G.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2006***, *128*, 12662; Adolfsson, H. *Angew. Chem. Int. Ed.* ***2005***, *44*, 3340.
[1352] Martin, N.J.A.; List, B. *J. Am. Chem. Soc.* ***2006***, *128*, 13368.
[1353] Brunel, J.M. *Synlett* ***2007***, 330; Ding, B.; Zhang, Z.; Liu, Y.; Sugiya, M.; Imamoto, T.; Zhang, W. *Org. Lett.* ***2013***, *15*, 3690.
[1354] Guo, S.; Yang, P.; Zhou, J. *Chem. Commun.* ***2015***, *51*, 12115.
[1355] Che, J.; Lam, Y. *Synlett* ***2010***, 2415.
[1356] Van Arman, S.A.; Zimmet, A.J.; Murray, I.E. *J. Org. Chem.* ***2016***, *81*, 3528.
[1357] Ebner, C.; Pfaltz, A. *Tetrahedron* ***2011***, *67*, 10287.
[1358] Nguyen, Q.P.B.; Kim, J.N.; Kim, T.H. *Tetrahedron* ***2012***, *68*, 6513.
[1359] Quinn, J.F.; Razzano, D.A.; Golden, K.C.; Gregg, B.T. *Tetrahedron Lett.* ***2008***, *49*, 6137.
[1360] Li, X.; Li, L.; Tang, Y.; Zhong, L.; Cun, L.; Zhu, J.; Liao, J.; Deng, J. *J. Org. Chem.* ***2010***, *75*, 2981.
[1361] Naskar, S.; Bhattacharjee, M. *Tetrahedron Lett.* ***2007***, *48*, 465.
[1362] See Mori, A.; Fujita, A.; Kajiro, H.; Nishihara, Y.; Hiyama, T. *Tetrahedron* ***1999***, *55*, 4573.
[1363] Huang, S.; Voigtritter, K.R.; Unger, J.B.; Lipshutz, B.H. *Synlett* ***2010***, 2041.
[1364] Boudjouk, P.; Choi, S.-B.; Hauck, B.J.; Rajkumar, A.B. *Tetrahedron Lett.* ***1998***, *39*, 3951.
[1365] Ito, H.; Ishizuka, T.; Arimoto, K.; Miura, K.; Hosomi, A. *Tetrahedron Lett.* ***1997***, *38*, 8887.
[1366] Magnus, P.; Waring, M.J.; Scott, D.A. *Tetrahedron Lett.* ***2000***, *41*, 9731.
[1367] Keinan, E.; Perez, D. *J. Org. Chem.* ***1987***, *52*, 2576.
[1368] See Jurkauskas, V.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 2892; Lipshutz, B.H.; Servesko, J.M.; Taft, B.R. *J. Am. Chem. Soc.* ***2004***, *126*, 8352.
[1369] Hughes, G.; Kimura, M.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2003***, *125*, 11253.
[1370] Hirasawa, S.; Nagano, H.; Kameda, Y. *Tetrahedron Lett.* ***2004***, *45*, 2207.
[1371] Kotani, S.; Osakama, K.; Sugiura, M.; Nakajima, M. *Org. Lett.* ***2011***, *13*, 3968.

conjugated carboxylic acids with a Rh catalyst used base-free conditions,[1372] and an Ir catalyst has also been used with tetrasubstituted alkene units of conjugated acids.[1373] The enantioselective hydrogenation of α,β-disubstituted nitroalkenes using a Rh catalyst has been reported.[1374]

Optically active homogeneous hydrogenation catalysts have been used to achieve the enantioselective hydrogenation[1375] of many prochiral conjugated substrates.[1376] For example,[1377] hydrogenation of (*Z*)-2-acetamido-3-phenylacrylic acid with a suitable catalyst gives (+)- or (−)-acetylphenylalanine (depending on which enantiomer of the catalyst is used) with an enantiomeric excess as high as 96%.[1378] Prochiral substrates that give such high optical yields generally contain functional groups such as a carbonyl group,[1379] amide groups, cyano groups, or combinations of such groups.[1380] The catalyst in such cases[1381] is usually a Ru[1382] or Rh complex[1383] with chiral phosphine ligands.[1384] Good asymmetric induction[1385] has been achieved using chiral Rh complexes with other chiral additives.[1386] Iridium complexes have been used with excellent enantioselectivity.[1387] The role of solvent has been examined.[1388] Asymmetric hydrogenation of conjugated carboxylic acids in an ionic liquid is known using a chiral Ru complex.[1389]

The C═C unit of conjugated aldehydes has been reduced using $AlMe_3$ with a catalytic amount of CuBr[1390] and with ammonium formate/Pd/C.[1391] Polymer-supported formate

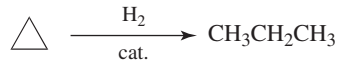
[1372] Yan, Q.; Kong, D.; Zhao, W.; Zi, G.; Hou, G. *J. Org. Chem.* ***2016***, *81*, 2070.
[1373] Song, S.; Zhu, S.-F.; Li, Y.; Zhou, Q.-L. *Org. Lett.* ***2013***, *15*, 3722.
[1374] Li, S.; Huang, K.; Zhang, X. *Chem. Commun.* ***2014***, *50*, 8878.
[1375] See Gridnev, I.D.; Imamoto, T. *Acc. Chem. Res.* ***2004***, *37*, 633.
[1376] Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* ***1989***, *45*, 6901 (pp. 6902–6916); Jardine, F.H. in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 751–775; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 53–87; Knowles, W.S. *Acc. Chem. Res.* ***1983***, *16*, 106; Brunner, H. *Angew. Chem. Int. Ed.* ***1983***, *22*, 897. See also, Knowles, W.S. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1999.
[1377] See Ashby, M.T.; Halpern, J. *J. Am. Chem. Soc.* ***1991***, *113*, 589; Heiser, B.; Broger, E.A.; Crameri, Y. *Tetrahedron: Asymmetry* ***1991***, *2*, 51; Burk, M.J. *J. Am. Chem. Soc.* ***1991***, *113*, 8518.
[1378] Koenig, K.E. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, p. 74.
[1379] Reetz, M.T.; Mehler, G. *Angew. Chem. Int. Ed.* ***2000***, *39*, 3889.
[1380] Koenig, K.E. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, pp. 83–101.
[1381] Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 8–12. See Mortreux, A.; Petit, F.; Buono, G.; Peiffer, G. *Bull. Soc. Chim. Fr.* ***1987***, 631.
[1382] See Wu, H.-P.; Hoge, G. *Org. Lett.* ***2004***, *6*, 3645.
[1383] Kanazawa, Y.; Tsuchiya, Y.; Kobayashi, K.; Shiomi, T.; Itoh, J.-i.; Kikuchi, M.; Yamamoto, Y.; Nishiyama, H. *Chem. Eur. J.* ***2006***, *12*, 63.
[1384] Fu, Y.; Guo, X.-X.; Zhu, S.-F.; Hu, A.-G.; Xie, J.-H.; Zhou, Q.-L. *J. Org. Chem.* ***2004***, *69*, 4648; Fu, Y.; Hou, G.-H.; Xie, J.-H.; Xing, L.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* ***2004***, *69*, 8157; Hoge, G.; Wu, H.-P.; Kissel, W.S.; Pflum, D.A.; Greene, D.J.; Bao, J. *J. Am. Chem. Soc.* ***2004***, *126*, 5966; Ikeda, S.-i.; Sanuki, R.; Miyachi, H.; Miyashita, H.; Taniguchi, M.; Odashima, K. *J. Am. Chem. Soc.* ***2004***, *126*, 10331; Hattori, G.; Hori, T.; Miyake, Y.; Nishibayashi, Y.J. *Am. Chem. Soc.* ***2007***, *129*, 12930.
[1385] Zhu, G.; Zhang, X. *J. Org. Chem.* ***1998***, *63*, 9590; Burk, M.J.; Casy, G.; Johnson, N.B. *J. Org. Chem.* ***1998***, *63*, 6084.
[1386] Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* ***1997***, *30*, 97.
[1387] Li, S.; Zhu, S.-F.; Zhang, C.-M.; Song, S.; Zhou, Q.-L. *J. Am. Chem. Soc.* ***2008***, *130*, 8584; Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. *Angew. Chem. Int. Ed.* ***2008***, *47*, 10133.
[1388] Heller, D.; Drexler, H.-J.; Spannenberg, A.; Heller, B.; You, J.; Baumann, W. *Angew. Chem. Int. Ed.* ***2002***, *41*, 777.
[1389] Brown, R.A.; Pollet, P.; McKoon, E.; Eckert, C.A.; Liotta, C.L.; Jessop, P.G. *J. Am. Chem. Soc.* ***2001***, *123*, 1254.
[1390] Kabbara, J.; Flemming, S.; Nickisch, K.; Neh, H.; Westermann, J. *Synlett* ***1994***, 679.
[1391] Ranu, B.C.; Sarkar, A. *Tetrahedron Lett.* ***1994***, *35*, 8649.

has been used for the 1,4-reduction of conjugated ketones[1392] and conjugated acids using a Rh catalyst and microwave irradiation.[1393] Isopropanol and an Ir catalyst give conjugate reduction of conjugated ketones.[1394] The reaction of conjugated ketones with aluminum chlorides, followed by treatment with water, generates the saturated ketone.[1395]

The use of frustrated Lewis pair dihydrogen activation gave selective hydrogenation of the carbon–carbon triple bond of conjugated ynones.[1396] The Rh-catalyzed enantioselective hydrogenation of unsaturated phosphonates has been reported.[1397]

Enzymatic reduction of conjugated systems requires reaction with certain purified or whole cell enzymes. Baker's yeast reduces conjugated nitro compounds to nitroalkanes[1398] and also reduces the C=C unit of conjugated ketones.[1399] Other enzymatic reductions are possible. A reductase from *Nicotiana tabacum* reduced a conjugated ketone to the saturated ketone, with excellent enantioselectivity.[1400] Enzyme YNAR-I and NADP-H reduces conjugated nitro compounds to nitroalkanes.[1401] Conjugated nitro compounds are reduced in the presence of *Clostridium sporogenes*.[1402]

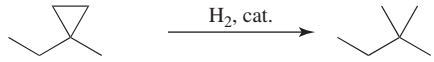
19-38 Reductive Cleavage of Cyclopropanes



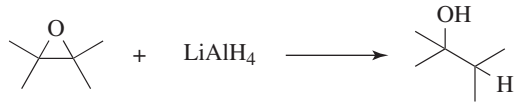
Cyclopropanes can be cleaved by catalytic hydrogenolysis.[1403] Among the catalysts used have been Ni, Pd, Rh,[1404] and Pt. The reaction can often be run under mild conditions.[1405] Certain cyclopropane rings, especially cyclopropyl ketones and aryl-substituted cyclopropanes,[1406] can be reductively cleaved by an alkali metal (generally Na or Li) in liquid ammonia.[1407] Similar reductions have been accomplished photochemically in the presence of $LiClO_4$.[1408] This reaction is an excellent way to introduce a *gem*-dimethyl

[1392] Basu, B.; Bhuiyan, Md.M.H.; Das, P.; Hossain, I. *Tetrahedron Lett.* ***2003***, *44*, 8931.
[1393] Desai, B.; Danks, T.N. *Tetrahedron Lett.* ***2001***, *42*, 5963.
[1394] Sakaguchi, S.; Yamaga, T.; Ishii, Y. *J. Org. Chem.* ***2001***, *66*, 4710.
[1395] Koltunov, K.Yu.; Repinskaya, I.B.; Borodkin, G.I. *Russ. J. Org. Chem.* ***2001***, *37*, 1534.
[1396] Xu, B.-H.; Kehr, G.; Fröhlich, R.; Wibbeling, B.; Schirmer, B.; Grimme, S.; Erker, G. *Angew. Chem. Int. Ed.* ***2011***, *50*, 7183.
[1397] Konno, T.; Shimizu, K.; Ogata, K.; Fukuzawa, S.-i. *J. Org. Chem.* ***2012***, *77*, 3318.
[1398] Kawai, Y.; Inaba, Y.; Tokitoh, N. *Tetrahedron: Asymmetry* ***2001***, *12*, 309.
[1399] Filho, E.P.S.; Rodrigues, J.A.R.; Moran, P.J.S. *Tetrahedron: Asymmetry* ***2001***, *12*, 847; Kawai, Y.; Hayashi, M.; Tokitoh, N. *Tetrahedron: Asymmetry* ***2001***, *12*, 3007.
[1400] Shimoda, K.; Kubota, N.; Hamada, H. *Tetrahedron: Asymmetry* ***2004***, *15*, 2443.
[1401] Kawai, Y.; Inaba, Y.; Hayashi, M.; Tokitoh, N. *Tetrahedron Lett.* ***2001***, *42*, 3367.
[1402] Fryszkowska, A.; Fisher, K.; Gardiner, J.M.; Stephens, G.M. *J. Org. Chem.* ***2008***, *73*, 4295.
[1403] See Charton, M. in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 588–592; Newham, J. *Chem. Rev.* ***1963***, *63*, 123; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, *NY*, ***1967***, pp. 469–474. See To, C.T.; Chan, K.S. *Tetrahedron Lett.* ***2016***, *57*, 4664.
[1404] Bart, S.C.; Chirik, P.J. *J. Am. Chem. Soc.* ***2003***, *125*, 886.
[1405] See Woodworth, C.W.; Buss, V.; Schleyer, P.v.R. *Chem. Commun.* ***1968***, 569.
[1406] See Walborsky, H.M.; Aronoff, M.S.; Schulman, M.F. *J. Org. Chem.* ***1970***, *36*, 1036.
[1407] For a review, see Staley, S.W. *Sel. Org. Transform.* ***1972***, *2*, 309.
[1408] Cossy, J.; Furet, N. *Tetrahedron Lett.* ***1993***, *34*, 8107.

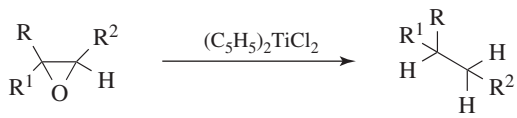
unit into a molecule. Hydrogenation of a cyclopropane ring, for example, gave the *gem*-dimethyl unit.



19-39 Reduction of Epoxides



Reduction of epoxides is a special case of **19-61** and is easily carried out.[1409] A common reagent is $LiAlH_4$,[1410] which reacts by the S_N2-type mechanism, giving inversion of configuration. An epoxide on a substituted cyclohexane ring cleaves in such a direction as to give an axial alcohol. As expected for an S_N2 mechanism, the hydrogen atom is usually delivered to the less-substituted carbon. The reaction has also been carried out with other reagents, for example, sodium amalgam in EtOH, Li in ethylenediamine,[1411] and by catalytic hydrogenolysis.[1412] Chemoselective and regioselective ring opening of allylic epoxides and of epoxy ketones and esters has been achieved with SmI_2,[1413] with $HCOOH/NEt_3$and a Pd catalyst,[1414] and with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al; also known as Vitride).[1415] Highly hindered epoxides can be conveniently reduced, without rearrangement, with lithium triethylborohydride (called Super Hydride).[1416] For certain substrates, the epoxide ring can be opened the other way by reduction with Pd/C and $HCOONH_4$,[1417] or with BH_3 in THF.[1418] The usual product of epoxide reductions is the alcohol, but epoxides are reduced all the way to the alkane by titanocene dichloride[1419] and by Et_3SiH/BH_3.[1420]

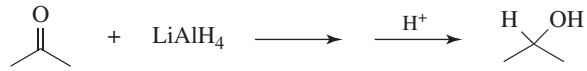


[1409] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1019–1027.
[1410] See Healy, E.F.; Lewis, J.D.; Minniear, A.B. *Tetrahedron Lett.* ***1994***, *35*, 6647.
[1411] Brown, H.C.; Ikegami, S.; Kawakami, J.H. *J. Org. Chem.* ***1970***, *35*, 3243.
[1412] See Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 478–485; Oshima, M.; Yamazaki, H.; Shimizu, I.; Nizar, M.; Tsuji, J. *J. Am. Chem. Soc.* ***1989***, *111*, 6280.
[1413] Molander, G.A.; La Belle, B.E.; Hahn, G. *J. Org. Chem.* ***1986***, *51*, 5259. See also, Miyashita, M.; Hoshino, M.; Suzuki, T.; Yoshikoshi, A. *Chem. Lett.* ***1988***, 507.
[1414] Noguchi, Y.; Yamada, T.; Uchiro, H.; Kobayashi, S. *Tetrahedron Lett.* ***2000***, *41*, 7493, 7499.
[1415] Gao, Y.; Sharpless, K.B. *J. Org. Chem.* ***1988***, *53*, 4081.
[1416] Krishnamurthy, S.; Schubert, R.M.; Brown, H.C. *J. Am. Chem. Soc.* ***1973***, *95*, 8486.
[1417] Ley, S.V.; Mitchell, C.; Pears, D.; Ramarao, C.; Yu, J.Q.; Zhou, W. *Org. Lett.* ***2003***, *5*, 4665.
[1418] See Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 345–348. See Yamamoto, Y.; Toi, H.; Sonoda, A.; Murahashi, S. *J. Chem. Soc., Chem. Commun.* ***1976***, 672.
[1419] van Tamelen, E.E.; Gladys, J.A. *J. Am. Chem. Soc.* ***1974***, *96*, 5290.
[1420] Fry, J.L.; Mraz, T.J. *Tetrahedron Lett.* ***1979***, 849.

Epoxy ketones are selectively reduced with lithium naphthalenide,[1421] or a Ca-mediated $NaBH_4$ reduction[1422] to the β-hydroxy ketone. Other reduction methods can lead to the epoxy alcohol. Reduction of epoxy amides with SmI_2 in methanol gave the α-hydroxy amide.[1423] Silica-coated magnetic nanoparticles, organic hydride, and 1-benzyl-1,4-dihydronicotinamide showed efficient activity in the catalytic reduction of α,β-epoxy ketones to β-hydroxy ketones.[1424] The reduction of α,β-epoxy ketones or 1,2-diketones to the corresponding β-hydroxy ketones or α-hydroxy ketones used a catalytic amount of BNAH (1-benzyl-1,4-dihydronicotinamide) or BNA^+Br^- in the presence of $HCOOH/Et_3N$.[1425]

Epi-sulfides can be reduced to give the alkene using Bu_3SnH in the presence of BEt_3.[1426]

19-40 Reduction of Aldehydes and Ketones to Alcohols[1427]



Aldehydes can be reduced to primary alcohols, and ketones to secondary alcohols, by a number of reducing agents.[1428] Among the most used are metal hydrides such as $LiAlH_4$, $NaBH_4$, and related compounds.[1429] The hydride affinity of various aldehydes and ketones[1430] and their thermodynamic hydricity[1431] have been determined. Hydride reagents have two main advantages over many other reducing agents: They do not reduce unactivated carbon-carbon double or triple bonds (with the exception of propargylic alcohols),[1432] and with $LiAlH_4$ all four hydrogen atoms are theoretically usable for reduction. Methods are available for titering hydride reagents.[1433] The scope of these reagents with ketones is similar to that with aldehydes.

The reaction is broad and general. Lithium aluminum hydride easily reduces aliphatic, aromatic, alicyclic, and heterocyclic aldehydes or ketones, containing double or triple bonds and/or nonreducible groups such as NR_3, OH, OR, and F. If the molecule contains a group reducible by $LiAlH_4$ (e.g., NO_2, CN, COOR), then that group is usually reduced. Since

[1421] Jankowska, R.; Liu, H.-J.; Mhehe, G.L *Chem. Commun.* ***1999***, 1581.
[1422] Forkel, N.V.; Henderson, D.A.; Fuchter, M.J. *Tetrahedron Lett.* ***2014***, *55*, 5511.
[1423] Concellón, J.M.; Bardales, E. *Org. Lett.* ***2003***, *5*, 4783.
[1424] Xu, H.-J.; Wan, X.; Shen, Y.-Y.; Xu, S.; Feng, Y.-S. *Org. Lett.* ***2012***, *14*, 1210.
[1425] Huang, Q.; Wu, J.-W.; Xu, H.-J. *Tetrahedron Lett.* ***2013***, *54*, 3877.
[1426] Uenishi, J.; Kubo, Y. *Tetrahedron Lett.* ***1994***, *35*, 6697.
[1427] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 310–344.
[1428] See Hudlicky, M. *Reductions in Organic Chemistry*, Ellis Horwood, Chichester, ***1984***, pp. 96–129. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1075–1113.
[1429] See Abdel-Magid, A.F. (Ed.) *Reductions in Organic Synthesis*, American Chemical Society, Washington, ***1996***; Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides*, VCH, NY, ***1991***; Hajos, A. *Complex Hydrides*, Elsevier, NY, ***1979***. See Feng, Y.-S.; Yang, C.-Y.; Huang, Q.; Xu, H.-J. *Tetrahedron* ***2012***, *68*, 5053.
[1430] Zhu, X.-Q.; Chen, X.; Mei, L.-R. *Org. Lett.* ***2011***, *13*, 2456.
[1431] Wiedner, E.S.; Chambers, M.B.; Pitman, C.L.; Bullock, R.M.; Miller, A.J.M.; Appel, A. *Chem. Rev.* ***2016***, *116*, 8655.
[1432] See Meta, C.T.; Koide, K. *Org. Lett.* ***2004***, *6*, 1785.
[1433] Hoye, T.R.; Aspaas, A.W.; Eklov, B.M.; Ryba, T.D. *Org. Lett.* ***2005***, *7*, 2205.

$LiAlH_4$ reacts readily with water and alcohols, protic solvents must be excluded. Despite limited solubility, common solvents are ether and THF. Lithium aluminum hydride reduces even sterically hindered ketones.

The compound $NaBH_4$ (sodium borohydride) has a similar scope, but is less reactive so it is more selective and so may be used in molecules that also contain NO_2, Cl, COOR, CN, and so on. Another advantage of $NaBH_4$ is that it can be used in water or alcoholic solvents, and so is available to reduce compounds, such as sugars, that are not soluble in ethers.[1434] Other solvents can be used with some modification of the borohydride. For example, butyltriphenylphosphonium borohydride reduces aldehydes to alcohols in dichloromethane.[1435] Reduction with $NaBH_4$ activated by solid acid has been reported.[1436] A polymer-bound phase-transfer material that uses $NaBH_4$ in wet THF has also been reported.[1437] Sodium borohydride on alumina, under microwave irradiation, is an effective reagent.[1438] Sodium borohydride has been used on silica gel.[1439] The aqueous borohydride reduction of carbonyls used sealed tube microwave conditions.[1440]

Addition of cerium salts to sodium borohydride leads to a reagent, presumably cerium borohydride (known as the *Luche reagent*),[1441] that gives very selective 1,2-reduction of conjugated aldehydes and ketones.[1442] The carbonyl of a conjugated ketone is reduced faster than that of a normal ketone. A cerium-free *Luche reduction* (1,2-reduction) on rehydrated alumina has been reported.[1443]

When a functional group is selectively attacked in the presence of a different functional group, the reaction is said to be *chemoselective*.[1444] A number of reagents have been found to reduce aldehydes much faster than they reduce ketones. Among these reagents[1445] are sodium triacetoxyborohydride,[1446] $NaBH_4/HCO_2H$,[1447] and zinc borohydride in THF.[1448] Ketones can be chemoselectively reduced in the presence of aldehydes with $NaBH_4$ in aqueous EtOH at −15 °C in the presence of cerium trichloride ($CeCl_3$).[1449] The reagent lithium *n*-dihydropyridylaluminum hydride reduces diaryl ketones much better than dialkyl or alkyl aryl ketones.[1450] Most other hydrides reduce diaryl ketones more slowly than other types of ketones. Saturated ketones can be reduced in the presence of α,β-unsaturated ketones with zinc borohydride.[1451]

[1434] See Toda, F.; Kiyoshige, K.; Yagi, M. *Angew. Chem. Int. Ed.* ***1989***, *28*, 320.
[1435] Hajipour, A.R.; Mallakpour, S.E. *Synth. Commun.* ***2001***, *31*, 1177.
[1436] Cho, B.T.; Kang, S.K.; Kim, M.S.; Ryu, S.R.; An, D.K. *Tetrahedron* ***2006***, *62*, 8164.
[1437] Tamami, B.; Mahdavi, H. *Tetrahedron* ***2003***, *59*, 821.
[1438] Varma, R.S.; Saini, R.K. *Tetrahedron Lett.* ***1997***, *38*, 4337.
[1439] Liu, W.-y.; Xu, Q.-h.; Ma, Y.-x. *Org. Prep. Proceed. Int.* ***2000***, *32*, 596.
[1440] Murphree, S.S.; Mason, J.D.; Bean, T.G.; Perry, M.C. *Synth. Commun.* ***2012***, *42*, 1979.
[1441] Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis*, 2nd ed., Wiley-Interscience, NJ, ***2005***, p. 805.
[1442] Crimmins, M.T.; O'Mahoney, R. *J. Org. Chem.* ***1989***, *54*, 1157.
[1443] Jones-Mensah, E.; Nickerson, L.A.; Deobald, J.L.; Knox, H.J.; Ertel, A.B.; Magolan, J. *Tetrahedron* ***2016***, *72*, 3748.
[1444] See Luibrand, R.T.; Taigounov, I.R.; Taigounov, A.A. *J. Org. Chem.* ***2001***, *66*, 7254.
[1445] See Borbaruah, M.; Barua, N.C.; Sharma, R.P. *Tetrahedron Lett.* ***1987***, *28*, 5741.
[1446] See Nutaitis, C.F.; Gribble, G.W. *Tetrahedron Lett.* ***1983***, *24*, 4287.
[1447] Blanton, J.R. *Synth. Commun.* ***1997***, *27*, 2093.
[1448] Ranu, B.C.; Chakraborty, R. *Tetrahedron Lett.* ***1990***, *31*, 7663; See Ranu, B. *Synlett* ***1993***, 885.
[1449] See Li, K.; Hamann, L.G.; Koreeda, M. *Tetrahedron Lett.* ***1992***, *33*, 6569.
[1450] Lansbury, P.T.; Peterson, J.O. *J. Am. Chem. Soc.* ***1962***, *84*, 1756.
[1451] Sarkar, D.C.; Das, A.R.; Ranu, B.C. *J. Org. Chem.* ***1990***, *55*, 5799.

In general, $NaBH_4$ reduces carbonyl compounds in the order aldehydes > α,β-unsaturated aldehydes > ketones > α,β-unsaturated ketones, and a carbonyl group of one type can be selectively reduced in the presence of a carbonyl group of a less reactive type.[1452] A number of reagents will preferentially reduce the less sterically hindered of two carbonyl compounds, but by the use of diisobutylaluminum hydride (DIBALH, *i*-Bu_2AlH) in the presence of the Lewis acid methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide), it was possible selectively to reduce the *more hindered* of a mixture of two ketones.[1453] Diisobutylaluminum hydride is a strong reducing reagent, reducing most functional groups, and is most commonly used for the reduction of functional groups other than aldehydes or ketones. It is obvious that reagents can often be found to reduce one kind of carbonyl function in the presence of another.[1454] Quinones are reduced to hydroquinones by $LiAlH_4$, $SnCl_2$/HCl, or sodium hydrosulfite $Na_2S_2O_4$, as well as by other reducing agents.

Sodium bis(2-methoxyethoxy)aluminum hydride ($NaAlH_2(OC_2H_4OMe)_2$; Red-Al) was prepared by Vit in 1967,[1455] and its reducing power is close to that of lithium aluminum hydride. In addition, it is stable to dry air (it does not ignite in even moist air or oxygen) and is thermally stable up to 200 °C. The greatest practical utility of Red-Al is its solubility in aromatic hydrocarbon and ether solvents, which allows it to be conveniently used for applications that require inverse addition of hydrides. Red-Al essentially reacts in the same way as $LiAlH_4$, reducing aldehydes, ketones[1456] and acid derivatives to alcohols.[1457] Reduction of conjugated carbonyls gives primarily 1,2-reduction to an allylic alcohol.[1458] Other functional groups can be reduced.[1459]

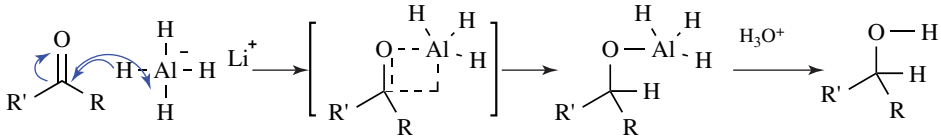
The C═C units in compounds that contain C═O double bonds are generally not affected by metallic hydrides. The C═C unit may be isolated or conjugated, but double bonds that are conjugated with the C═O group may or may not be reduced, depending on the substrate, reagent, and reaction conditions.[1460] Some reagents that reduce only the C═O bonds of α,β-unsaturated aldehydes and ketones are AlH_3,[1461] $NaBH_4$, or $LiAlH_4$ in the presence of lanthanide salts,[1462] Co complexes,[1463] $NaBH_4/LiClO_4$,[1464] $NaBH_3(OAc)$,[1465] and

[1452] Ward, D.E.; Rhee, C.K. *Can. J. Chem.* ***1989***, *67*, 1206.
[1453] Maruoka, K.; Araki, Y.; Yamamoto, H. *J. Am. Chem. Soc.* ***1988***, *110*, 2650.
[1454] For lists, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1089–1092, and references given in Ward, D.E.; Rhee, C.K. *Can. J. Chem.* ***1989***, *67*, 1206.
[1455] Vit, J.; Másensky, B.; Machácek, J. *French Patent*, 1 515 582 ***1968*** (*Chem. Abstr. 70*: 115009x, ***1967***); Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 2, Wiley, New York, ***1969***, p. 382; Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 3, Wiley, New York, ***1972***, p. 260.
[1456] See Stotter, P.L.; Friedman, M.D.; Minter, D.E. *J. Org. Chem.* ***1985***, *50*, 29.
[1457] Zurflüh, R.; Dunham, L.L.; Spain, V.L.; Siddall, J.B. *J. Am. Chem. Soc.* ***1970***, *92*, 425.
[1458] See McCarry, B.E.; Markezich, R.L.; Johnson, W.S *J. Am. Chem. Soc.* ***1973***, *95*, 4416.
[1459] See Kesenheimer, C.; Groth, U. *Org. Lett.* ***2006***, *8*, 2507; White, J.D.; Choi, Y. *Org. Lett.* ***2000***, *2*, 2373; Gao, Y.; Sharpless, K.B. *J. Org. Chem.* ***1988***, *53*, 4081. Maloney, D.J.; Hecht, S.M. *Org. Lett.* ***2005***, *7*, 4297.
[1460] See Keinan, E.; Greenspoon, N. in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, ***1989***, pp. 923–1022.
[1461] Dilling, W.L.; Plepys, R.A. *J. Org. Chem.* ***1970***, *35*, 2971.
[1462] See Fukuzawa, S.; Fujinami, T.; Yamauchi, S.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* ***1986***, 1929. See also, Chênevert, R.; Ampleman, G. *Chem. Lett.* ***1985***, 1489; Varma, R.S.; Kabalka, G.W. *Synth. Commun.* ***1985***, *15*, 985.
[1463] Ohtsuka, Y.; Koyasu, K.; Ikeno, T.; Yamada, T. *Org. Lett.* ***2001***, *3*, 2543.
[1464] Halimjani, A.Z.; Saidi, M.R. *Synth. Commun.* ***2005***, *35*, 2271.
[1465] Nutaitis, C.F.; Bernardo, J.E. *J. Org. Chem.* ***1989***, *54*, 5629.

$Zn(BH_4)_2$[1466] on Y zeolite.[1467] Also, both $LiAlH_4$[1468] and $NaBH_4$[1469] predominantly reduce only the C=O bonds of C=C—C=O systems in most cases, although substantial amounts of fully saturated alcohols have been found in some cases.[1468] A mixture of $InCl_3$ and $NaBH_4$ reduced both the C=C and C=O units of conjugated ketones.[1470]

The reagent lithium tri-*sec*-butylborohydride $LiBH(sec\text{-}Bu)_3$ (L-Selectride) reduces cyclic and bicyclic ketones in a highly stereoselective manner.[1471] For example, 2-methylcyclohexanone gave *cis*-2-methylcyclohexanol with an isomeric purity greater than 99%. Both L-Selectride and the potassium salt (K-Selectride) reduce carbonyls in cyclic and acyclic molecules with high diastereoselectivity.[1472] The more usual reagents, for example, $LiAlH_4$ and $NaBH_4$, reduce relatively unhindered cyclic ketones either with little or no stereoselectivity[1473] or give predominant formation of the more stable isomer (axial attack).[1474] Cyclohexanones that have a large degree of steric hindrance near the carbonyl group usually give predominant formation of the less stable alcohol, even with $LiAlH_4$ and $NaBH_4$.

With most hydride reagents there is an initial attack on the carbon of the carbonyl group by a hydride equivalent (H^-), but with BH_3[1475] the initial attack is on the oxygen. Detailed mechanisms are not known in most cases.[1476] With $LiAlH_4$ or $NaBH_4$, the attacking species is the AlH_4^- (or BH_4^-) ion, which, in effect, transfers H^- to the acyl carbon via a four-center transition state (**26**) to give the alkoxyaluminate.[1477] Hydrolysis in a second step gives the alcohol.



26

The mechanism is probably the same for $NaBH_4$, except that B replaces Al in the sequence shown. Evidence that the cation plays an essential role, at least in some cases, is that when the Li^+ was effectively removed from $LiAlH_4$ (by the addition of a crown ether), the reaction did not take place.[1478] For $NaBH_4$, the Na^+ does not seem to participate

[1466] For a review of the reactivity of this reagent, see Ranu, B. *Synlett* ***1993***, 885.
[1467] Sreekumar, R.; Padmakumar, R.; Rugmini, P. *Tetrahedron Lett.* ***1998***, *39*, 5151.
[1468] Johnson, M.R.; Rickborn, B. *J. Org. Chem.* ***1970***, *35*, 1041.
[1469] Chaikin, S.W.; Brown, W.G. *J. Am. Chem. Soc.* ***1949***, *71*, 122.
[1470] Ranu, B.C.; Samanta, S. *Tetrahedron* ***2003***, *59*, 7901.
[1471] Krishnamurthy, S.; Brown, H.C. *J. Am. Chem. Soc.* ***1976***, *98*, 3383.
[1472] K-Selectride: Lawson, E.C.; Zhang, H.-C.; Maryanoff, B.E. *Tetrahedron Lett.* ***1999***, *40*, 593.
[1473] Caro, B.; Boyer, B.; Lamaty, G.; Jaouen, G. *Bull. Soc. Chim. Fr.* ***1983***, II-281; Boone, J.R.; Ashby, E.C. *Top. Stereochem.* ***1979***, *11*, 53; Wigfield, D.C. *Tetrahedron* ***1979***, *35*, 449; Tramontini, M. *Synthesis* ***1982***, 605.
[1474] See Mukherjee, D.; Wu, Y.; Fronczek, F.R.; Houk, K.N. *J. Am. Chem. Soc.* ***1988***, *110*, 3328.
[1475] See Brown, H.C.; Wang, K.K.; Chandrasekharan, J. *J. Am. Chem. Soc.* ***1983***, *105*, 2340.
[1476] See Caro, B.; Boyer, B.; Lamaty, G.; Jaouen, G. *Bull. Soc. Chim. Fr.* ***1983***, II-281; Boone, J.R.; Ashby, E.C. *Top. Stereochem.* ***1979***, *11*, 53; Wigfield, D.C. *Tetrahedron* ***1979***, *35*, 449.
[1477] Ashby, E.C.; Boone, J.R. *J. Am. Chem. Soc.* ***1976***, *98*, 5524. House, H.O. *Modern Synthetic Reactions*, 2nd ed., Benjamin, Menlo Park, CA, ***1972***, p. 49 and citations 5, 12, and 14 therein.
[1478] Pierre, J.; Handel, H. *Tetrahedron Lett.* ***1974***, 2317. See also, Loupy, A.; Seyden-Penne, J.; Tchoubar, B. *Tetrahedron Lett.* ***1976***, 1677; Ashby, E.C.; Boone, J.R. *J. Am. Chem. Soc.* ***1976***, *98*, 5524.

in the transition state, but kinetic evidence shows that an OR group from the solvent does participate and remains attached to B.[1479]

The question of whether the initial complex in the $LiAlH_4$ reduction can reduce another carbonyl to give $(H{-}C{-}O)_2Al^-H_4$ and so on has been controversial. It has been shown[1480] that this is probably not the case but that, more likely, the initially formed alkoxyaluminate disproportionates to $(H{-}C{-}O)_4Al^-$ and AlH_4^-, which is the only attacking species. Disproportionation has also been reported in the $NaBH_4$ reaction.[1481]

An alkoxyaluminate is essentially $LiAlH_4$ with one of the hydrogen atoms replaced by an alkoxy group, that is, $LiAlH_3OR$. The fact that alkoxyaluminates and other alkoxy derivatives of $LiAlH_4$ are less reactive than $LiAlH_4$ itself has led to the use of such compounds as reducing agents that are less reactive and more selective than $LiAlH_4$.[1482] An example is $LiAlH(O\text{-}t\text{-}Bu)_3$. As an example of chemoselectivity in this reaction it may be mentioned that $LiAlH(O\text{-}t\text{-}Bu)_3$ has been used to reduce only the keto group in a molecule containing both keto and carboxylic ester groups.[1483] However, the use of such reagents is sometimes complicated by the disproportionation mentioned above, which may cause $LiAlH_4$ to be the active species, even if the reagent is an alkoxy derivative. Another highly selective reagent (reducing aldehydes and ketones, but not other functional groups), which does not disproportionate, is potassium triisopropoxyborohydride.[1484]

Other reagents reduce aldehydes and ketones to alcohols.[1485]

1. *Hydrogen and a catalyst*.[1486] Catalytic hydrogenation of alkenes and alkynes is discussed in **19-34**. Aldehydes and ketones are readily reduced to alcohols. Common heterogeneous catalysts for carbonyls are Pt and Ru,[1487] Au,[1488] Ag,[1489] Mn,[1490] Pd,[1491] and homogeneous catalysts are commonly used,[1492] especially for

[1479] Wigfield, D.C.; Gowland, F.W. *J. Org. Chem.* ***1977***, *42*, 1108. See, however, Kayser, M.M.; Eliev, S.; Eisenstein, O. *Tetrahedron Lett.* ***1983***, *24*, 1015.

[1480] Haubenstock, H.; Eliel, E.L. *J. Am. Chem. Soc.* ***1962***, *84*, 2363; Malmvik, A.; Obenius, U.; Henriksson, U. *J. Chem. Soc., Perkin Trans. 2* ***1986***, 1899, 1905.

[1481] Malmvik, A.; Obenius, U.; Henriksson, U. *J. Org. Chem.* ***1988***, *53*, 221.

[1482] For reviews of reductions with alkoxyaluminum hydrides, see Málek, J. *Org. React.* ***1988***, *36*, 249; ***1985***, *34*, 1; Málek, J.; Cerny, M. *Synthesis* ***1972***, 217.

[1483] Levine, S.G.; Eudy, N.H. *J. Org. Chem.* ***1970***, *35*, 549; Heusler, K.; Wieland, P.; Meystre, C. *Org. Synth.* ***V***, 692.

[1484] Brown, C.A.; Krishnamurthy, S.; Kim, S.C. *J. Chem. Soc., Chem. Commun.* ***1973***, 391.

[1485] See Feoktistov, L.G.; Lund, H. in Baizer, M.M.; Lund, H. *Organic Electochemistry*, Marcel Dekker, NY, ***1983***, pp. 315–358 (pp. 315–326). See also, Coche, L.; Moutet, J. *J. Am. Chem. Soc.* ***1987***, *109*, 6887.

[1486] Abdel-Magid, A.F. (Ed.), *Reductions in Organic Synthesis*, American Chemical Society, Washington, DC, ***1996***, pp. 31–50; Parker, D. in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 979–1047; Tanaka, K. in Cerveny, L. *Catalytic Hydrogenation*, Elsevier, NY, ***1986***, pp. 79–104; Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 66–77; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY., ***1967***, pp. 238–290; Fleischer, S.; Zhou, S.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* ***2013***, *52*, 5120.

[1487] Tan, X.; Wang, G.; Zhu, Z.; Ren, C.; Zhou, J.; Lv, H.; Zhang, X.; Chung, L.W.; Zhang, L.; Zhang, X. *Org. Lett.* ***2016***, *18*, 1518; Puylaert, P.; van Heck, R.; Fan, Y.; Spannenberg, A.; Baumann, W.; Beller, M.; Medlock, J.; Bonrath, W.; Lefort, L.; Hinze, S.; de Vries, J.G. *Chem. Eur. J.* ***2017***, *23*, 847.

[1488] Cano, I.; Chapman, A.M.; Urakawa, A.; van Leeuwen, P.W.N.M. *J. Am. Chem. Soc.* ***2014***, *136*, 2520.

[1489] Jia, Z.; Zhou, F.; Liu, M.; Li, X.; Chan, A.S.C.; Li, C.-J. *Angew. Chem. Int. Ed.* ***2013***, *52*, 11871.

[1490] Elangovan, S.; Topf, C.; Fischer, S.; Jiao, H.; Spannenberg, A.; Baumann, W.; Ludwig, R.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* ***2016***, *138*, 8809.

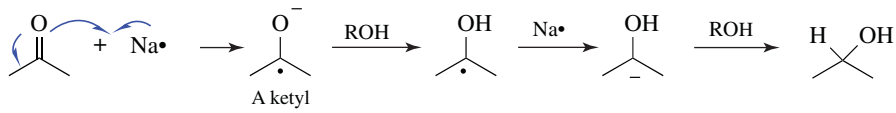
[1491] Lee, J.K.; Kim, M.-J. *Tetrahedron Lett.* ***2011***, *52*, 499.

[1492] See Heck, R.F. *Organotransition Metal Chemistry*, Academic Press, NY, ***1974***, pp. 65–70; Enthaler, S.; Hagemann, B.; Erre, G.; Junge, K.; Beller, M. *Chem. Asian J.* ***2006***, *1*, 598.

asymmetric hydrogenation. Frustrated Lewis pairs have been used to enable catalytic hydrogenation.[1493] Before the discovery of the metal hydrides, hydrogenation was one of the most common ways of effecting this reduction, but it suffers from the fact that C=C, C≡C, C=N, and C≡N bonds are also susceptible to reduction and there is often little or no selectivity for the C=O group.[1494] For aromatic aldehydes and ketones, reduction to the hydrocarbon (**19-66**) is a side reaction via hydrogenolysis of the initially produced alcohol (**19-59**). The mechanism of catalytic hydrogenation of aldehydes and ketones is probably similar to that of reaction **19-34**.[1495] A Pt/Co catalyst has been developed for the 1,2-reduction of conjugated aldehydes.[1496] Iron catalysts[1497] have been reported to show high chemoselectivity for the reduction of aldehydes with an isolated C=C bond.[1498]

2. *Sodium in ethanol*.[1499] This procedure is called the *Bouveault-Blanc procedure* and was more popular for the reduction of carboxylic esters (**19-42**) than of aldehydes or ketones before the discovery of $LiAlH_4$.

   Formation of a ketyl intermediate that is converted to a radical and then a carbanion prior to protonation[1500] has been suggested for the reaction with sodium in ethanol.[1501] The ketyl intermediate can be isolated.[1502]



A ketyl

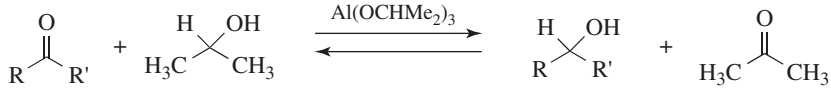
   Lithium is often a superior metal for alkali metal reductions.[1503]

3. *Other metal reductions*. A single carbonyl group of an α-diketone can be reduced to give an α-hydroxy ketone by heating with Zn powder in aqueous DMF[1504] or by heating with Zn in methanol in the presence of benzyltriethylammonium chloride.[1505] Aluminum and NaOH in aqueous methanol reduces ketones.[1506] β-Hydroxy ketones are reduced with good *anti* selectivity using an excess of SmI_2 in water,[1507] and other ketones or aldehydes are reduced with SmI_2[1508] in aqueous THF[1509] or with SmI_2

[1493] Marek, A.; MarPedersen, M.H.F. *Tetrahedron* ***2015***, *71*, 917; Mahdi, T.; Stephan, D.W. *Angew. Chem. Int. Ed.* ***2015***, *54*, 8511. See Scott, D.J.; Fuchter, M.J.; Ashley, A.E. *J. Am. Chem. Soc.* ***2014***, *136*, 15813.
[1494] See Narasimhan, C.S.; Deshpande, V.M.; Ramnarayan, K. *J. Chem. Soc., Chem. Commun.* ***1988***, 99.
[1495] See, however, Pavlenko, N.V. *Russ. Chem. Rev.* ***1989***, *58*, 453.
[1496] Wu, B.; Huang, H.; Yang, J.; Zheng, N.; Fu, G. *Angew. Chem. Int. Ed.* ***2012***, *51*, 3440.
[1497] Wienhöfer, G.; Westerhaus, F.A.; Junge, K.; Ludwig, R.; Beller, M. *Chem. Eur. J.* ***2013***, *19*, 7701.
[1498] Lu, X.; Cheng, R.; Turner, N.; Liu, Q.; Zhang, M.; Sun, X. *J. Org. Chem.* ***2014***, *79*, 9355.
[1499] See House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 152–160.
[1500] Pradhan, S.K. *Tetrahedron* ***1986***, *42*, 6351; Huffman, J.W. *Acc. Chem. Res.* ***1983***, *16*, 399. See Rautenstrauch, V. *Tetrahedron* ***1988***, *44*, 1613; Song, W.M.; Dewald, R.R. *J. Chem. Soc., Perkin Trans. 2* ***1989***, 269; Rassat, A. *Pure Appl. Chem.* ***1977***, *49*, 1049.
[1501] House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, p. 151. See, however, Giordano, C.; Perdoncin, G.; Castaldi, G. *Angew. Chem. Int. Ed.* ***1985***, *24*, 499.
[1502] See Rautenstrauch, V.; Geoffroy, M. *J. Am. Chem. Soc.* ***1976***, *98*, 5035; ***1977***, *99*, 6280.
[1503] Rees, N.V.; Baron, R.; Kershaw, N.M.; Donohoe, T.J.; Compton, R.G. *J. Am. Chem. Soc.* ***2008***, *130*, 12256.
[1504] Kreiser, W. *Liebigs Ann. Chem.* ***1971***, *745*, 164.
[1505] Kardile, G.B.; Desai, D.G.; Swami, S.S. *Synth. Commun.* ***1999***, *29*, 2129.
[1506] Bhar, S.; Guha, S. *Tetrahedron Lett.* ***2004***, *45*, 3775.
[1507] Keck, G.E.; Wager, C.A.; Sell, T.; Wager, T.T. *J. Org. Chem.* ***1999***, *64*, 2172.
[1508] See Prasad, E.; Flowers II, R.A. *J. Am. Chem. Soc.* ***2002***, *124*, 6895.
[1509] Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* ***2002***, *43*, 7197.

in alcohols.[1510] Other metals can be used, including Mg in alcohols.[1511] Titanocene and Mn in water reduced acetophenone to the benzylic alcohol.[1512] 1,2-Diketones were reduced to the α-hydroxy ketone with TiI_4 in acetonitrile, followed by hydrolysis.[1513] Ammonia and aqueous $TiCl_3$ in methanol reduces ketones.[1514] Ketones were reduced to the alcohol by treatment with a lithium•water dispersion and either $FeCl_2 \cdot 4H_2O$ or $CuCl_2 \cdot 2H_2O$ in THF.[1515] Ketones were reduced to alcohols using a Ni/Al alloy and 2.8 kbar pressure in an aqueous medium.[1516] Aromatic ketones have been reduced using a Rh complex.[1517] Functionalized acetylenic ketones have been reduced.[1518]

4. *Isopropyl alcohol and aluminum isopropoxide*.[1519] This is called the *Meerwein-Ponndorf-Verley reduction*.[1520] It is reversible, and the reverse reaction is known as the *Oppenauer oxidation* (see **19-3**):

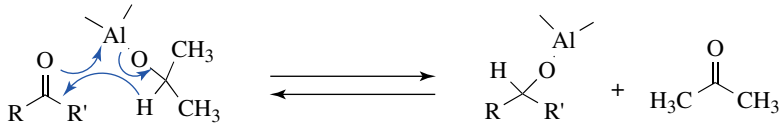


The equilibrium is shifted by removal of the acetone by distillation. There is a report of the reduction of benzaldehyde to benzyl alcohol by heating with propan-2-ol at 225 °C for 1 day.[1521] The reaction usually takes place under very mild conditions and is highly specific for aldehydes and ketones, so that C=C bonds (including those conjugated with the C=O bonds) and many other functional groups can be present without themselves being reduced.[1522] This high specificity includes acetals, so that one of two carbonyl groups in a molecule can be specifically reduced if the other is first converted to an acetal. β-Keto esters, β-diketones, and other ketones and aldehydes with a relatively high enol content do not give this reaction. Zeolites have been used as a medium for this reduction.[1523] Indium tri(isopropoxide)[1524] and ytterbium triflate[1525] have been used as catalysts.

[1510] Fukuzawa, S.-i.; Nakano, N.; Saitoh, T. *Eur. J. Org. Chem.* ***2004***, 2863. See Upadhyay, S.K.; Hoz, S. *J. Org. Chem.* ***2011***, *76*, 1355.
[1511] Kim, J.Y.; Kim, H.D.; Seo, M.J.; Kim, H.R.; No, Z.; Ha, D.-C.; Lee, G.H. *Tetrahedron Lett.* ***2006***, *47*, 9; Chopade, P.R.; Davis, T.A.; Prasad, E.; Flowers II, R.A. *Org. Lett.* ***2004***, *6*, 2685.
[1512] Rosales, A.; Muñoz-Bascón, J.; Roldan-Molina, E.; Castañeda, M.A.; Padial, N.M.; Gansäuer, A.; Rodríguez-García, I.; Oltra, J.E. *J. Org. Chem.* ***2014***, *79*, 7672.
[1513] Hayakawa, R.; Sahara, T.; Shimizu, M. *Tetrahedron Lett.* ***2000***, *41*, 7939.
[1514] Clerici, A.; Pastori, N.; Porta, O. *Eur. J. Org. Chem.* ***2001***, 2235.
[1515] Kennedy, N.; Cohen, T. *J. Org. Chem.* ***2015***, *80*, 8134.
[1516] Tomin, A.; Lazarev, A.; Bere, M.P.; Redjeb, H.; Török, B. *Org. Biomol. Chem.* ***2012***, *10*, 7321.
[1517] Aupoix, A.; Bournaud, C.; Vo-Thanh, G. *Eur. J. Org. Chem.* ***2011***, 2772.
[1518] Fang, Z.; Wills, M. *J. Org. Chem.* ***2013***, *78*, 8594.
[1519] McNerney, B.; Whittlesey, B.; Cordes, D.B.; Krempner, C. *Chem. Eur. J.* ***2014***, *20*, 14959.
[1520] See Maruoka, K.; Saito, S.; Concepcion, A.B.; Yamamoto, H. *J. Am. Chem. Soc.* ***1993***, *115*, 1183. For a microwave-induced version of this reaction, see Barbry, D.; Torchy, S. *Tetrahedron Lett.* ***1997***, *38*, 2959.
[1521] Bagnell, L.; Strauss, C.R. *Chem. Commun.* ***1999***, 287.
[1522] See Namy, J.L.; Souppe, J.; Collin, J.; Kagan, H.B. *J. Org. Chem.* ***1984***, *49*, 2045; Okano, T.; Matsuoka, M.; Konishi, H.; Kiji, J. *Chem. Lett.* ***1987***, 181.
[1523] Corma, A.; Domine, M.E.; Nemeth, L.; Valencia, S. *J. Am. Chem. Soc.* ***2002***, *124*, 3194.
[1524] Lee, J.; Ryu, T.; Park, S.; Lee, P.H. *J. Org. Chem.* ***2012***, *77*, 4821.
[1525] Mollica, A.; Genovese, S.; Pinnen, F.; Stefanucci, A.; Curini, M.; Epifano, F. *Tetrahedron Lett.* ***2012***, *53*, 890.

This reduction can be done catalytically[1526] and an aluminum-free, Zr/zeolite catalyst has been developed.[1527] Microwave irradiation of a ketone with propan-2-ol, KOH, and activated alumina gives good yields of the alcohol.[1528] When the carbonyl substrate has a stereogenic center, the reaction proceeds with good diastereoselectivity.[1529] A combination of propan-2-ol with BINOL and $AlMe_3$ leads to reduction of α-chloro ketones to the chlorohydrin with good enantioselectivity.[1530]

The Meerwein-Ponndorf-Verley reaction usually[1531] involves a cyclic transition state, as shown:[1532]



but in some cases 2 molar equivalents of aluminum alkoxide are involved: one attacking the carbon and the other the oxygen, a conclusion that stems from the finding that in these cases the reaction was 1.5 order in alkoxide.[1533] *The alcohol solvent acts as a hydrogen donor in this reaction*.[1534] Although, for simplicity, the alkoxide is shown as a monomer, it actually exists as trimers and tetramers, which are the actual reactive species.[1535] It is noted that supercritical propan-2-ol has been used for reduction of ketones, without the need for a catalyst.[1536]

5. *Boranes*. Borane (BH_3) and substituted boranes reduce aldehydes and ketones in a manner similar to their addition to C=C bonds (**15-11**).[1537] That is, the boron adds to the oxygen and the hydrogen to the carbon.[1538] The resulting borate is then hydrolyzed to the alcohol. A variety of alkylboranes can be used for reduction.[1539] Both 9-BBN[1540] (**15-11**) and BH_3/Me_2S[1541] reduce only the C=O group of conjugated aldehydes and ketones.[1542] Tributylborane in ionic solvents reduces aldehydes to alcohols.[1543] Enantioselective borane reductions lead to chiral alcohols.[1544] Spiroborate esters have been used for enantioselective

[1526] Campbell, E.J.; Zhou, H.; Nguyen, S.T. *Org. Lett.* ***2001***, *3*, 2391. See Albrecht, M.; Crabtree, R.H.; Mata, J.; Peris, E. *Chem. Commun.* ***2002***, 32.
[1527] Zhu, Y.; Chuah, G.; Jaenicke, S. *Chem. Commun.* ***2003***, 2734.
[1528] Kazemi, F.; Kiasat, A.R. *Synth. Commun.* ***2002***, *32*, 2255.
[1529] Yin, J.; Huffman, M.A.; Conrad, K.M.; Armstrong III, J.D. *J. Org. Chem.* ***2006***, *71*, 840.
[1530] Campbell, E.J.; Zhou, H.; Nguyen, S.T. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1020.
[1531] See, however, Ashby, E.C.; Argyropoulos, J.N. *J. Org. Chem.* ***1986***, *51*, 3593; Yamataka, H.; Hanafusa, T. *Chem. Lett.* ***1987***, 643.
[1532] Warnhoff, E.W.; Reynolds-Warnhoff, P.; Wong, M.Y.H. *J. Am. Chem. Soc.* ***1980***, *102*, 5956.
[1533] Moulton, W.N.; Van Atta, R.E.; Ruch, R.R. *J. Org. Chem.* ***1961***, *26*, 290.
[1534] Galian, R.E.; Litwinienko, G.; Pérez-Prieto, J.; Ingold, K.U. *J. Am. Chem. Soc.* ***2007***, *129*, 9280.
[1535] Shiner Jr., V.J.; Whittaker, D. *J. Am. Chem. Soc.* ***1969***, *91*, 394.
[1536] Kamitanaka, T.; Matsuda, T.; Harada, T. *Tetrahedron* ***2007***, *63*, 1429.
[1537] See Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 324–335. See Abe, M.; Yamataka, H. *J. Phys. Org. Chem.* ***2012***, *25*, 502.
[1538] See Brown, H.C.; Korytnyk, W. *J. Am. Chem. Soc.* ***1960***, *82*, 3866.
[1539] Bae, J.W.; Lee, S.H.; Jung, Y.J.; Yoon, C.-O.M.; Yoon, C.M. *Tetrahedron Lett.* ***2001***, *42*, 2137.
[1540] Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* ***1975***, *40*, 1864; Lane, C.F. *Aldrichimica Acta* ***1976***, *9*, 31.
[1541] Mincione, E. *J. Org. Chem.* ***1978***, *43*, 1829.
[1542] Bartoli, G.; Bosco, M.; Bellucci, M.C.; Daplozzo, R.; Marcantoni, E.; Sambri, L. *Org. Lett.* ***2000***, *2*, 45.
[1543] Kabalka, G.W.; Malladi, R.R. *Chem. Commun.* ***2000***, 2191.
[1544] Du, D.-M.; Fang, T.; Xu, J.; Zhang, S.-W. *Org. Lett.* ***2006***, *8*, 1327; Krzemiński, M.P.; Wojtczak, A. *Tetrahedron Lett.* ***2005***, *46*, 8299.

reduction,[1545] and chiral boronic esters have also been used.[1546] Germanium and tin hydride compounds have been used as catalysts for the hydroboration of carbonyl compounds.[1547] Ruthenium-catalyzed reduction with boranes is known.[1548] Aluminum monohydride has been used as a catalyst.[1549] Pinacolborane has been used, catalyzed by an alkoxide.[1550] A copper/carbene-catalyzed hydroboration of aldehydes and ketones has been reported.[1551] *N*-Heterocyclic carbene boranes reduce aldehydes and ketones, promoted by silica gel.[1552] Magnesium-catalyzed hydroboration has been reported.[1553]

Alane (AlH_3) derivatives can also be used, including diisobutylaluminum hydride.[1554]

6. *Tin hydrides.* Tributyltin hydride reduces aldehydes to primary alcohols by simply heating in methanol.[1555] A mixture of Bu_3SnH and phenylboronic acid (**12-27**) reduces aldehydes in dichloromethane.[1556] Using triaryltin hydrides with $BF_3{\bullet}OEt_2$, where aryl is 2,6-diphenylbenzyl, selective reduction of aliphatic aldehydes in the presence of a conjugated aldehyde was achieved.[1557] Tris(trimethylsilyl)methane has been used as a tin-free radical reducing agent.[1558]
7. *Cannizzaro reaction.* In the Cannizzaro reaction (see **19-85**), aldehydes without an α hydrogen are reduced to alcohols.
8. *Silanes.* In the presence of bases, certain silanes can selectively reduce carbonyls.[1559] Transition metal complexes also catalyze hydrosilylation of ketones,[1560] including Mn,[1561] Ag,[1562] Ni,[1563] Fe,[1564] Zn,[1565] Cs,[1566] or Pd.[1567] A Ru catalyst was used for

[1545] Stepanenko, V.; De Jesús, M.; Correa, W.; Guzmán, I.; Vázquez, C.; de la Cruz, W.; Ortiz-Marciales, M.; Barnes, C.L. *Tetrahedron Lett.* ***2007***, *48*, 5799.
[1546] Eagon, S.; Kim, J.; Yan, K.; Haddenham, D.; Singaram, B. *Tetrahedron Lett.* ***2007***, *48*, 9025.
[1547] Hadlington, T.J.; Hermann, M.; Frenking, G.; Jones, C. *J. Am. Chem. Soc.* ***2014***, *136*, 3028.
[1548] Kaithal, A.; Chatterjee, B.; Gunanathan, C. *Org. Lett.* ***2015***, *17*, 4790.
[1549] Jakhar, V.K.; Barman, M.Kr.; Nembenna, S. *Org. Lett.* ***2016***, *18*, 4710.
[1550] Query, I.P.; Squier, P.A.; Larson, E.M.; Isley, N.A.; Clark, T.B. *J. Org. Chem.* ***2011***, *76*, 6452.
[1551] Bagherzadeh, S.; Mankad, N.P. *Chem. Commun.* ***2016***, *52*, 3844.
[1552] Taniguchi, T.; Curran, D.P. *Org. Lett.* ***2012***, *14*, 4540; Wang, M.-H.; Chen, L.-Y. *Tetrahedron Lett.* ***2017***, *58*, 732.
[1553] Arrowsmith, M.; Hadlington, T.J.; Hill, M.S.; Kocok-Köhn, G. *Chem. Commun.* ***2012***, *48*, 4567.
[1554] Nakamura, S.; Kuroyanagi, M.; Watanabe, Y.; Toru, T. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 3143.
[1555] Kamiura, K.; Wada, M. *Tetrahedron Lett.* ***1999***, *40*, 9059; Adams, C.M.; Schemenaur, J.E. *Synth. Commun.* ***1990***, *20*, 2359. For a review, see Kuivila, H.G. *Synthesis* ***1970***, 499.
[1556] Yu, H.; Wang, B. *Synth. Commun.* ***2001***, *31*, 2719.
[1557] Sasaki, K.; Komatsu, N.; Shivakawa, S.; Maruoka, K. *Synlett* ***2002***, 575.
[1558] Perchyonok, V.T. *Tetrahedron Lett.* ***2006***, *47*, 5163.
[1559] See Varjosaari, S.E.; Skrypai, V.; Suating, P.; Hurley, J.J.M.; Gilbert, T.M.; Adler, M.J. *Eur. J. Org. Chem.* ***2017***, 229.
[1560] For a review, see Díez-González, S.; Nolan, S.P. *Org. Prep. Proceed. Int.* ***2007***, *39*, 523. See Chen, T.; Liu, X.-G.; Shi, M. *Tetrahedron* ***2007***, *63*, 4874; Malkov, A.V.; Stewart-Liddon, A.J.P.; McGeoch, G.D.; Ramírez-López, P.; Kočovský, P. *Org. Biomol. Chem.* ***2012***, *10*, 4864.
[1561] Mukhopadhyay, T.K.; Flores, M.; Groy, T.L.; Trovitch, R.J. *J. Am. Chem. Soc.* ***2014***, *136*, 882.
[1562] Jia, Z.; Liu, M.; Li, X.; Chan, A.S.C.; Li, C.-J. *Synlett* ***2013***, *24*, 2049.
[1563] Wu, F.-F.; Zhou, J.-N.; Fang, Q.; Hu, Y.-H.; Li, S.; Zhang, X.-C.; Chan, A.S.C.; Wu, J. *Chem. Asian J.* ***2012***, *7*, 2527.
[1564] Dieskau, A.P.; Begouin, J.-M.; Plietker, B. *Eur. J. Org. Chem.* ***2011***, 5291; Zhu, K.; Shaver, M.P.; Thomas, S.P. *Eur. J. Org. Chem.* ***2015***, 2119.
[1565] Junge, K.; Möller, K.; Wendt, B.; Das, S.; Gördes, D.; Thurow, K.; Beller, M. *Chem. Asian J.* ***2012***, *7*, 314.
[1566] Zhao, M.; Xie, W.; Cui, C. *Chem. Eur. J.* ***2014***, *20*, 9259.
[1567] Chouthaiwale, P.V.; Rawat, V.; Sudalai, A. *Tetrahedron Lett.* ***2012***, *53*, 148.

the reduction of aldehydes in the presence of ketones.[1568] Thiol-capped Au nanoparticles were used in a flow system (Sec. 7.D) using an organosilane as a reducing agent.[1569] Controlling temperature and solvent leads to different ratios of *syn* and *anti* products.[1570] Silanes reduce ketones in the presence of BF_3•OEt_2.[1571] Piers and Parks discovered that $B(C_6F_5)_3$ catalyzed carbonyl hydrosilation,[1572] and this reaction is now referred to as the *Piers hydrosilation*. *N*-Heterocyclic carbenes have used to catalyze the hydrosilation of carbonyl compounds.[1573]

9. *Ammonium formates*. Sodium formate and trialkylammonium formates can be used to reduce aldehydes and ketones to the corresponding alcohol. Decanal was reduced to decan-1-ol, for example, using sodium formate in *N*-methyl-2-pyrrolidinone as a solvent.[1574] A mixture of formic acid and ethyl magnesium bromide was used to reduce decanal to decan-1-ol in 70% yield.[1575] Transfer hydrogenation also occurs with formic acid/triethylamine and a Ru catalyst,[1576] in water[1577] or with a Pd catalyst.[1578] Transfer hydrogenation[1579] is the addition of hydrogen to a molecule from a source other than gaseous H_2. The reduction of aryl ketones by hydrogen transfer has been reported using *sec*-BuOH as the hydrogen donor in the presence of KOH.[1580] The transfer hydrogenation of aldehydes and ketones has been reported using flow conditions (Sec. 7.D) and hydrous zirconia[1581] or immobilized iridium.[1582]
10. *Enzymatic reductions.* Successful asymmetric reductions (see section A[1112]) have been achieved with biologically derived reducing agents,[1583] such as baker's yeast,[1584] enzymes from other organisms,[1585] or with other biocatalysts.[1586] Biocatalytic reduction of cyclic ketones using an alcohol dehydrogenase gave the axially chiral (*R*)-alcohol.[1587] Ionic liquids have been used in conjunction with enzymatic

[1568] Yumino, S.; Hashimoto, T.; Tahara, A.; Nagashima, H. *Chem. Lett.* ***2014***, *43*, 1829.
[1569] Sugie, A.; Song, H.; Horie, T.; Ohmura, N.; Kanie, K.; Muramatsu, A.; Mori, A. *Tetrahedron Lett.* ***2012***, *53*, 4457.
[1570] See Yamamoto, Y.; Matsuoka, K.; Nemoto, H. *J. Am. Chem. Soc.* ***1988***, *110*, 4475.
[1571] Smonou, I. *Tetrahedron Lett.* ***1994***, *35*, 2071.
[1572] Parks, D.J.; Piers, W.E. *J. Am. Chem. Soc.* ***1996***, *118*, 9440.
[1573] Zhao, Q.; Curran, D.P.; Malacria, M.; Fensterbank, L.; Goddard, J.-P.; Lacôte, E. *Synlett* ***2012***, *23*, 433.
[1574] Babler, J.H.; Sarussi, S.J. *J. Org. Chem.* ***1981***, *46*, 3367.
[1575] Babler, J.H.; Invergo, B.J. *Tetrahedron Lett.* ***1981***, *22*, 621.
[1576] Morris, D.J.; Hayes, A.M.; Wills, M. *J. Org. Chem.* ***2006***, *71*, 7035.
[1577] Wu, X.; Li, X.; King, F.; Xiao, J. *Angew. Chem. Int. Ed.* ***2005***, *44*, 3407.
[1578] Wang, A.; Wang, Z.; Liu, J.; Gui, Q.; Chen, X.; Tan, Z.; Shi, J.-C. *Synth. Commun.* ***2014***, *44*, 280.
[1579] Ito, J.-i.; Nishiyama, H. *Tetrahedron Lett.* ***2014***, *55*, 3133.
[1580] Srinivasan, S.; Manisankar, P. *Synth. Commun.* ***2010–2011***, *41*, 1338.
[1581] Battilocchio, C.; Hawkins, J.M.; Ley, S.V. *Org. Lett.* ***2013***, *15*, 2278.
[1582] Rojo, M.V.; Guetzoyan, L.; Baxendale, I.R. *Org. Biomol. Chem.* ***2015***, *13*, 1768.
[1583] For a review, see Sih, C.J.; Chen, C. *Angew. Chem. Int. Ed.* ***1984***, *23*, 570.
[1584] See Wolfson, A.; Dlugy, C.; Tavor, D.; Blumenfeld, J.; Shotland, Y. *Tetrahedron: Asymmetry* ***2006***, *17*, 2043; Yadav, J.S.; Reddy, G.S.K.K.; Sabitha, G.; Krishna, A.D.; Prasad, A.R.; Rahaman, H.U.R.; Rao, K.V.; Rao, A.B. *Tetrahedron: Asymmetry* ***2007***, *18*, 717; Yıldız, T.; Çanta, N.; Yusufoğlu, A. *Tetrahedron: Asymmetry* ***2014***, *25*, 340.
[1585] See Moore, J.C.; Pollard, D.J.; Kosjek, B.; Devine, P.N. *Acc. Chem. Res.* ***2007***, *40*, 1412; Hoyos, P.; Sansottera, G.; Fernández, M.; Molinari, F.; Sinisterra, J.V.; Alcántara, A.R. *Tetrahedron* ***2008***, *64*, 7929; Lavandera, I.; Höller, B.; Kern, A.; Ellmer, U.; Glieder, A.; de Wildeman, S.; Kroutil, W. *Tetrahedron: Asymmetry* ***2008***, *19*, 1954. For enzymatic reduction of thioketones, see Nielsen, J.K.; Madsen, J.Ø. *Tetrahedron: Asymmetry* ***1994***, *5*, 403.
[1586] Nakamura, K.; Yamanaka, R.; Matsuda, T.; Harada, T. *Tetrahedron: Asymmetry* ***2003***, *14*, 2659.
[1587] Agudo, R.; Roiban, G.-D.; Reetz, M.T. *J. Am. Chem. Soc.* ***2013***, *135*, 1665.

reduction,[1588] and enzymatic reduction has been done in supercritical CO_2.[1589] The chemoenzymatic reduction of 2-oxoacids has been reported, with good enantioselectivity.[1590] The bioreduction of ethyl 3-oxohexanoate has been reported.[1591] New biocatalysts have been used or developed.[1592] The bioreduction of acetophenone derivatives used red marine algae bacteria.[1593]

For other reduction reactions of aldehydes and ketones see **19-66**, **19-80**, and **19-85**.

Asymmetric Reduction[1594]

Unsymmetrical ketones are prochiral (Sec. 4.M); that is, reduction creates a new stereogenic center. The relative effectiveness of various reagents for reduction of eight other types of ketone was determined, using several different reducing agents.[1595] The ketones examined included heterocyclic, aralkyl, β-keto esters, β-keto acids,[1596] and so on.[1583] Much effort has been put into finding optically active reducing agents that will produce one enantiomer of the alcohol enantioselectively.[1597] Each reagent tends to show a specificity for certain types of ketones.[1598] Good enantioselectivity is usually obtained with the proper reagent.[1599] Substituents that are remote to the carbonyl group can play a role in facial selectivity of the reduction.[1600] Asymmetric reduction has been accomplished using bioreagents such as enzymes: see item 10 in the list above.

[1588] Matsuda, T.; Yamagishi, Y.; Koguchi, S.; Iwai, N.; Kitazume, T. *Tetrahedron Lett.* ***2006***, *47*, 4619; Bräutigam, S.; Bringer-Meyer, S.; Weuster-Botz, D. *Tetrahedron: Asymmetry* ***2007***, *18*, 1883.

[1589] Matsuda, T.; Marukado, R.; Mukouyama, M.; Harada, T.; Nakamura, K. *Tetrahedron: Asymmetry* ***2008***, *19*, 2272.

[1590] Sivanathan, S.; Körber, F.; Tent, J.A.; Werner, S.; Scherkenbeck, J. *J. Org. Chem.* ***2015***, *80*, 2554.

[1591] Ramos, A. de S.; Ribeiro, J.B.; Lopes, R. de O.; Leite, S.G.F.; de Souza, R.O.M.A. *Tetrahedron Lett.* ***2011***, *52*, 6127.

[1592] Kurbanoglu, E.B.; Zilbeyaz, K.; Kurbanoglu, N.I. *Tetrahedron: Asymmetry* ***2011***, *22*, 345; Tang, Y.; Li, X.; Lian, C.; Zhu, J.; Deng, J. *Tetrahedron: Asymmetry* ***2011***, *22*, 1530; Vitale, P.; Perna, F.M.; Perrone, M.G.; Scilimati, A. *Tetrahedron: Asymmetry* ***2011***, *22*, 1985; Mahajabeen, P.; Chadha, A. *Tetrahedron: Asymmetry* ***2011***, *22*, 2156; de Paula, B.R.S.; Zampieri, D.S.; Rodrigues, J.A.R.; Moran, P.J.S. *Tetrahedron: Asymmetry* ***2013***, *24*, 973; Salvi, N.A.; Chattopadhyay, S. *Tetrahedron: Asymmetry* ***2016***, *27*, 188; Contente, M.L.; Serra, I.; Palazzolo, L.; Parravicini, C.; Gianazza, E.; Eberini, I.; Pinto, A.; Guidi, B.; Molinari, F.; Romano, D. *Org. Biomol. Chem.* ***2016***, *14*, 3404.

[1593] Mouad, A.M.; Martins, M.P.; Debonsi, H.M.; de Oliveira, A.L.L.; de Felicio, R.; Yokoya, N.S.; Fujii, M.T.; de Menezes, C.B.A.; Fantinatti-Garboggini, F.; Porto, A.L.M. *Helv. Chim. Acta* ***2011***, *94*, 1506.

[1594] Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 344–364.

[1595] Brown, H.C.; Park, W.S.; Cho, B.T.; Ramachandran, P.V. *J. Org. Chem.* ***1987***, *52*, 5406.

[1596] Wang, Z.; La, B.; Fortunak, J.M.; Meng, X.-J.; Kabalka, G.W. *Tetrahedron Lett.* ***1998***, *39*, 5501.

[1597] See Singh, V.K. *Synthesis* ***1992***, 605; Midland, M.M. *Chem. Rev.* ***1989***, *89*, 1553; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 105–130; in Morrison, J.D. *Asymmetric Synthesis*, Academic Press, NY, ***1983***, the articles by Midland, M.M., Vol. 2, pp. 45–69, and Grandbois, E.R.; Howard, S.I.; Morrison, J.D., Vol. 2, pp. 71–90; Haubenstock, H. *Top. Stereochem.* ***1983***, *14*, 231.

[1598] For a list of many of these reducing agents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1097–1111.

[1599] See Midland, M.M.; Kazubski, A.; Woodling, R.E. *J. Org. Chem.* ***1991***, *56*, 1068.

[1600] Kaselj, M.; Gonikberg, E.M.; le Noble, W.J. *J. Org. Chem.* ***1998***, *63*, 3218.

Asymmetric reduction with very high enantioselectivity has also been achieved with achiral reducing agents and optically active catalysts.[1601] Homogeneous catalytic asymmetric hydrogenation[1602] leads to reduction of substrates with high enantioselectivity.[1603] Several catalytic systems have been developed, including those using a Ru,[1604] Fe,[1605] Cu,[1606] Mn,[1607] or Ir[1608] catalyst. The development of new chiral ligands is an active area of research, for use with metal catalysts.[1609] A chirally modified Pt catalyst has been used,[1610] as have Fe complexes.[1611] β-Keto esters are reduced enantioselectively, for example.[1612] A variety of chiral additives and/or ligands have been used with catalytic hydrogenation reactions, and many functional groups can be tolerated.[1613] Asymmetric catalytic hydrogenation has been done in ionic liquids.[1614]

The use of chiral metal complexes leads to chiral hydrogen transfer.[1615] Asymmetric transfer hydrogenation has been reported using an Fe complex to reduce ketones to the

[1601] See Smith, M.B. *Organic Synthesis*, 4th ed., Elsevier, London, ***2017***, pp. 344–364. See Boukachabia, M.; Zeror, S.; Collin, J.; Fiaud, J.-C.; Zouioueche, L.A. *Tetrahedron Lett.* ***2011***, *52*, 1485.

[1602] Yoshimura, M.; Tanaka, S.; Kitamura, M. *Tetrahedron Lett.* ***2014***, *55*, 3635. See Echeverria, P.-G.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. *Synthesis* ***2016***, *48*, 2523.

[1603] See Huang, H.; Okuno, T.; Tsuda, K.; Yoshimura, M.; Kitamura, M. *J. Am. Chem. Soc.* ***2006***, *128*, 8716; Xie, J.-H.; Zhou, Z.-T.; Kong, W.-L.; Zhou, Q.-L. *J. Am. Chem. Soc.* ***2007***, *129*, 1868; Truppo, M.D.; Pollard, D.; Devine, P. *Org. Lett.* ***2007***, *9*, 335; Lu, S.-M.; Bolm, C. *Angew. Chem. Int. Ed.* ***2008***, *47*, 8920; Jiang, H.-y.; Yang, C.-f.; Li, C.; Fu, H.-y.; Chen, H.; Li, R.-x.; Li, X.-j. *Angew. Chem. Int. Ed.* ***2008***, *47*, 9240; Martins, J.E.D.; Wills, M. *Tetrahedron* ***2009***, *65*, 5782; Li, W.; Hou, G.; Wang, C.; Jiang, Y.; Zhang, X. *Chem. Commun.* ***2010***, 3979.

[1604] Matsumura, K.; Arai, N.; Hori, K.; Saito, T.; Sayo, N.; Ohkuma, T. *J. Am. Chem. Soc.* ***2011***, *133*, 10696; Tao, X.; Li, W.; Ma, X.; Li, X.; Fan, W.; Zhu, L.; Xie, X.; Zhang, Z. *J. Org. Chem.* ***2012***, *77*, 8401; Chen, X.; Zhou, H.; Zhang, K.; Li, J.; Huang, H. *Org. Lett.* ***2014***, *16*, 3912; Guo, H.; Liu, D.; Butt, N.A.; Liu, Y.; Zhang, W. *Tetrahedron* ***2012***, *68*, 3295; Yamamura, T.; Nakatsuka, H.; Tanaka, S.; Kitamura, M. *Angew. Chem. Int. Ed.* ***2013***, *52*, 9313.

[1605] Smith, S.A.M.; Lagaditis, P.O.; Lüpke, A.; Lough, A.J.; Morris, R.H. *Chem. Eur. J.* ***2017***, *23*, 7212.

[1606] Junge, K.; Wendt, B.; Addis, D.; Zhou, S.; Das, S.; Fleischer, S.; Beller, M. *Chem. Eur. J.* ***2011***, *17*, 101.

[1607] Garbe, M.; Junge, K.; Walker, S.; Wei, Z.; Jiao, H.; Spannenberg, A.; Bachmann, S.; Scalone, M.; Beller, M. *Angew. Chem. Int. Ed.* ***2017***, *56*, 11237.

[1608] Wu, W.; Liu, S.; Duan, M.; Tan, X.; Chen, C.; Xie, Y.; Lan, Y.; Dong, X.-Q.; Zhang, X. *Org. Lett.* ***2016***, *18*, 2938; Irrgang, T.; Friedrich, D.; Kempe, R. *Angew. Chem. Int. Ed.* ***2011***, *50*, 2183; Xie, J.-H.; Liu, X.-Y.; Xie, J.-B.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* ***2011***, *50*, 7329.

[1609] See Noyori, R. *Science* ***1990***, *248*, 1194; Noyori, R.; Takaya, H. *Acc. Chem. Res.* ***1990***, *23*, 345; Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth. 67*, 20; Patchett, R.; Magpantay, I.; Saudan, L.; Schotes, C.; Mezzetti, A.; Santoro, F. *Angew. Chem. Int. Ed.* ***2013***, *52*, 10352; Zhu, Q.; Shi, D.; Xia, C.; Huang, H. *Chem. Eur. J.* ***2011***, *17*, 7760; Arenas, I.; Boutureira, O.; Matheu, M.I.; Díaz, Y.; Castillón, S. *Eur. J. Org. Chem.* ***2015***, 3666.

[1610] Maeda, N.; Hungerbühler, K.; Baiker, A. *J. Am. Chem. Soc.* ***2011***, *133*, 19567.

[1611] Lagaditis, P.O.; Sues, P.E.; Sonnenberg, J.F.; Wan, K.Y.; Lough, A.J.; Morris, R.H. *J. Am. Chem. Soc.* ***2014***, *136*, 1367.

[1612] Taber, D.F.; Silverberg, L.J. *Tetrahedron Lett.* ***1991***, *32*, 4227. See also, Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* ***1988***, *110*, 629.

[1613] See Sun, L.; Tang, M.; Wang, H.; Wei, D.; Liu, L. *Tetrahedron: Asymmetry* ***2008***, *19*, 779; Ohkuma, T.; Hattori, T.; Ooka, H.; Inoue, T.; Noyori, R. *Org. Lett.* ***2004***, *6*, 2681; Lei, A.; Wu, S.; He, M.; Zhang, X. *J. Am. Chem. Soc.* ***2004***, *126*, 1626; Sun, Y.; Wan, X.; Guo, M.; Wang, D.; Dong, X.; Pan, Y.; Zhang, Z. *Tetrahedron: Asymmetry* ***2004***, *15*, 2185. Also see Sandoval, C.A.; Ohkuma, T.; Muñiz, K.; Noyori, R. *J. Am. Chem. Soc.* ***2003***, *125*, 13490.

[1614] Ngo, H.L.; Hu, A.; Lin, W. *Chem. Commun.* ***2003***, 1912.

[1615] Xie, J.-H.; Bao, D.-H.; Zhou, Q.-L. *Synthesis* ***2015***, *47*, 460; Bolje, A.; Hohloch, S.; van der Meer, M.; Košmrlj, J.; Sarkar, B. *Chem. Eur. J.* ***2015***, *21*, 6756. For reviews, see Foubelo, F.; Nájera, C.; Yus, M. *Tetrahedron: Asymmetry* ***2015***, *26*, 769; Li, Y.-Y.; Yu, S.-L.; Shen, W.-Y.; Gao, J.-X. *Acc. Chem. Res.* ***2015***, *48*, 2587.

corresponding alcohol.[1616] Ru,[1617] Mn,[1618] Ir,[1619] and Wilkinson-type catalysts,[1620] and Fe complexes[1621] have also been used. A Ru/PNNP catalyst has been used for the 1,2-reduction of conjugated ketones.[1622] New chiral ligands have been developed.[1623] Sugar-based ligands have been developed for asymmetric transfer hydrogenation.[1624] Aldehydes have been reduced to the alcohol by reaction with a *Hantzsch ester*, catalyzed by an organoborane in the presence of tri(3,5-trifluoromethyl)phenylborane.[1625] Organocatalysts have been developed for the asymmetric transfer hydrogenation of conjugated aldehydes.[1626] The enantioselective reduction of β-keto esters via pH-independent transfer hydrogenation in water has been reported.[1627]

Another approach is reduction with BH_3/THF or catecholborane,[1628] using oxazaborolidines[1629] or other chiral compounds[1630] as a catalyst. The Co-catalyzed hydroboration of aryl ketones with pinacolborane has been reported.[1631] Chiral sulfonamides have been used as additives,[1632] and other chiral additives can be used.[1633] Spiroborate esters were used.[1634]

Lithium aluminum hydride in combination with a chiral diol[1635] or other chiral ligands[1636] leads to enantioselective reduction, often in the presence of a transition metal complex.[1637] Chiral additives have also been used with $NaBH_4$.[1638] Examples include

[1616] Lagaditis, P.O.; Lough, A.J.; Morris, R.H. *J. Am. Chem. Soc.* ***2011***, *133*, 9662.

[1617] Touge, T.; Hakamata, T.; Nara, H.; Kobayashi, T.; Sayo, N.; Saito, T.; Kayaki, Y.; Ikariya, T. *J. Am. Chem. Soc.* ***2011***, *133*, 14960; Dub, P.A.; Ikariya, T. *J. Am. Chem. Soc.* ***2013***, *135*, 2604; Johnson, T.C.; Totty, W.G.; Wills, M. *Org. Lett.* ***2012***, *14*, 5230; Kišić, A.; Stephan, M.; Mohar, B. *Org. Lett.* ***2013***, *15*, 1614; Watson, A.J.A.; Fairbanks, A.J. *Eur. J. Org. Chem.* ***2013***, 6784; Bhoslae, S.S.; Singh, K.S. *Synth. Commun.* ***2015***, *45*, 1411; Babin, M.; Clément, R.; Gagnon, J.; Fontaine, F.-G. *New J. Chem.* ***2012***, 1548. See Lundberg, H.; Adolfsson, H. *Tetrahedron Lett.* ***2011***, *52*, 2754; Moran, J.; Krische, M.J. *Pure Appl. Chem.* ***2012***, *84*, 1729.

[1618] Bruneau-Voisine, A.; Wang, D.; Dorcet, V.; Roisnel, T.; Darcel, C.; Sortais, J.-B. *Org. Lett.* ***2017***, *19*, 3656.

[1619] Ak, B.; Aydemir, M.; Durap, F.; Meriç, N.; Elma, D.; Baysal, A. *Tetrahedron: Asymmetry* ***2015***, *26*, 1307; Tian, C.; Gong, L.; Meggers, E. *Chem. Commun.* ***2016***, *52*, 4207.

[1620] Bogár, K.; Krumlinde, P.; Bacsik, Z.; Hedin, N.; Bäckvall, J.-E. *Eur. J. Org. Chem.* ***2011***, 4409.

[1621] Sonnenberg, J.F.; Coombs, N.; Dube, P.A.; Morris, R.H. *J. Am. Chem. Soc.* ***2012***, *134*, 5893; Bigler, R.; Huber, R.; Mezzetti, A. *Angew. Chem. Int. Ed.* ***2015***, *54*, 5171; Smith, S.A.M.; Morris, R.H. *Synthesis* ***2015***, *47*, 1775.

[1622] Lu, S.-M.; Gao, Q.; Li, J.; Liu, Y.; Li, C. *Tetrahedron Lett.* ***2013***, *54*, 7013.

[1623] Han, M.-L.; Hu, X.-P.; Huang, J.-D.; Chen, L.-G.; Zheng, Z. *Tetrahedron: Asymmetry* ***2011***, *22*, 222; Coll, M.; Pàrmies, O.; Adolfsson, H.; Diéguez, M. *Chem. Commun.* ***2011***, *47*, 12188.

[1624] For a review, see Margalef, J.; Pàmies, O.; Diéguez, M. *Tetrahedron Lett.* ***2016***, *57*, 1301.

[1625] Hamasaka, G.; Tsuji, H.; Uozumi, Y. *Synlett* ***2015***, *26*, 2037.

[1626] Zhang, B.-H.; Shi, L.-X.; Guo, R.-X. *Helv. Chim. Acta* ***2013***, *96*, 2152.

[1627] Ariger, M.A.; Carreira, E.M. *Org. Lett.* ***2012***, *14*, 4522.

[1628] See Ford, A.; Woodward, S. *Angew. Chem. Int. Ed.* ***1999***, *38*, 335.

[1629] See Jones, S.; Atherton, J.C.C. *Tetrahedron: Asymmetry* ***2000***, *11*, 4543; Gilmore, N.J.; Jones, S.; Muldowney, M.P. *Org. Lett.* ***2004***, *6*, 2805; Huertas, R.E.; Corella, J.A.; Soderquist, J.A. *Tetrahedron Lett.* ***2003***, *44*, 4435.

[1630] See Kawanami, Y.; Murao, S.; Ohga, T.; Kobayashi, N. *Tetrahedron* ***2003***, *59*, 8411; Basavaiah, D.; Reddy, G.J.; Chandrashekar, V. *Tetrahedron: Asymmetry* ***2004***, *15*, 47; Zhang, Y.-X.; Du, D.-M.; Chen, X.; Lü, S.-F.; Hua, W.-T. *Tetrahedron: Asymmetry* ***2004***, *15*, 177; Lindsay, D.M.; McArthur, D. *Chem. Commun.* ***2010***, 2474.

[1631] Guo, J.; Chen, J.; Lu, Z. *Chem. Commun.* ***2015***, *51*, 5725.

[1632] Li, G.-Q.; Yan, Z.-Y.; Niu, Y.-N.; Wu, L.-Y.; Wei, H.-L.; Liang, Y.-M. *Tetrahedron: Asymmetry* ***2008***, *19*, 816.

[1633] Hu, J.-b.; Zhao, G.; Yang, G.-s.; Ding, Z.-d. *J. Org. Chem.* ***2001***, *66*, 303; Zhou, H.; Lü, S.; Xie, R.; Chan, A.S.C.; Yang, T.-K. *Tetrahedron Lett.* ***2001***, *42*, 1107; Basavaiah, D.; Reddy, G.J.; Chandrashekar, V. *Tetrahedron: Asymmetry* ***2001***, *12*, 685.

[1634] Krzemiński, M.P.; Ćwiklińska, M. *Tetrahedron Lett.* ***2011***, *52*, 3919.

[1635] Ren, Y.; Tian, X.; Sun, K.; Xu, J.; Xu, X.; Lu, S. *Tetrahedron Lett.* ***2006***, *47*, 463.

[1636] Lange, D.A.; Neudörfl, J.-M.; Goldfuss, B. *Tetrahedron* ***2006***, *62*, 3704. In an ionic liquid: see Xiao, Y.; Malhotra, S.V. *Tetrahedron: Asymmetry* ***2006***, *17*, 1062.

[1637] For a review, see Daverio, P.; Zanda, M. *Tetrahedron: Asymmetry* ***2001***, *12*, 2225.

[1638] Kim, J.; Singaram, B. *Tetrahedron Lett.* ***2006***, *47*, 3901.

$LiBH_4/NiCl_2$ and a chiral amino alcohol,[1639] $NaBH_4$ with chiral Lewis acid complexes,[1640] or $NaBH_4/Me_3SiCl$ and a chiral ligand.[1641] A mixture of $NaBH_4$ and Me_3SiCl with a catalytic amount of a chiral, polymer-bound sulfonamide leads to asymmetric reduction.[1642] Potassium borohydride catalyzed by a Sc complex gave 1,2-reduction of enones with good enantioselectivity.[1643] Reduction with sodium borohydride in a chiral ionic liquid has been used for reductions in water.[1644]

Enantioselective reduction is possible with the other methods mentioned above. Transition metal-catalyzed asymmetric transfer hydrogenation is effective for the preparation of chiral alcohols.[1645] Reduction with silanes and transition metal catalysts, such as Ru[1646] or Fe,[1647] is also very effective. Chiral Ru catalysts have been used with triethylammonium formate for the enantioselective reduction.[1648] The transition metal-catalyzed hydrosilylation of ketones gives chiral alcohols in the presence of suitable chiral ligands.[1649] Enantioselective reduction was observed with $PhSiH_3$ and Cu compounds with a chiral ligand,[1650] with a mixture of Ru and Ag catalysts,[1651] or with $Mn(dpm)_3$ and oxygen (dpm = diphenylmethylene).[1652] Enantioselective hydrosilylation is possible using chiral organocatalysts.[1653] A chiral Sm complex has been used in conjunction with propan-2-ol.[1654] Chiral mercapto alcohols have also been used for asymmetric reduction.[1655] An asymmetric *Piers hydrosilation* has been reported.[1656] The hydrosilation reduction of ketones was catalyzed by a *N*-heterocyclic carbene/Ir complex,[1657] and a Co-catalyzed asymmetric hydrosilation has been reported.[1658] Asymmetric reduction of ketones has also been achieved with an achiral reducing agent, if the ketone is complexed to an optically active transition metal Lewis acid.[1659]

[1639] Molvinger, K.; Lopez, M.; Court, J. *Tetrahedron Lett.* ***1999***, *40*, 8375.
[1640] Nozaki, K.; Kobori, K.; Uemura, T.; Tsutsumi, T.; Takaya, H.; Hiyama, T. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 1109.
[1641] Jiang, B.; Feng, Y.; Zheng, J. *Tetrahedron Lett.* ***2000***, *41*, 10281.
[1642] Zhao, G.; Hu, J.-b.; Qian, Z.-s.; Yin, X.-x. *Tetrahedron: Asymmetry* ***2002***, *13*, 2095.
[1643] He, P.; Liu, X.; Zheng, H.; Li, W.; Lin, L.; Feng, X. *Org. Lett.* ***2012***, *14*, 5134.
[1644] See Singh, A.; Chopra, H.K. *Tetrahedron: Asymmetry* ***2017***, *28*, 414.
[1645] Wu, X.; Li, X.; Zanotti-Gerosa, A.; Pettman, A.; Liu, J.; Mills, A.J.; Xiao, J. *Chem. Eur. J.* ***2008***, *14*, 2209; Ito, M.; Shibata, Y.; Watanabe, A.; Ikariya, T. *Synlett* ***2009***, 1621; Zani, L.; Eriksson, L.; Adolfsson, H. *Eur. J. Org. Chem.* ***2008***, 4655.
[1646] Hayashi, T.; Hayashi, C.; Uozumi, Y. *Tetrahedron: Asymmetry* ***1995***, *6*, 2503.
[1647] Zuo, Z.; Zhang, L.; Leng, X.; Huang, Z. *Chem. Commun.* ***2015***, *51*, 5073.
[1648] Liu, P.N.; Gu, P.M.; Wang, F.; Tu, Y.Q. *Org. Lett.* ***2004***, *6*, 169; Wu, X.; Li, X.; Hems, W.; King, F.; Xiao, J. *Org. Biomol. Chem.* ***2004***, *2*, 1818; Schlatter, A.; Kundu, M.K.; Woggon, W.-D. *Angew. Chem. Int. Ed.* ***2004***, *43*, 6731.
[1649] Inagaki, T.; Yamada, Y.; Phong, L.T.; Furuta, A.; Ito, J.-i.; Nishiyama, H. *Synlett* ***2009***, 253; Ghoshal, A.; Sarkar, A.R.; Manickam, G.; Kumaran, R.S.; Jayashankaran, J. *Synlett* ***2010***, 1459.
[1650] Lipshutz, B.H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* ***2003***, *125*, 8779.
[1651] Gade, L.H.; César, V.; Bellemin-Laponnaz, S. *Angew. Chem. Int. Ed.* ***2004***, *43*, 1014.
[1652] Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F. *Tetrahedron Lett.* ***2001***, *42*, 6651.
[1653] Zhou, L.; Wang, Z.; Wei, S.; Sun, J. *Chem. Commun.* ***2007***, 2977.
[1654] Ohno, K.; Kataoka, Y.; Mashima, K. *Org. Lett.* ***2004***, *6*, 4695.
[1655] Yang, T.-K.; Lee, D.-S. *Tetrahedron: Asymmetry* ***1999***, *10*, 405.
[1656] Süsse, L.; Hermeke, J.; Oestreich, M. *J. Am. Chem. Soc.* ***2016***, *138*, 6940.
[1657] Shinohara, K.; Kawabata, S.; Nakamura, H.; Manabe, Y.; Sakaguchi, S. *Eur. J. Org. Chem.* ***2014***, 5532.
[1658] Yu, F.; Zhang, X.-C.; Wu, F.-F.; Zhou, J.-N.; Fang, W.; Wu, J.; Chan, A.S.C. *Org. Biomol. Chem.* ***2011***, *9*, 5652.
[1659] Dalton, D.M.; Gladysz, J.A. *J. Organomet. Chem.* ***1989***, *370*, C17.

Enantioselective reduction is not usually possible for aldehydes,[1660] since the products are primary alcohols in which the reduced carbon is not chiral, but deuterated aldehydes RCDO give a chiral product, and these have been reduced enantioselectively with *B*-(3-pinanyl)-9-borabicyclo[3.3.1]nonane (*Alpine-Borane*) with almost complete optical purity.[1661] Other chiral boranes can be used to reduce aldehydes or ketones.[1662]

There are other stereochemical aspects to the reduction of aldehydes and ketones. If there is a stereogenic center α to the carbonyl group,[1663] even an achiral reducing agent can give more of one diastereomer than of the other (a diastereoselective reduction). Such reductions have been carried out with considerable success.[1664] In most such cases *Cram's rul*e (Sec. 4.H, category 1) is followed, but exceptions are known.[1665]

OS **I**, 90, 304, 554; **II**, 317, 545, 598; **III**, 286; **IV**, 15, 25, 216, 660; **V**, 175, 294, 595, 692; **VI**, 215, 769, 887; **VII**, 129, 215, 241, 402, 417; **VIII**, 302, 312, 326, 527; **IX**, 58, 362, 676.

19-41 Reduction of Carboxylic Acids to Alcohols

$$\mathrm{RCOOH} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{RCH_2OH}$$

Carboxylic acids are easily reduced to primary alcohols by $LiAlH_4$.[1666] The conditions are particularly mild, the reduction proceeding quite well at room temperature. Other hydrides have also been used,[1667] but not $NaBH_4$ (see Table 19.2).[1668] A combination of $NaBH_4$ and an arylboronic acid (**12-27**) is also effective.[1669] A mixture of $NaBH_4$, Me_2SO_4, and $B(OMe)_3$ is effective for the reduction of hydroxyl-substituted aromatic carboxylic acids.[1670] Benzyltriethylammonium borohydride in dichloromethane reduces carboxylic acids to the alcohol.[1671] Catalytic hydrogenation is generally ineffective,[1672] although a Ru-catalyzed hydrogenation has been reported.[1673] A mixture of $NaBH_4$ and I_2 has been used to reduce amino acids to amino alcohols.[1674]

[1660] See, however, Li, X.; List, B. *Chem. Commun.* ***2007***, 1739. See also, Giacomini, D.; Galletti, P.; Quintavalla, A.; Gucciardo, G.; Paradisi, F. *Chem. Commun.* ***2007***, 4038.

[1661] Midland, M.M.; Greer, S.; Tramontano, A.; Zderic, S.A. *J. Am. Chem. Soc.* ***1979***, *101*, 2352. See also, Midland, M.M.; Zderic, S.A. *J. Am. Chem. Soc.* ***1982***, *104*, 525.

[1662] Ramachandran, P.V.; Pitre, S.; Brown, H.C. *J. Org. Chem.* ***2002***, *67*, 5315. For a discussion of the sources of stereoselectivity, see Xu, J.; Wei, T.; Zhang, Q. *J. Org. Chem.* ***2004***, *69*, 6860.

[1663] See Bloch, R.; Gilbert, L.; Girard, C. *Tetrahedron Lett.* ***1988***, *53*, 1021; Evans, D.A.; Chapman, K.T.; Carreira, E.M. *J. Am. Chem. Soc.* ***1988***, *110*, 3560.

[1664] See Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 131–148; Oishi, T.; Nakata, T. *Acc. Chem. Res.* ***1984***, *17*, 338.

[1665] See Yamamoto, Y.; Matsuoka, K.; Nemoto, H. *J. Am. Chem. Soc.* ***1988***, *110*, 4475.

[1666] See Gaylord, N.G. *Reduction with Complex Metal Hydrides*, Wiley, NY, ***1956***, pp. 322–373.

[1667] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1114–1116. Zinc borohydride has also been used; see Narashimhan, S.; Madhavan, S.; Prasad, K.G. *J. Org. Chem.* ***1995***, *60*, 5314.

[1668] See, however, Fujisawa, T.; Mori, T.; Sato, T. *Chem. Lett.* ***1983***, 835.

[1669] Tale, R.H.; Patil, K.M.; Dapurkar, S.E. *Tetrahedron Lett.* ***2003***, *44*, 3427.

[1670] Zhou, Y.; Gao, G.; Li, H.; Qu, J. *Tetrahedron Lett.* ***2008***, *49*, 3260.

[1671] Narashimhan, S.; Swarnalakshmi, S.; Balakumar, R. *Synth. Commun.* ***2000***, *30*, 941.

[1672] See Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 78–79.

[1673] Cui, X.; Li, Y.; Topf, C.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* ***2015***, *54*, 10596.

[1674] McKennon, M.J.; Meyers, A.I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* ***1993***, *58*, 3568.

Carboxylic acids were reduced to the corresponding alcohol by reaction with $SmI_2/H_2O/NEt_3$.[1675] The reaction of carboxylic acids with 1-propanephosphonic acid cyclic anhydride (T3P) and DIPEA, in the presence of $NaBH_4$, gave the corresponding primary alcohol.[1676] Carboxylic acids were reduced to primary alcohols using 1,1,3,3-tetramethyldisiloxane (TMDS) and a Cu catalyst.[1677] The reaction of carboxylic acids with phenylsilane and $(COD)Fe(CO)_3$ as catalyst under UV irradiation gave the primary alcohol, whereas reaction with TMDS and (*t*-PBO)$Fe(CO)_3$ as catalyst under thermal activation gave the aldehyde.[1678]

Carboxylic acids were mixed with the hyperthermophile *Pyrococcus furiosus*, which catalyzed the hydrogenation and gave the corresponding primary alcohol without reduction of a variety of functional groups that may be present.[1679]

Borane (BH_3) is particularly useful because carboxyl groups and esters are selectively reduced in the presence of many other groups, although the reaction with double bonds takes place at about the same rate in ether solvents.[1680] For many years, borane was the reagent of choice for this reduction. Borane also reduces carboxylic acid salts.[1681] Aluminum hydride reduces COOH groups without affecting carbon-halogen bonds in the same molecule. The reduction has also been carried out with SmI_2 in basic media[1682] or aqueous H_3PO_4,[1683] or simply with SmI_2 in water.[1684]

OS **III**, 60; **VII**, 221; 530; **VIII**, 26, 434, 528.

19-42 Reduction of Carboxylic Acid Derivatives

$$\mathrm{RCOOR'} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{RCH_2OH + R'OH}$$

Lithium aluminum hydride reduces carboxylic esters to give 2 molar equivalents of alcohol, as shown.[1685] The reaction is of wide scope and has been used to reduce many esters. Where the interest is in obtaining R′OH, this is a method that is often a working equivalent of "hydrolyzing" esters. Reduction of lactones yields diols.[1686] Among the reagents used for this reduction[1687] are DIBALH, lithium triethylborohydride, $LiAlH(Ot\text{-}Bu)_3$,[1688] and BH_3/SMe_2 in refluxing THF.[1689] Although $NaBH_4$ reduces other esters but it is usually so

[1675] Szostak, M.; Spain, M.; Procter, D.J. *Org. Lett.* ***2012***, *14*, 840.
[1676] Nagendra, G.; Madhu, C.; Vishwanatha, T.M.; Sureshbabu, V.V. *Tetrahedron Lett.* ***2012***, *53*, 5059.
[1677] Zhang, Y.J.; Dayoub, W.; Chen, G.-R.; Lemaire, M. *Tetrahedron* ***2012***, *68*, 7400.
[1678] Castro, L.C.M.; Li, H.; Sortais, J.-B.; Darcel, C. *Chem. Commun.* ***2012***, *48*, 10514.
[1679] Ni, Y.; Hagedoorn, P.-L.; Xu, J.-H.; Arends, I.W.C.E.; Hollman, F. *Chem. Commun.* ***2012***, *48*, 12056.
[1680] Brown, H.C.; Stocky, T.P. *J. Am. Chem. Soc.* ***1977***, *99*, 8218; Chen, M.H.; Kiesten, E.I.S.; Magano, J.; Rodriguez, D.; Sexton, K.E.; Zhang, J.; Lee, H.T. *Org. Prep. Proceed. Int.* ***2002***, *34*, 665.
[1681] Yoon, N.M.; Cho, B.T. *Tetrahedron Lett.* ***1982***, *23*, 2475.
[1682] Kamochi, Y.; Kudo, T. *Bull. Chem. Soc. Jpn.* ***1992***, *65*, 3049.
[1683] Kamochi, Y.; Kudo, T. *Tetrahedron* ***1992***, *48*, 4301.
[1684] Kamochi, Y.; Kudo, T. *Chem. Lett.* ***1993***, 1495.
[1685] See Gaylord, N.G. *Reduction with Complex Metal Hydrides*, Wiley, NY, ***1956***, pp. 391–531.
[1686] For a ring size-selective reduction using SmI_2/H_2O, see Duffy, L.A.; Matsubara, H.; Procter, D.J. *J. Am. Chem. Soc.* ***2008***, *130*, 1136.
[1687] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1116–1120.
[1688] Ayers, T.A. *Tetrahedron Lett.* ***1999***, *40*, 5467.
[1689] See Choi, Y.M.; Narasimhan, S. *J. Org. Chem.* ***1982***, *47*, 3153.

slow that it is not the reagent of choice, but there are many exceptions.[1690] However, it is generally possible to reduce an aldehyde or ketone without reducing an ester function in the same molecule. Note that $NaBH_4$ reduces esters in the presence of certain compounds (see Table 19.2).[1691] Note that $NaBH_4$ in DMF/MeOH reduces aryl carboxylic esters to benzylic alcohols,[1692] and $NaBH_4$/LiCl with microwave irradiation also reduces esters to primary alcohols.[1693]

Carboxylic esters can also be reduced to alcohols by hydrogenation over copper chromite catalysts,[1694] although high pressures and temperatures are required. Ester functions generally survive low-pressure catalytic hydrogenations, but homogeneous catalytic hydrogenation procedures have been developed.[1695] Before the discovery of $LiAlH_4$, the most common way of carrying out the reaction was with sodium in ethanol, a method known as the *Bouveault-Blanc procedure*.[1696] This procedure is still sometimes used where selectivity is necessary (see also, reactions **19-67**, **19-69**, and **19-62**). The ester moiety of β-keto esters has been selectively reduced using LiHMDS and $LiAlH_4$.[1697] The reduction of carboxylic acids to the corresponding alcohol proceeded via the *in situ* formation of hydroxy benzotriazole esters followed by reaction with sodium borohydride.[1698] Esters were reduced to alcohols via reaction with SmI_2/H_2O.[1699] Esters have been reduced to the alcohol by Fe,[1700] Mn,[1701] Ru,[1702] Ni/Re,[1703] or cobalt-catalyzed[1704] catalytic hydrogenation. Lactones were reduced to the diol via catalytic hydrogenation using a Ru catalyst, and lactams

[1690] For example, see Brown, M.S.; Rapoport, H. *J. Org. Chem.* ***1963***, *28*, 3261; Boechat, N.; da Costa, J.C.S.; Mendonca, J. de S.; de Oliveira, P.S.M.; DeSouza, M.V.N. *Tetrahedron Lett.* ***2004***, *45*, 6021.

[1691] See also, Soai, K.; Oyamada, H.; Takase, M.; Ookawa, A. *Bull. Chem. Soc. Jpn.* ***1984***, *57*, 1948; Guida, W.C.; Entreken, E.E.; Guida, W.C. *J. Org. Chem.* ***1984***, *49*, 3024.

[1692] Zanka, A.; Ohmori, H.; Okamoto, T. *Synlett* ***1999***, 1636.

[1693] Feng, J.-C.; Liu, B.; Dai, L.; Yang, X.-L.; Tu, S.-J. *Synth. Commun.* ***2001***, *31*, 1875.

[1694] For a review, see Adkins, H. *Org. React.* ***1954***, *8*, 1.

[1695] Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. *Angew. Chem. Int. Ed.* ***2006***, *45*, 1113.

[1696] Chablay, E. *Compt. Rend* ***1913***, *156*, 1020; Bouveault, L.; Blanc, G. *Bull. Soc. Chim. Fr.* ***1904***, *31*, 666; Bouveault, L.; Blanc, G. *Compt. Rend.* ***1903***, *136*, 1676. See Bodnar, B.S.; Vogt, P.F. *J. Org. Chem.* ***2009***, *74*, 2598. Also see Han, M.; Ma, X.; Yao, S.; Ding, Y.; Yan, Z.; Adijiang, A.; Wu, Y.; Li, H.; Zhang, Y.; Lei, P.; Ling, Y.; An, J. *J. Org. Chem.* ***2017***, *82*, 1285; An, J.; Work, D.N.; Kenyon, C.; Procter, D.J. *J. Org. Chem.* ***2014***, *79*, 6743.

[1697] Sivagurunathan, K.; Kamil, S.R.M.; Shafi, S.S.; Ali Khan, F.L.; Ragavan, R.V. *Tetrahedron Lett.* ***2011***, *52*, 1205.

[1698] Morales-Serna, J.A.; García-Ríos, E.; Bernal, J.; Paleo, E.; Gaviño, E.; Cárdenas, J. *Synthesis* ***2011***, *43*, 1375.

[1699] Szostak, M.; Spain, M.; Procter, D.J. *Chem. Commun.* ***2011***, *47*, 10254.

[1700] Chakraborty, S.; Dai, H.; Bhattacharya, P.; Fairweather, N.T.; Gibson, M.S.; Krause, J.A.; Guan, H. *J. Am. Chem. Soc.* ***2014***, *136*, 7869; Werkmeister, S.; Junge, K.; Wendt, B.; Alberico, E.; Jiao, H.; Baumann, W.; Junge, H.; Gallou, F.; Beller, M. *Angew. Chem. Int. Ed.* ***2014***, *53*, 8722; Dupau, P.; Do, M.-L.T.; Gaillard, S.; Renaud, J.-L. *Angew. Chem. Int. Ed.* ***2014***, *53*, 13004.

[1701] Elangovan, S.; Garbe, M.; Jiao, H.; Spannenberg, A.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* ***2016***, *55*, 15364; Widegren, M.B.; Harkness, G.J.; Slawin, A.M.Z.; Cordes, D.B.; Clarke, M.L. *Angew. Chem. Int. Ed.* ***2017***, *56*, 5825.

[1702] Tan, X.; Wang, Q.; Liu, Y.; Wang, F.; Lv, H.; Zhang, X. *Chem. Commun.* ***2015***, *51*, 12193; Junge, K.; Wendt, B.; Westerhaus, F.A.; Spannenberg, A.; Jiao, H.; Beller, M. *Chem. Eur. J.* ***2012***, *18*, 9011; Filonenko, G.A.; Aguila, M.J.B.; Schulpen, E.N.; van Putten, R.; Wiecko, J.; Müller, C.; Lefort, L.; Hensen, E.J.M.; Pidko, E.A. *J. Am. Chem. Soc.* ***2015***, *137*, 7620; Ogata, O.; Nakayama, Y.; Nara, H.; Fujiwhara, M.; Kayaki, Y. *Org. Lett.* ***2016***, *18*, 3894.

[1703] Liu, K.; Pritchard, J.; Lu, L.; van Putten, R.; Verhoeven, M.W.G.M.; Schitkamp, M.; Huang, X.; Lefort, L.; Kiely, C.J.; Hensen, E.J.M.; Pidko, E.A. *Chem. Commun.* ***2017***, *54*, 9761.

[1704] Srimani, D.; Mukherjee, A.; Goldberg, A.F.G.; Leitus, G.; Diskin-Posner, Y.; Shimon, L.J.W.; Ben David, Y.; Milstein, D. *Angew. Chem. Int. Ed.* ***2015***, *54*, 12357.

were reduced to the amino alcohol.[1705] Esters were reduced to alcohols by reaction with KOH and $PhSiH_3$.[1706] Lactones were reduced to diols using SmI_2/H_2O.[1707] Silanes, such as Ph_2SiH_2, with a catalytic amount of triphenylphosphine and a Rh catalyst reduced esters to primary alcohols.[1708] Aliphatic silanes, such as $EtMe_2SiH$, also reduced esters with a Ru catalyst.[1709] Esters were reduced to alcohols using $(EtO)_2MeSiH$ and a zinc catalyst.[1710] Esters were reduced to alcohols using polymethylhydrosiloxane and an Fe catalyst.[1711]

Amides were reduced to alcohols with SmI_2/amine/water.[1712] Lactams were hydrogenated using a Ru catalyst to give the amino alcohol with $(Me_3Si)_2NK$ at 100 °C.[1713] Amides were reduced to the corresponding amine by hydrogenation using a Pd/Re/graphite catalyst at 120–160 °C.[1714] Secondary and tertiary *N*-substituted 2,2,2-trifluoroacetamides were hydrogenated using Fe/PNP pincer complexes to give a cleavage reaction and formation of an amine and trifluoroethanol.[1715] The Ru-catalyzed hydrogenation of *N*-acylamine derivatives with KO*t*-Bu or NaOEt gave ethanol and the amine.[1716] Tertiary amides reacted with $PhSiH_3$ and a boronic acid catalyst to give the tertiary amine.[1717] The Rh-catalyzed reaction with $PhSiH_3$ reduced β-lactams to the azetidine.[1718]

OS **II**, 154, 325, 372, 468; **III**, 671; **IV**, 834; **VI**, 781; **VII**, 356; **VIII**, 155; **IX**, 251.

19-43 Reduction of Acyl Halides

$$\text{RCOCl} \xrightarrow[-78\ ^\circ\text{C}]{\text{LiAlH(O}t\text{-Bu)}_3} \text{RCHO}$$

Acyl halides can be reduced to aldehydes[1719] by treatment with lithium tri-*tert*-butoxyaluminum hydride in diglyme at −78 °C.[1720] The R group may be alkyl or aryl and may contain many types of substituents, including NO_2, CN, and EtOOC groups. The reaction stops at the aldehyde stage because steric hindrance prevents further reduction with this reagent. Acyl halides can also be reduced to aldehydes by hydrogenolysis with Pd-on-barium sulfate as catalyst in what is called the *Rosenmund reduction*.[1721] A convenient hydrogenolysis procedure involves Pd-on-charcoal as the catalyst, with

[1705] Ito, M.; Ootsuka, T.; Watari, R.; Shiibashi, A.; Himizu, A.; Ikariya, T. *J. Am. Chem. Soc.* ***2011***, *133*, 4240.
[1706] Fernández-Salas, J.A.; Manzani, S.; Nolan, S.P. *Chem. Commun.* ***2013***, *49*, 9758.
[1707] Szostak, M.; Collins, K.D.; Fazakerley, N.; Spain, M.; Procter, D.J. *Org. Biomol. Chem.* ***2012***, *10*, 5820.
[1708] Ohta, T.; Kamiya, M.; Kusui, K.; Michibata, T.; Nobutomo, M.; Furukawa, I. *Tetrahedron Lett.* ***1999***, *40*, 6963.
[1709] Matsubara, K.; Iura, T.; Maki, T.; Nagashima, H. *J. Org. Chem.* ***2002***, *67*, 4985.
[1710] Das, S.; Möller, K.; Junge, K.; Beller, M. *Chem. Eur. J.* ***2011***, *17*, 7414. See Kovalenko, O.O.; Adolfsson, H. *Chem. Eur. J.* ***2015***, *21*, 2785.
[1711] Junge, K.; Wendt, B.; Zhou, S.; Beller, M. *Eur. J. Org. Chem.* ***2013***, 2061.
[1712] Szostak, M.; Spain, M.; Eberhart, A.J.; Procter, D.J. *J. Am. Chem. Soc.* ***2014***, *136*, 2268.
[1713] John, J.M.; Bergens, S.H. *Angew. Chem. Int. Ed.* ***2011***, *50*, 10377.
[1714] Stein, M.; Breit, B. *Angew. Chem. Int. Ed.* ***2013***, *52*, 2231.
[1715] Garg, J.A.; Chakraborty, S.; Ben-David, Y.; Milstein, D. *Chem. Commun.* ***2016***, *52*, 5285.
[1716] Shi, L.; Tan, X.; Long, J.; Xiong, X.; Yang, S.; Xue, P.; Lv, H.; Zhang, X. *Chem. Eur. J.* ***2017***, *23*, 546.
[1717] Chardon, A.; El Dine, T.M.; Legay, R.; De Paolis, M.; Rouden, J.; Blanchet, J. *Chem. Eur. J.* ***2017***, *23*, 2005.
[1718] Bornschein, C.; Lennox, A.J.J.; Werkmeister, S.; Junge, K.; Beller, M. *Eur. J. Org. Chem.* ***2015***, 1915.
[1719] See Fuson, R.C. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 211–232; Wheeler, O.H. in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***, pp. 231–251.
[1720] Cha, J.S.; Brown, H.C. *J. Org. Chem.* ***1993***, *58*, 4732 and references cited therein.
[1721] See Rylander, P.N. *Catalytic Hydrogenation Over Platinum Metals*, Academic Press, NY, ***1967***, pp. 398–404; Maier, W.F.; Chettle, S.J.; Rai, R.S.; Thomas, G. *J. Am. Chem. Soc.* ***1986***, *108*, 2608.

ethyldiisopropylamine as acceptor of the liberated HCl and acetone as the solvent.[1722] The reduction of acyl halides to aldehydes has also been carried out[1723] with Bu_3SnH,[1724] by an $InCl_3$-catalyzed reaction with Bu_3SnH,[1725] using $NaBH_4$ in a mixture of DMF and THF,[1726] by Sm/PBu_3,[1727] and with formic acid/NH_4OH.[1728] Polymethylhydrosiloxane (PMHS) reduces acid chlorides to aldehydes in the presence of a Pd catalyst.[1729] In some of these cases, the mechanisms are free radical. Acid chlorides are reduced to aldehydes with Bu_3SnH and a Ni catalyst.[1730] Acid chlorides reacted with diisobutyl(morpholino)aluminum and then lithium diisobutylmethoxy aluminum hydride to give the aldehyde, or with the organolithium reagents to give a ketone.[1731] Acid chlorides were reduced to the aldehyde by reaction with Et_3SiH with a Pd catalyst.[1732]

Note that acid chlorides can be reduced (R—COCl → R—H) using $(Me_3Si)_3SiH$/AIBN.[1733]

OS **III**, 551, 627; **VI**, 529, 1007. Also see, OS **III**, 818; **VI**, 312.

19-44 Reduction of Carboxylic Acids, Esters, and Anhydrides to Aldehydes[1734]

RCOOH ⟶ RCHO ⟵ RCOOR′

With most reducing agents, reduction of carboxylic acids generally gives the primary alcohol (**19-41**) and the isolation of aldehydes is not feasible. However, simple straight-chain carboxylic acids have been reduced to aldehydes[1735] by treatment with Li in $MeNH_2$ or NH_3 followed by hydrolysis of the resulting imine,[1736] with thexylchloroborane/SMe_2 or thexylbromoborane/SMe_2[1737] (see **15-11** for the thexyl group), $Me_2N{=}CHCl^+\ Cl^-$ in pyridine,[1738] and with diaminoaluminum hydrides.[1739] Benzoic acid derivatives were reduced to benzaldehyde derivatives with NaH_2PO_2, a diacylperoxide, and a Pd catalyst.[1740] Caproic

[1722] Peters, J.A.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* ***1981***, *100*, 21. See also, Burgstahler, A.W.; Weigel, L.O.; Shaefer, C.G. *Synthesis* ***1976***, 767.

[1723] See Leblanc, J.C.; Moise, C.; Tirouflet, J. *J. Organomet. Chem.* ***1985***, *292*, 225; Corriu, R.J.P.; Lanneau, G.F.; Perrot, M. *Tetrahedron Lett.* ***1988***, *29*, 1271. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1265–1266.

[1724] See Lusztyk, J.; Lusztyk, E.; Maillard, B.; Ingold, K.U. *J. Am. Chem. Soc.* ***1984***, *106*, 2923.

[1725] Inoue, K.; Yasuda, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* ***2000***, *41*, 113.

[1726] Babler, J.H. *Synth. Commun.* ***1982***, *12*, 839. See Entwistle, I.D.; Boehm, P.; Johnstone, R.A.W.; Telford, R.P. *J. Chem. Soc., Perkin Trans. 1* ***1980***, 27.

[1727] Jia, X.; Liu, X.; Li, J.; Zhao, P.; Zhang, Y. *Tetrahedron Lett.* ***2007***, *48*, 971.

[1728] Shamsuddin, K.M.; Zubairi, Md.O.; Musharraf, M.A. *Tetrahedron Lett.* ***1998***, *39*, 8153.

[1729] Lee, K.; Maleczka Jr., R.E. *Org. Lett.* ***2006***, *8*, 1887.

[1730] Malanga, C.; Mannucci, S.; Lardicci, L. *Tetrahedron Lett.* ***1997***, *38*, 8093.

[1731] Park, J.K.; Shin, W.K.; An, D.K. *Tetrahedron Lett.* ***2013***, *54*, 3199.

[1732] Fujihara, T.; Cong, C.; Iwai, T.; Terao, J.; Tsuji, Y. *Synlett* ***2012***, *23*, 2389.

[1733] Ballestri, M.; Chatgilialoglu, C.; Cardi, N.; Sommazzi, A. *Tetrahedron Lett.* ***1992***, *33*, 1787.

[1734] For a review, see Cha, J.S. *Org. Prep. Proced. Int.* ***1989***, *21*, 451.

[1735] See Lanneau, G.F.; Perrot, M. *Tetrahedron Lett.* ***1987***, *28*, 3941; Cha, J.S.; Kim, J.E.; Yoon, M.S.; Kim, Y.S. *Tetrahedron Lett.* ***1987***, *28*, 6231. See also the lists in Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1265–1268.

[1736] Bedenbaugh, A.O.; Bedenbaugh, J.H.; Bergin, W.A.; Adkins, J.D. *J. Am. Chem. Soc.* ***1970***, *92*, 5774.

[1737] **Chloro**, see Brown, H.C.; Cha, J.S.; Yoon, N.M.; Nazer, B. *J. Org. Chem.* ***1987***, *52*, 5400; **Bromo**, see Cha, J.S.; Kim, J.E.; Lee, K.W. *J. Org. Chem.* ***1987***, *52*, 5030.

[1738] Fujisawa, T.; Mori, T.; Tsuge, S.; Sato, T. *Tetrahedron Lett.* ***1983***, *24*, 1543.

[1739] Cha, J.S.; Kim, J.M.; Jeoung, M.K.; Kwon, O.O.; Kim, E.J. *Org. Prep. Proceed. Int.* ***1995***, *27*, 95.

[1740] Gooßen, L.J.; Ghosh, K. *Chem. Commun.* ***2002***, 836.

and isovaleric acids have been reduced to aldehydes in 50% yields or better with DibalH at −75 to −70 °C.[1741] The chemoselective reduction of carbonyl groups in the presence of aldehydes has been reported.[1742]

Carboxylic acids reacted with trialkylsilanes with $B(C_6F_5)_3$ as catalyst to give the disilyl acetal, and a subsequent acidic workup gave the aldehyde.[1743] An Fe catalyst has also been used, with R_2SiH_2 and UV irradiation,[1744] and a Mn-catalyzed hydrosilation is known.[1745] Carboxylic acids were reduced to aldehydes by a Ru-catalyzed reaction with 1,2-bis(dimethylsilyl)benzene followed by hydrolysis of the resulting cyclic disilylacetal.[1746]

The Ir-catalyzed hydrosilation of esters with $EtMe_2SiH$ and 1,3,5-trimethoxybenzene gave the aldehyde.[1747] *N*-Protected α-amino acids were reduced to the chiral α-amino aldehydes using 1,1′-carbonyldiimidazole/DibalH.[1748] Carboxylic acids were reduced to the aldehyde by a reaction with $(TMS)_3SiH$ and an Ir catalyst under photoredox conditions.[1749]

Carboxylic esters have been reduced to aldehydes with DibalH at −70 °C with diaminoaluminum hydrides,[1750] and with $LiAlH(O\text{-}t\text{-}Bu)_3$ at 0 °C for phenolic esters.[1751] Esters have been reduced to the aldehyde using flow conditions (Sec. 7.D).[1752] Esters were reduced to aldehydes via an Ir-catalyzed hydrosilation reaction.[1753] Pretreatment of the acid with Me_3SiCl followed by reduction with DibalH also gives the aldehyde.[1754] Aldehydes have also been prepared by reducing ethyl thiol esters (RCOSEt) with Et_3SiH and a Pd/C catalyst.[1755] Thioesters have been reduced to the aldehyde with lithium metal in THF at −78 °C, followed by quenching with methanol.[1756]

Anhydrides, both aliphatic and aromatic, as well as mixed anhydrides of carboxylic and carbonic acids, have been reduced to aldehydes in moderate yields with disodium tetracarbonylferrate, $Na_2Fe(CO)_4$.[1757] Heating a carboxylic acid, presumably to form the anhydride, and then reaction with Na/EtOH leads to the aldehyde.[1758]

OS **VI**, 312; **VIII**, 241, 498.

[1741] Zakharkin, L.I.; Sorokina, L.P. *J. Gen. Chem. USSR* ***1967***, *37*, 525. See Song, J.I.; An, D.K. *Chem. Lett.* ***2007***, *36*, 886.
[1742] Bastug, G.; Dierick, S.; Lebreux, F.; Markó, I.E. *Org. Lett.* ***2012***, *14*, 1306.
[1743] Bézier, D.; Park, S.; Brookhart, M. *Org. Lett.* ***2013***, *15*, 496.
[1744] Li, H.; Castro, L.C.M.; Zheng, J.; Roisnel, T.; Dorcet, V.; Sortais, J.-B.; Darcel, C. *Angew. Chem. Int. Ed.* ***2013***, *52*, 8045.
[1745] Zheng, J.; Chevance, S.; Darcel, C.; Sortais, J.-B. *Chem. Commun.* ***2013***, *49*, 10010.
[1746] Miyamoto, K.; Motoyama, Y.; Nagashima, H. *Chem. Lett.* ***2012***, *41*, 229.
[1747] Corre, Y.; Rysak, V.; Capet, F.; Djukic, J.-P.; Agbossou-Niedercorn, F.; Michon, C. *Chem. Eur. J.* ***2016***, *22*, 14036.
[1748] Ivkovic, J.; Lembacher-Fadum, C.; Breinbauer, R. *Org. Biomol. Chem.* ***2015***, *13*, 10456.
[1749] Zhang, M.; Li, N.; Tao, X.; Ruzi, R.; Yu, S.; Zhu, C. *Chem. Commun.* ***2017***, *54*, 10128.
[1750] Cha, J.S.; Kim, J.M.; Jeoung, M.K.; Kwon, O.O.; Kim, E.J. *Org. Prep. Proceed. Int.* ***1995***, *27*, 95.
[1751] See Weissman, P.M.; Brown, H.C. *J. Org. Chem.* ***1966***, *31*, 283.
[1752] Webb, D.; Jamison, T.F. *Org. Lett.* ***2012***, *14*, 568; Muñoz, J. de M.; Alcázar, J.; de la Hoz, A.; Díaz-Ortiz, A. *Eur. J. Org. Chem.* ***2012***, 260.
[1753] Cheng, C.; Brookhart, M. *Angew. Chem. Int. Ed.* ***2012***, *51*, 9422.
[1754] Chandrasekhar, S.; Kumar, M.S.; Muralidhar, B. *Tetrahedron Lett.* ***1998***, *39*, 909.
[1755] Fukuyama, T.; Lin, S.; Li, L. *J. Am. Chem. Soc.* ***1990***, *112*, 7050.
[1756] Penn, J.H.; Owens, W.H. *Tetrahedron Lett.* ***1992***, *33*, 3737.
[1757] Watanabe, Y.; Yamashita, M.; Mitsudo, T.; Igami, M.; Takegami, Y. *Bull. Chem. Soc. Jpn.* ***1975***, *48*, 2490; Watanabe, Y.; Yamashita, M.; Mitsudo, T.; Igami, M.; Tomi, K.; Takegami, Y. *Tetrahedron Lett.* ***1975***, 1063.
[1758] Shi, Z.; Gu, H. *Synth. Commun.* ***1997***, *27*, 2701.

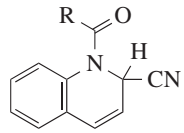
19-45 Reduction of Amides to Aldehydes

$$RCONR'_2 + LiAlH_4 \longrightarrow RCHO + NHR'_2$$

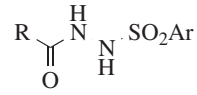
N,*N*-Disubstituted amides can be reduced to amines with $LiAlH_4$ (see **19-68**), but reduction to an aldehyde is possible.[1759] Keeping the amide in excess gives the aldehyde rather than the amine. Sometimes it is not possible to prevent further reduction and primary alcohols are obtained instead. Other reagents[1760] that give good yields of aldehydes are DibalH,[1761] $LiAlH(O\text{-}t\text{-}Bu)_3$, diaminoaluminum hydrides,[1762] and disiamylborane (see **15-11** for the disiamyl group).[1763]

Aldehydes have been prepared from carboxylic acids or acyl halides by first converting them to certain types of amides that are easily reducible. There are several examples:[1764]

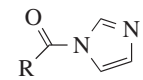
1. *Reissert compounds.*[1765] Compounds such as **27** are prepared from the acyl halide by treatment with quinoline and cyanide ion. Treatment of **27** with sulfuric acid gives the corresponding aldehyde.



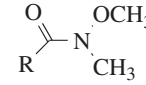
27



28



29



30

2. *Acyl sulfonylhydrazides*. Compounds such as **28** are cleaved with base to give aldehydes. This reaction is known as the *McFadyen-Stevens reduction* and is applicable *only* to aromatic aldehydes or aliphatic aldehydes with no α hydrogen.[1766] Diimide RCON=NH (see **19-71**) has been proposed as an intermediate in this reaction.[1767]
3. *Acyl imidazoles*. Compounds **29**[1768] can be reduced to aldehydes with $LiAlH_4$.
4. *Weinreb amides*. An *N*-methoxy-*N*-methyl amide such as **30** is referred to as a Weinreb amide.[1769] Reduction with an excess of $LiAlH_4$ or DibalH leads to the corresponding aldehyde.[1770] Magnesium borohydride has been used for the reduction of

[1759] Fuson, R.C. in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 220–225.
[1760] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp.1269–1271.
[1761] Zakharkin, L.I.; Khorlina, I.M. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1959***, 2046.
[1762] Muraki, M.; Mukaiyama, T. *Chem. Lett.* ***1975***, 875.
[1763] Godjoian, G.; Singaram, B. *Tetrahedron Lett.* ***1997***, *38*, 1717.
[1764] See Craig, J.C.; Ekwurieb, N.N.; Fu, C.C.; Walker, K.A.M. *Synthesis* ***1981***, 303.
[1765] See Popp, F.D.; Uff, B.C. *Heterocycles* ***1985***, *23*, 731; Popp, F.D. *Bull. Soc. Chim. Belg.* ***1981***, *90*, 609. See Bridge, A.W.; Hursthouse, M.B.; Lehmann, C.W.; Lythgoe, D.J.; Newton, C.G. *J. Chem. Soc., Perkin Trans. 1* ***1993***, 1839 for isoquinoline Reissert salts.
[1766] Dudman, C.C.; Grice, P.; Reese, C.B. *Tetrahedron Lett.* ***1980***, *21*, 4645.
[1767] See Cacchi, S.; Paolucci, G. *Gazz. Chem. Ital.* ***1974***, *104*, 221; Matin, S.B.; Craig, J.C.; Chan, R.P.K. *J. Org. Chem.* ***1974***, *39*, 2285.
[1768] For a review, see Staab, H.A.; Rohr, W. *Newer Methods Prep. Org. Chem.* ***1968***, *5*, 61.
[1769] Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* ***1981***, *22*, 3815; Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis*, 2nd ed., Wiley-Interscience, New Jersey, ***2005***, p. 866. See Sibi, M.P. *Org. Prep. Proceed. Int.* ***1993***, *25*, 15; Mentzel, M.; Hoffmann, H.M.R. *J. Prakt. Chem.* ***1997***, *339*, 517.
[1770] Wang, J.; Xu, H.; Gao, H.; Su, C.-Y.; Phillips, D.L. *Organometallics* ***2010***, *29*, 42; Gondi, V.B.; Hagihara, K.; Rawal, V.H. *Chem. Commun.* ***2010***, *46*, 904.

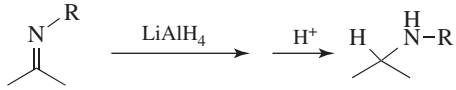
Weinreb amides to aldehydes.[1771] Amides reacted with a Mo catalyst and tetramethyldisiloxane to give the aldehyde at lower reaction temperatures after workup, and the amine (**19-38**) with reaction at higher temperatures.[1772]

5. See also, the *Sonn-Müller Method* (**19-48**).
6. *Schwartz's reagent* (**15-12**) [$(C_5H_5)_2ZrHCl$, zirconocene hydrochloride or zirconocene chloride hydride] has been used to reduce amides to aldehydes, even in the presence of esters.[1773] The *in situ* generation of (Cp_2ZrCl_2/$LiAlH(O\textit{t}\text{-}Bu)_3$) was used for the reduction of amides to aldehydes.[1774]

OS **VIII**, 68. See OS **IV**, 641, **VI**, 115 for the preparation of Reissert compounds.

C. Attack at Non-Carbonyl Multiple Bonded Heteroatoms

19-46 Reduction of the Carbon-Nitrogen Double Bond (C=N)



Imines and *Schiff bases* (R ≠ H),[1775] hydrazones,[1776] and other C=N compounds can be reduced with $LiAlH_4$, $NaBH_4$,[1777] Na/EtOH, hydrogen and a catalyst, as well as with other reducing agents.[1778] Metal-free catalytic hydrogenation is known.[1779] Transfer hydrogenation of imines leads to amines.[1780] A mixture of Sm/I_2[1781] or In/NH_4Cl[1782] also reduces imines. Iminium salts are reduced by $LiAlH_4$ to the corresponding amine, although the hydrogen on the nitrogen arises from hydrolysis.[1783] Silanes[1784] with a triarylborane catalyst reduced *N*-sulfonyl imines,[1785] as did TiI_4.[1786] Imines are reduced with $SmBr_2$ in HMPA,[1787] with propan-2-ol and a Ru catalyst,[1788] and with triethylammonium formate and

[1771] Bailey, C.L.; Clary, J.W.; Tansakul, C.; Klabunde, L.; Anderson, C.L.; Joh, A.Y.; Lill, A.T.; Peer, N.; Braslau, R.; Singaram, B. *Tetrahedron Lett.* ***2015***, *56*, 706.
[1772] Tinnis, F.; Volkov, A.; Slagbrand, T.; Adolfsson, H. *Angew. Chem. Int. Ed.* ***2016***, *55*, 4562.
[1773] Leighty, M.W.; Spletstoser, J.T.; Georg, G.I. *Org. Synth.* ***2011***, *88*, 427; White, J.M.; Tunoori, A.R.; Georg, G.I. *J. Am. Chem. Soc.* ***2000***, *122*, 11995.
[1774] Zhao, Y.; Snieckus, V. *Org. Lett.* ***2014***, *16*, 390.
[1775] Schiff, H *Ann. Chem. Pharm.* ***1864***, *131*, 118; See Verdaguer, X.; Lange, U.E.W.; Buchwald, S.L. *Angew. Chem. Int. Ed.* ***1998***, *37*, 1103.
[1776] See Burk, M.J.; Feaster, J.E. *J. Am. Chem. Soc.* ***1992***, *114*, 6266.
[1777] Bhattacharyya, S.; Neidigh, K.A.; Avery, M.A.; Williamson, J.S. *Synlett* ***1999***, 1781. For reduction with a Ni catalyst, see Liu, S.; Yang, Y.; Zhen, X.; Li, J.; He, H.; Feng, J.; Whiting, A. *Org. Biomol. Chem.* ***2012***, *10*, 663. Also see Yang, Y.; Liu, S.; Li, J.; Tian, X.; Zhen, X.; Han, J. *Synth. Commun.* ***2012***, *42*, 2540.
[1778] See Harada, K. in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 276–293; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 123–138.
[1779] Chase, P.A.; Welch, G.C.; Jurca, T.; Stephan, D.W. *Angew. Chem. Int. Ed.* ***2007***, *46*, 8050.
[1780] Zhang, Z.; Schreiner, P.R. *Synlett* ***2007***, 1455.
[1781] Banik, B.K.; Zegrocka, O.; Banik, I.; Hackfeld, L.; Becker, F.F. *Tetrahedron Lett.* ***1999***, *40*, 6731.
[1782] Banik, B.K.; Hackfeld, L.; Becker, F.F. *Synth. Commun.* ***2001***, *31*, 1581.
[1783] Paukstelis, J.V.; Cook, A.G. in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, pp. 275–356.
[1784] See Malkov, A.V.; Mariani, A.; MacDougall, K.N.; Kocovsky, P. *Org. Lett.* ***2004***, *6*, 2253.
[1785] Blackwell, J.M.; Sonmor, E.R.; Scoccitti, T.; Piers, W.E. *Org. Lett.* ***2000***, *2*, 3921.
[1786] Shimizu, M.; Sahara, T.; Hayakawa, R. *Chem. Lett.* ***2001***, 792.
[1787] Knettle, B.W.; Flowers II, R.A. *Org. Lett.* ***2001***, *3*, 2321.
[1788] Samec, J.S.M.; Bäckvall, J.-E. *Chem. Eur. J.* ***2002***, *8*, 2955.

microwave irradiation.[1789] The borane-promoted hydrosilane reduction of imines has been explored.[1790] The reduction of imines was reported using a Au catalyst with $PhMe_2SiH$.[1791] The iodine-catalyzed Hantzch ester transfer hydrogenation of imines has been reported.[1792]

Enzymatic reduction of imines leads to chiral amines[1793] and reduction of imines has been carried out enantioselectively with myriad reagents.[1794] Catalytic hydrogenation[1795] with a chiral Ir,[1796] Re,[1797] Rh,[1798] Ru,[1799] Fe,[1800] Al,[1801] Co,[1802] or Pd[1803] catalyst is known. The asymmetric hydrogenation of imines used an Ir catalyst in supercritical CO_2.[1804] Catalytic hydrogenation of iminium salts with a chiral Ru catalyst gives the amine.[1805] Ligands have been developed for the metal-free, borane-catalyzed hydrogenation of imines.[1806] The asymmetric reduction of *tert*-butylsulfinyl ketimines used *N*-heterocyclic carbene boranes.[1807] Chiral Brønsted acids have also been used.[1808] Ketimines were reduced with catecholborane with good enantioselectivity.[1809] The metal-free catalytic hydrogenation of imines used $B(C_6F_5)_3$.[1810] Trichlorosilane-promoted C=N reductions in a coil reactor followed by *N*-deprotection under flow conditions (Sec. 7.D) gave enantiomers of 1-(3-alkoxyphenyl)ethylamine.[1811]

Catalytic transfer hydrogenation of imines with a chiral catalyst leads to chiral amines.[1812] Frustrated Lewis pairs catalyzed the asymmetric transfer hydrogenation of imines using ammonia•borane.[1813] Iron catalysts were used for asymmetric transfer hydrogenation.[1814] The asymmetric transfer hydrogenation of ketimines used a chiral phosphoric

[1789] Moghaddam, F.M.; Khakshoor, O.; Ghaffarzadeh, M. *J. Chem. Res. (S)* ***2001***, 525.
[1790] Hermeke, J.; Mewald, M.; Oestreich, M. *J. Am. Chem. Soc.* ***2013***, *135*, 17537.
[1791] Takale, B.S.; Tao, S.; Yu, X.; Feng, X.; Jin, T.; Bao, M.; Yamamoto, Y. *Tetrahedron* ***2015***, *71*, 7154.
[1792] Bachu, P.; Zhu, C.; Akiyama, T. *Tetrahedron Lett.* ***2013***, *54*, 3977.
[1793] Vaijayanthi, T.; Chadha, A. *Tetrahedron: Asymmetry* ***2008***, *19*, 93.
[1794] See Denmark, S.E.; Nakajima, N.; Nicaise, O.J.-C. *J. Am. Chem. Soc.* ***1994***, *116*, 8797; Fuller, J.C.; Belisle, C.M.; Goralski, C.T.; Singaram, B. *Tetrahedron Lett.* ***1994***, *35*, 5389. For a review of asymmetric reductions involving the C=N unit, see Zhu, Q.-C.; Hutchins, R.O. *Org. Prep. Proceed. Int.* ***1994***, *26*, 193.
[1795] For a review, see Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* ***2011***, *111*, 1713.
[1796] See Tang, W.; Lau, C.; Wu, X.; Xiao, J. *Synlett* ***2014***, *25*, 81; Villa-Marcos, B.; Tabg, W.; Wu, X.; Xiao, J. *Org. Biomol. Chem.* ***2013***, *11*, 6934.
[1797] Nolin, K.A.; Ahn, R.W.; Toste, F.D. *J. Am. Chem. Soc.* ***2005***, *127*, 12462.
[1798] Li, C.; Xiao, J. *J. Am. Chem. Soc.* ***2008***, *130*, 13208.
[1799] Chen, F.; Ding, Z.; Qin, J.; Wang, T.; He, Y.; Fan, Q.-H. *Org. Lett.* ***2011***, *13*, 4348; Chen, F.; Wang, T.; He, Y.; Ding, Z.; Li, Z.; Xu, L.; Fan, Q.-H. *Chem. Eur. J.* ***2011***, *17*, 1109.
[1800] For a diastereoselective hydrogenation, see Brenna, D.; Rossi, S.; Cozzi, F.; Benaglia, M. *Org. Biomol. Chem.* ***2017***, *15*, 5685.
[1801] Hatnean, J.A.; Thomson, J.W.; Chase, P.A.; Stephan, D.W. *Chem. Commun.* ***2014***, *50*, 301.
[1802] Akiyama, T.; Saito, K.; Janczak, S.; Lesnikowski, Z.J. *Synlett* ***2014***, *25*, 795.
[1803] Abe, H.; Amii, H.; Uneyama, K. *Org. Lett.* ***2001***, *3*, 313.
[1804] Lyubimov, S.E.; Rastorguev, E.A.; Petrovskii, P.V.; Kelbysheva, E.S.; Loim, N.M.; Davankov, V.A. *Tetrahedron Lett.* ***2011***, *52*, 1395.
[1805] Magee, M.P.; Norton, J.R. *J. Am. Chem. Soc.* ***2001***, *123*, 1778.
[1806] Liu, Y.; Du, H. *J. Am. Chem. Soc.* ***2013***, *135*, 6810.
[1807] Liu, T.; Chen, L.-y.; Sun, Z. *J. Org. Chem.* ***2015***, *80*, 11441.
[1808] Tang, W.; Johnston, S.; Li, C.; Iggo, J.A.; Bacsa, J.; Xiao, J. *Chem. Eur. J.* ***2013***, *19*, 14187.
[1809] Enders, D.; Rembiak, A.; Seppelt, M. *Tetrahedron Lett.* ***2013***, *54*, 470.
[1810] Heiden, Z.M.; Stephan, D.W. *Chem. Commun.* ***2011***, *47*, 5729.
[1811] Brenna, D.; Benaglia, M.; Porta, R.; Fernandes, S.; Burke, A.J. *Eur. J. Org. Chem.* ***2017***, 39.
[1812] Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* ***2005***, *7*, 3781.
[1813] Li, S.; Li, G.; Meng, W.; Du, H. *J. Am. Chem. Soc.* ***2016***, *138*, 12956.
[1814] Mikhailine, A.A.; Maishan, M.; Morris, R.H. *Org. Lett.* ***2012***, *14*, 4638; Castro, L.C.M.; Sortais, J.-B.; Darcel, C. *Chem. Commun.* ***2012***, *48*, 151; Pan, H.-J.; Ng, T.W.; Zhao, Y. *Org. Biomol. Chem.* ***2016***, *14*, 5490.

acid catalyst and 2-aryl indoline as the hydrogen donor.[1815] The Rh-catalyzed asymmetric transfer hydrogenation of imines in water used formic acid and triethylamine.[1816] The asymmetric transfer hydrogenation of imines used alcohols, an Ir catalyst, and a chiral phosphoric acid.[1817]

Conjugated *N*-sulfonyl imines are reduced to the conjugated sulfonamide with good enantioselectivity using a chiral Rh catalyst in the presence of LiF and $PhSnMe_3$.[1818] Silanes, such as $PhSiH_3$, can be used for the reduction of imines, and in the presence of a chiral Ti catalyst the resulting amine was formed with excellent enantioselectivity.[1819] The enantioselective reduction of aromatic imines is possible using trichlorosilane.[1820] Diazo compounds (ArN═NAr) are reductively cleaved to aniline derivatives with Zn and ammonium formate in methanol.[1821] Azobenzenes were reduced by SmI_2 in THF in the presence of an alcohol to give hydrazobenzene and imines were reduced to amines.[1822]

Enantioselective reduction of imines is possible using a mixture of *Escherichia. coli* whole cells and NH_3•BH_3.[1823] *E. coli* cells containing overexpressed (*R*)-selective ω-transaminase and the cofactor PLP were immobilized on methacrylate beads using continuous flow conditions (Sec. 7.D) for the reduction of imines, generated *in situ* from amines and keto ethers, to give amino ethers.[1824] *Hantzsch ester* (see **19-37**, **16-15**) reduction of imine esters, in the presence of a chiral phosphoric acid derivative, leads to chiral amino esters.[1825] The chiral disulfonimide-catalyzed asymmetric reduction of *N*-alkyl imines with Hantzsch esters in the presence of Boc_2O gave Boc-protected *N*-alkyl amines.[1826] The Zn complex-catalyzed and enantioselective hydrosilation of imines has been reported.[1827] The use of NADPH-dependent imine reductases is an important class of biocatalyst that reduces imines to chiral amines.[1828] Enantioselective imine reductions have been reported using imine reductases and artificial metalloenzymes.[1829] The chiral borane-catalyzed asymmetric hydrosilation of imines has been reported.[1830] Phosphinyl imines, R_2C═N─P(═O)Ar_2, are reduced with high enantioselectivity using a chiral Cu catalyst.[1831] A proline-based organocatalyst has been used for the enantioselective reduction of imines, with trichlorosilane.[1832] A Rh complex was used for the chemo- and enantioselective hydrogenation of allylic hydrazones to give chiral allylic hydrazines.[1833]

[1815] Saito, K.; Miyashita, H.; Akiyama, T. *Org. Lett.* ***2014***, *16*, 5312.
[1816] Shende, V.S.; Deshpande, S.H.; Shingote, S.K.; Joseph, A.; Kelkar, A.A. *Org. Lett.* ***2015***, *17*, 2878.
[1817] Pan, H.-J.; Zhang, Y.; Shan, C.; Yu, Z.; Lan, Y.; Zhao, Y. *Angew. Chem. Int. Ed.* ***2016***, *55*, 9615.
[1818] Hayashi, T.; Ishigedani, M. *Tetrahedron* ***2001***, *57*, 2589.
[1819] Hansen, M.C.; Buchwald, S.L. *Org. Lett.* ***2000***, *2*, 713.
[1820] For a review, see Guizzetti, S.; Benaglia, M. *Eur. J. Org. Chem.* ***2010***, 5529. See Malkov, A.V.; Vranková, K.; Sigerson, R.C.; Stončius, S.; Kočovský, P. *Tetrahedron* ***2009***, *65*, 9481.
[1821] Gowda, S.; Abiraj, K.; Gowda, D.C. *Tetrahedron Lett.* ***2002***, *43*, 1329.
[1822] Rao, C.N.; Hoz, S. *J. Org. Chem.* ***2011***, *76*, 9438.
[1823] Dunsmore, C.J.; Carr, R.; Fleming, T.; Turner, N.J. *J. Am. Chem. Soc.* ***2006***, *128*, 2224.
[1824] Andrade, L.H.; Kroutil, W.; Jamison, T.F. *Org. Lett.* ***2014***, *16*, 6092.
[1825] Li, G.; Liang, Y.; Antilla, J.C. *J. Am. Chem. Soc.* ***2007***, *129*, 5830.
[1826] Wakchaure, V.N.; Kaib, P.S.J.; Leutzsch, M.; List, B. *Angew. Chem. Int. Ed.* ***2015***, *54*, 11852.
[1827] Bezłada, A.; Szewczyk, M.; Mlynarski, J. *J. Org. Chem.* ***2016***, *81*, 336.
[1828] Grogan, G.; Turner, N.J. *Chem. Eur. J.* ***2016***, *22*, 1900.
[1829] Gamernara, D.; de Maria, P.D. *Org. Biomol. Chem.* ***2014***, *12*, 2989.
[1830] Zhu, X.; Du, H. *Org. Biomol. Chem.* ***2015***, *13*, 1013.
[1831] Lipshutz, B.H.; Shimizu, H. *Angew. Chem. Int. Ed.* ***2004***, *43*, 2228.
[1832] Kanemitsu, T.; Umehara, A.; Haneji, R.; Nagata, K.; Itoh, T. *Tetrahedron* ***2012***, *68*, 3893.
[1833] Hu, Q.; Hu, Y.; Liu, Y.; Zhang, Z.; Liu, Y.; Zhang, W. *Chem. Eur. J.* ***2017***, *23*, 1040.

Oximes are generally reduced to amines (**19-52**),[1834] but simple reduction to give hydroxylamines can be accomplished with borane[1835] or sodium cyanoborohydride.[1836] Oximes are reduced with hydrogen gas and a catalytic amount of 48% HBr.[1837] Hydrogenation of oximes with Pd/C and a Ni complex gives the imine, and in the presence of a lipase and ethyl acetate the final product was an acetamide, formed with high enantioselectivity.[1838] Oxime *O*-ethers are reduced with Bu_3SnH and $BF_3{\bullet}OEt_2$.[1839] Oxime ethers are reduced with borane and a chiral spiroborate ester catalyst.[1840] The Rh-catalyzed enantioselective hydrogenation of oxime acetals has been reported.[1841] The Ni-catalyzed asymmetric transfer hydrogenation of hydrazones and ketimines used formic acid/triethanolamine in ethanol.[1842]

Isocyanates have been catalytically hydrogenated to *N*-substituted formamides: RNCO → R—NH—CHO.[1843] Isothiocyanates were reduced to thioformamides with SmI_2 in HMPA/*t*-BuOH.[1844]

OS **III**, 328, 827; **VI**, 905; **VIII**, 110, 568. Also see, OS **IV**, 283.

19-47 The Reduction of Nitriles to Amines

$$R{-}C{\equiv}N + LiAlH_4 \longrightarrow R{-}CH_2{-}NH_2$$

Nitriles can be reduced to primary amines with many reducing agents,[1845] including $LiAlH_4$[1846] and $BH_3{\bullet}SMe_2$.[1847] The reagent $NaBH_4$ does not generally reduce nitriles, except in alcoholic solvents with a catalyst such as In,[1848] Ru,[1849] Fe,[1850] Co,[1851] or Ni.[1852]

[1834] See Bolm, C.; Felder, M. *Synlett* ***1994***, 655; Williams, D.R.; Osterhout, M.H.; Reddy, J.P. *Tetrahedron Lett.* ***1993***, *34*, 3271.
[1835] Kawase, M.; Kikugawa, Y. *J. Chem. Soc., Perkin Trans. 1* ***1979***, 643.
[1836] See Hutchins, R.O.; Natale, N.R. *Org. Prep. Proced. Int.* ***1979***, *11*, 201; Lane, C.F. *Synthesis* ***1975***, 135.
[1837] Davies, I.W.; Taylor, M.; Marcoux, J.-F.; Matty, L.; Wu, J.; Hughes, D.; Reider, P.J. *Tetrahedron Lett.* ***2000***, *41*, 8021.
[1838] Choi, Y.K.; Kim, M.J.; Ahn, Y.; Kim, M.-J. *Org. Lett.* ***2001***, *3*, 4099.
[1839] Ueda, M.; Miyabe, H.; Namba, M.; Nakabayashi, T.; Naito, T. *Tetrahedron Lett.* ***2002***, *43*, 4369.
[1840] Chu, Y.; Shan, Z.; Liu, D.; Sun, N. *J. Org. Chem.* ***2006***, *71*, 3998; Huang, K.; Merced, F.G.; Ortiz-Marciales, M.; Meléndez, H.J.; Correa, W.; De Jesús, M. *J. Org. Chem.* ***2008***, *73*, 4017.
[1841] Huang, K.; Li, S.; Chang, M.; Zhang, X. *Org. Lett.* ***2013***, *15*, 484.
[1842] Xu, H.; Yang, P.; Chuanprasit, P.; Hirao, H.; Zhou, J. *Angew. Chem. Int. Ed.* ***2015***, *54*, 5112.
[1843] Howell, H.G. *Synth. Commun.* ***1983***, *13*, 635.
[1844] Park, H.S.; Lee, I.S.; Kim, Y.H. *Chem. Commun.* ***1996***, 1805.
[1845] See Rabinovitz, M. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 307–340; Enthaler, S.; Addis, D.; Junge, K.; Erre, G.; Beller, M. *Chem. Eur. J.* ***2008***, *14*, 9491. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 875–878.
[1846] See Glaser, R.; Ulmer, L.; Coyle, S. *J. Org. Chem.* ***2013***, *78*, 1113.
[1847] See Brown, H.C.; Choi, Y.M.; Narasimhan, S. *Synthesis* ***1981***, 605.
[1848] Saavedra, J.Z.; Resendez, A.; Rovira, A.; Eagon, S.; Haddenham, D.; Singaram, B. *J. Org. Chem.* ***2012***, *77*, 221.
[1849] Lu, Z.; Willimas, T.J. *Chem. Commun.* ***2014***, *50*, 3512.
[1850] Chaakraborty, S.; Leitus, G.; Milstein, D. *Chem. Commun.* ***2016***, *52*, 1812.
[1851] Satoh, T.; Suzuki, S. *Tetrahedron Lett.* ***1969***, 4555. For a discussion of the mechanism, see Heinzman, S.W.; Ganem, B. *J. Am. Chem. Soc.* ***1982***, *104*, 6801.
[1852] Khurana, J.M.; Kukreja, G. *Synth. Commun.* ***2002***, *32*, 1265; Egli, R.A. *Helv. Chim. Acta* ***1970***, *53*, 47.

Lithium dimethylaminoborohydride ($LiBH_3NMe_2$) reduces aryl nitriles to the corresponding benzylamines.[1853]

The reduction of nitriles is of wide scope and has been applied to many nitriles. Catalytic hydrogenation converts nitriles to primary amines,[1854] but secondary amines, $(RCH_2)_2NH$, are often side products.[1855] These can be avoided by adding a compound, such as acetic anhydride, which removes the primary amine as soon as it is formed,[1856] or by the use of excess ammonia to drive the equilibria backward.[1857] Sponge Ni,[1858] Ni on silica gel,[1859] or Rh[1860] have been used for the catalytic hydrogenation of aryl nitriles to amines. Attempts to convert a nitrile to an imine by stopping the reaction with only 1 equivalent of hydrogen have failed, except where the imine is subsequently hydrolyzed (**19-48**).

Photoirradiation with visible light stimulates reaction with SmI_2 and methanol to reduce nitriles to amines.[1861] The use of $PhSiH_3$ and a Re catalyst has been used for the reduction of nitriles to amines.[1862] The reduction of nitriles using $B(C_6F_5)_3$ as a catalyst with hydrosilanes as a reductant gave primary amines, but bulky hydrosilanes gave the imine.[1863] Symmetrical secondary amines were prepared by the reductive amination of nitriles using H_2 and Pt nanowires as catalyst, and unsymmetrical secondary amines were prepared by identical reaction conditions with a primary amine.[1864] Tertiary alkyl amines were prepared from their corresponding alkyl nitriles using a heterogeneous Pd catalyst and ammonium formate in aprotic solvents.[1865] The Co-catalyzed transfer hydrogenation of nitriles has been reported.[1866]

N-Alkylnitrilium ions ($R{-}C{\equiv}N^{+}{-}R'$) are reduced to secondary amines by $NaBH_4$.[1867] Since nitrilium salts can be prepared by treatment of nitriles with trialkyloxonium salts (see **16-7**), this is a method for the conversion of nitriles to secondary amines. Note that the related compounds, the isonitriles ($R{-}^{+}N{\equiv}CO^{-}$, also called isocyanides) have been reduced to *N*-methylamines with $LiAlH_4$, as well as with other reducing agents.

OS **III**, 229, 358, 720; **VI**, 223.

19-48 The Reduction of Nitriles to Aldehydes

$$R{-}C{\equiv}N \xrightarrow[\text{2. Hydrolysis}]{\text{1. HCl, } SnCl_2} RCH{=}O$$

[1853] Thomas, S.; Collins, C.J.; Cuzens, J.R.; Spieciarich, D.; Goralski, C.T.; Singaram, B. *J. Org. Chem.* ***2001***, *66*, 1999.
[1854] See Reguillo, R.; Grellier, M.; Vautravers, N.; Vendier, L.; Sabo-Etienne, S. *J. Am. Chem. Soc.* ***2010***, *132*, 7854.
[1855] See Galán, A.; de Mendoza, J.; Prados, P.; Rojo, J.; Echavarren, A.M. *J. Org. Chem.* ***1991***, *56*, 452.
[1856] See Gould, F.E.; Johnson, G.S.; Ferris, A.F. *J. Org. Chem.* ***1960***, *25*, 1658.
[1857] For example, see Freifelder, M. *J. Am. Chem. Soc.* ***1960***, *82*, 2386.
[1858] Tanaka, K.; Nagasawa, M.; Kasuga, Y.; Sakamura, H.; Takuma, Y.; Iwatani, K. *Tetrahedron Lett.* ***1999***, *40*, 5885.
[1859] Takamizawa, S.; Wakasa, N.; Fuchikami, T. *Synlett* ***2001***, 1623.
[1860] Yan, Q.; Kong, D.; Li, M.; Hou, G.; Zi, G. *J. Am. Chem. Soc.* ***2015***, *137*, 10177.
[1861] Rao, C.N.; Hoz, S. *J. Org. Chem.* ***2012***, *77*, 4029. See Szostak, M.; Sautier, B.; Spain, M.; Procter, D.J. *Org. Lett.* ***2014***, *16*, 10092.
[1862] Cabrita, I.; Fernandes, A.C. *Tetrahedron* ***2011***, *67*, 8183.
[1863] Gandhamsetty, N.; Jeong, J.; Park, J.; Park, S.; Chang, S. *J. Org. Chem.* ***2015***, *80*, 7281.
[1864] Lu, S.; Wang, J.; Cao, X.; Li, X.; Gu, H. *Chem. Commun.* ***2014***, *50*, 3512.
[1865] Shares, J.; Yehl, J.; Kowalsick, A.; Byers, P.; Haaf, M.P. *Tetrahedron Lett.* ***2012***, *53*, 4426.
[1866] Shao, Z.; Fu, S.; Wei, M.; Zhou, S.; Liu, Q. *Angew. Chem. Int. Ed.* ***2016***, *55*, 14546.
[1867] Borch, R.F. *Chem. Commun.* ***1968***, 442.

There are two principal methods for the reduction of nitriles to aldehydes.[1868] In one of these, known as the *Stephen reduction*, the nitrile is treated with HCl to form an iminium salt, $R(Cl)C{=}N^+H_2\ Cl^-$. Subsequent reduction of the chloroiminium salt with anhydrous $SnCl_2$ gives RCH=NH, which precipitates as a complex with $SnCl_4$ and is then hydrolyzed (**16-2**) to the aldehyde. The Stephen reduction is most successful when R is aromatic, but it can be done for aliphatic R up to about six carbons.[1869] It is also possible to prepare the iminium salt in a different way, by treating ArCONHPh with PCl_5, which can then be converted to the aldehyde. This is known as the *Sonn-Müller method*. Aqueous formic acid in the presence of PtO_2, followed by treatment with aqueous acid, converts aryl nitriles to aryl aldehydes.[1870] The DibalH reduction of nitriles to an aldehyde was reported using flow conditions (Sec. 7.D).[1871] Nitriles were reduced to aldehydes using 1,1,3,3-tetramethyldisiloxane/triisopropoxyvanadium oxide.[1872]

The other way of reducing nitriles to aldehydes involves using a metal hydride reducing agent to add 1 molar equivalent of hydrogen, with subsequent hydrolysis, *in situ*, of the resulting imine (which is undoubtedly coordinated to the metal). This has been carried out with $LiAlH_4$, $LiAlH(OEt)_3$,[1873] $LiAlH(NR_2)_3$,[1874] and DibalH.[1875] The metal hydride method is useful for aliphatic and aromatic nitriles.

OS **III**, 626, 818; **VI**, 631.

19-49 Reduction of Nitro Compounds to Amines

$$RNO_2 \xrightarrow[HCl]{Zn} RNH_2$$

Both aliphatic[1876] and aromatic nitro compounds can be reduced to amines, although the reaction has been applied much more often to aromatic nitro compounds, owing to their greater availability. Many reducing agents have been used to reduce aromatic nitro compounds, including Zn, Sn, Pt,[1877] Ru/SiO_2,[1878] Fe,[1879] or Fe (or sometimes other metals)

[1868] Rabinovitz, M. in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, p. 307. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1271–1272.

[1869] Zil'berman, E.N.; Pyryalova, P.S. *J. Gen. Chem. USSR* ***1963***, *33*, 3348.

[1870] Xi, F.; Kamal, F.; Schenerman, M.A. *Tetrahedron Lett.* ***2002***, *43*, 1395.

[1871] Muñoz, J. de M.; Alcázar, J.; de la Hoz, A.; Díaz-Ortiz, A. *Tetrahedron Lett.* ***2011***, *52*, 6058.

[1872] Laval, S.; Dayoub, W.; Pehlivan, L.; Métay, E.; Delbrayelle, D.; Mignani, G.; Lemaire, M. *Tetrahedron Lett.* ***2014***, *55*, 23.

[1873] Brown, H.C.; Shoaf, C.J. *J. Am. Chem. Soc.* ***1964***, *86*, 1079. For a review of reductions with this and related reagents, see Málek, J. *Org. React.* ***1988***, *36*, 249 (see pp. 287–289, 438–448).

[1874] Cha, J.S.; Lee, S.E.; Lee, H.S. *Org. Prep. Proceed. Int.* ***1992***, *24*, 331. Also see, Cha, J.S.; Jeoung, M.K.; Kim, J.M.; Kwon, O.O.; Lee, J.C. *Org. Prep. Proceed. Int.* ***1994***, *26*, 583.

[1875] Marshall, J.A.; Andersen, N.H.; Schlicher, J.W. *J. Org. Chem.* ***1970***, *35*, 858.

[1876] See Ioffe, S.L.; Tartakovskii, V.A.; Novikov, S.S. *Russ. Chem. Rev.* ***1966***, *35*, 19.

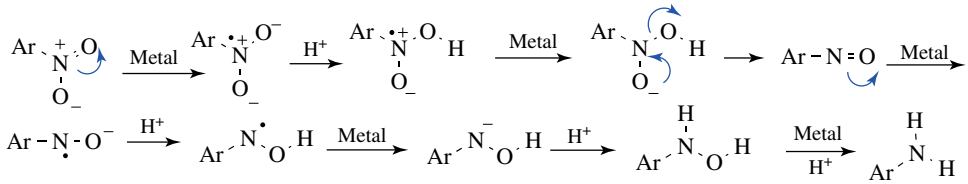
[1877] Kasparian, A.J.; Savarin, C.; Allgeier, A.M.; Walker, S.D. *J. Org. Chem.* ***2011***, *76*, 9841; Kotha, S.S.; Sharma, N.; Sekar, G. *Tetrahedron Lett.* ***2016***, *57*, 1410.

[1878] Tamura, M.; Yuasa, N.; Nakagawa, Y.; Tomishige, K. *Chem. Commun.* ***2017***, *53*, 3377.

[1879] Wienhöfer, G.; Baseda-Krüger, M.; Ziebart, C.; Westerhaus, F.A.; Baumann, W.; Jackstell, R.; Junge, K.; Beller, M. *Chem. Commun.* ***2013***, *49*, 9089; Morse, J.R.; Callejas, J.F.; Darling, A.J.; Schaak, R.E. *Chem. Commun.* ***2017***, *53*, 4807; Cantillo, D.; Moghaddam, M.M.; Kappe, C.O. *J. Org. Chem.* ***2013***, *78*, 4530.

and acid, and catalytic hydrogenation.[1880] Chemoselective catalytic hydrogenation of nitro compounds is possible.[1881] Indium metal in aqueous ethanol with ammonium chloride[1882] or with water in aqueous THF[1883] also reduces aromatic nitro compounds to the corresponding aniline derivative. Indium metal in methanol, with acetic anhydride and acetic acid, converts aromatic nitro compounds to the acetanilide.[1884] Both Sm metal in methanol with ultrasound,[1885] and a mixture of SmI_2/water and an amine reduce nitro compounds.[1886] Alternative reduction methods use ultrasound with Al(Hg) in aqueous THF[1887] or with stannous chloride in an ionic liquid.[1888] The reaction with sulfides or polysulfides is called the *Zinin reduction*.[1889] Amines are also the products when nitro compounds, both alkyl and aryl, are reduced with $HCOONH_4$/Pd/C.[1890] With optically active alkyl substrates this method gives retention of configuration.[1891]

The mechanisms of these reductions have not been much studied, although it is usually presumed that, at least with some reducing agents, nitroso compounds and hydroxylamines are intermediates. Both of these types of compounds give amines when exposed to most of these reducing agents (**19-51**), and hydroxylamines can be isolated (**19-50**). With metals and acid the following path has been suggested:[1892]



Lithium aluminum hydride reduces aliphatic nitro compounds to amines, but with aromatic nitro compounds the products with this reagent are azo compounds (**19-84**). The $LiAlH_4/TiCl_4$ reduction of aromatic nitro compound to the corresponding aniline was reported.[1893] Most metal hydrides, including $NaBH_4$ and BH_3, do not reduce nitro groups at all, although both aliphatic and aromatic nitro compounds have been reduced to amines

[1880] For reviews, see Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 104–116, *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 168–202. See Deshpande, R.M.; Mahajan, A.N.; Diwakar, M.M.; Ozarde, P.S.; Chaudhari, R.V. *J. Org. Chem.* ***2004***, *69*, 4835.

[1881] Takasaki, M.; Motoyama, Y.; Higashi, K.; Yoon, S.-H.; Mochida, I.; Nagashima, H. *Org. Lett.* ***2008***, *10*, 1601. See also Gelder, E.A.; Jackson, S.D.; Lok, C.M. *Chem. Commun.* ***2005***, 522; Chen, Y.; Wang, C.; Liu, H.; Qiu, J.; Bao, X. *Chem. Commun.* ***2005***, 5298.

[1882] Banik, B.K.; Suhendra, M.; Banik, I.; Becker, F.F. *Synth. Commun.* ***2000***, *30*, 3745.

[1883] Lee, J.G.; Choi, K.I.; Koh, H.Y.; Kim, Y.; Kang, Y.; Cho, Y.S. *Synthesis* ***2001***, 81.

[1884] Kim, B.H.; Han, R.; Piao, F.; Jun, Y.M.; Baik, W.; Lee, B.M. *Tetrahedron Lett.* ***2003***, *44*, 77.

[1885] Basu, M.K.; Becker, F.F.; Banik, B.K. *Tetrahedron Lett.* ***2000***, *41*, 5603.

[1886] Ankner, T.; Hilmersson, G. *Tetrahedron Lett.* ***2007***, *48*, 5707.

[1887] Fitch, R.W.; Luzzio, F.A. *Tetrahedron Lett.* ***1994***, *35*, 6013.

[1888] Rai, G.; Jeong, J.M.; Lee, Y.-S.; Kim, H.W.; Lee, D.S.; Chung, J.-K.; Lee, M.C. *Tetrahedron Lett.* ***2005***, *46*, 3987.

[1889] For a review of the Zinin reduction, see Porter, H.K. *Org. React.* ***1973***, *20*, 455.

[1890] See Abiraj, K.; Srinivasa, G.R.; Gowda, D.C. *Synth. Commun.* ***2005***, *35*, 223.

[1891] Barrett, A.G.M.; Spilling, C.D. *Tetrahedron Lett.* ***1988***, *29*, 5733.

[1892] House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, p. 211.

[1893] Di Gioia, M.L.; Leggio, A.; Guarino, I.F.; Leotta, V.; Romio, E.; Liguori, A. *Tetrahedron Lett.* ***2015***, *56*, 5341.

with $NaBH_4$ and various catalysts, such as $NiCl_2$ or $CoCl_2$[1894] and $ZrCl_4$.[1895] Borohydride exchange resin (BER) in the presence of $Ni(OAc)_2$, however, gives the amine.[1896] Transition metal sulfides and $NaBH_4$ were used to reduce nitrobenzene derivatives.[1897] Treatment of aromatic nitro compounds with $NaBH_4$ alone has resulted in reduction of the *ring* to a cyclohexane ring with the nitro group still intact[1898] or in cleavage of the nitro group from the ring.[1899] With $(NH_4)_2S$ or other sulfides or polysulfides it is often possible to reduce just one of two or three nitro groups on an aromatic ring or on two different rings in one molecule.[1900] Baker's yeast reduces aromatic nitro compounds to aniline derivatives.[1901] A combination of $NaH_2PO_2/FeSO_4$ with microwave irradiation reduces aromatic nitro compounds to aniline derivatives.[1902] Hydrazine on alumina, with $FeCl_3$ and microwave irradiation, accomplishes this reduction.[1903] Hydrazine/formic acid with Raney nickel in methanol reduces aromatic nitro compounds.[1904] Nitrobenzene was reduced to aniline using $SnCl_2$ and HCl.[1905]

With some reducing agents, especially with aromatic nitro compounds, the reduction can be stopped at an intermediate stage, and hydroxylamines (**19-50**), hydrazobenzenes, azobenzenes (**19-84**), and azoxybenzenes (**19-83**) can be obtained in this manner. However, nitroso compounds, which are often postulated as intermediates, are too reactive to be isolated, if indeed they are intermediates. Reduction by metals in mineral acids cannot be stopped, but always produces the amine.

The Cl_3SiH-mediated reduction of nitro compounds to the amine has been reported.[1906] Nitro groups were reduced to the corresponding amine in the designer surfactant TPGS-750-M in water, using Zn dust and ammonium chloride.[1907] Aromatic nitro compounds were reduced to the aromatic amine with B_2pin_2 in propan-2-ol.[1908] Nitro groups have been reduced using carbonyl iron powder using aqueous micellar catalysis.[1909]

Transfer hydrogenation is used to reduce nitro compounds.[1910] The transfer hydrogenation of nitroarenes to amines used a Rh catalyst and microwave irradiation.[1911] Transfer hydrogenation has been used with flow conditions (Sec. 7.D).[1912] The Ru-catalyzed

[1894] See He, Y.; Zhao, H.; Pan, X.; Wang, S. *Synth. Commun.* ***1989***, *19*, 3047 and cited references.
[1895] Chary, K.P.; Ram, S.R.; Iyengar, D.S. *Synlett* ***2000***, 683.
[1896] Yoon, N.M.; Choi, J. *Synlett* ***1993***, 135.
[1897] Piña Jr., S.; Cedillo, D.M.; Tamez, C.; Izquierdo, N.; Parsons, J.G.; Gutierrez, J.J. ***2014***, *55*, 5468.
[1898] See Severin, T.; Adam, M. *Chem. Ber.* ***1963***, *96*, 448.
[1899] Kaplan, L.A. *J. Am. Chem. Soc.* ***1964***, *86*, 740. See also, Swanwick, M.G.; Waters, W.A. *Chem. Commun.* ***1970***, 63.
[1900] See Ono, A.; Terasaki, S.; Tsuruoka, Y. *Chem. Ind. (London)* ***1983***, 477; Ayyangar, N.R.; Kalkote, U.R.; Lugad, A.G.; Nikrad, P.V.; Sharma, V.K. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 3159.
[1901] Baik, W.; Han, J.L.; Lee, K.C.; Lee, N.H.; Kim, B.H.; Hahn, J.-T. *Tetrahedron Lett.* ***1994***, *35*, 3965.
[1902] Meshram, H.M.; Ganesh, Y.S.S.; Sekhar, K.C.; Yadav, J.S. *Synlett* ***2000***, 993.
[1903] Vass, A.; Dudás, J.; Tóth, J.; Varma, R.S. *Tetrahedron Lett.* ***2001***, *42*, 5347.
[1904] Gowda, S.; Gowda, D.C. *Tetrahedron* ***2002***, *58*, 2211.
[1905] Yamabe, S.; Yamazaki, S. *J. Phys. Org. Chem.* ***2016***, *29*, 361.
[1906] Orlandi, M.; Benaglia, M.; Tosi, F.; Annunziata, R.; Cozzi, F. *J. Org. Chem.* ***2016***, *81*, 3037; Orlandi, M.; Bonsignore, F.T.M.; Benaglia, M. *Org. Lett.* ***2015***, *17*, 3941.
[1907] Kelly, S.M.; Lipshutz, B.H. *Org. Lett.* ***2014***, *16*, 98. See Feng, J.; Handa, S.; Gallou, F.; Lipshutz, B.H. *Angew. Chem. Int. Ed.* ***2016***, *55*, 8979.
[1908] Lu, H.; Geng, Z.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *Org. Lett.* ***2016***, *18*, 2774.
[1909] Lee, N.R.; Bikovtseva, A.A.; Cortes-Clerget, M.; Gallou, F.; Lipshutz, B.H. *Org. Lett.* ***2017***, *19*, 6518.
[1910] Soltani, O.; Ariger, M.A.; Carreira, E.M. *Org. Lett.* ***2009***, *11*, 4196.
[1911] Guha, N.R.; Bhattacherjee, D.; Das, P. *Tetrahedron Lett.* ***2014***, *55*, 2912. See Wei, Y.; Wu, J.; Xue, D.; Wang, C.; Liu, Z.; Zhang, Z.; Chen, G.; Xiao, J. *Synlett* ***2014***, *25*, 1295.
[1912] Hutchings, M.; Wirth, T. *Synlett* ***2016***, *27*, 1832.

transfer hydrogenation reaction has been reported,[1913] and Ir metal has been used as a catalyst.[1914] The Co-catalyzed transfer hydrogenation using hydrazine has been reported.[1915] The Au/Fe-catalyzed reduction of nitro compounds using TMDS was reported.[1916] Aromatic nitro compounds were reduced to aryl amines using Fe or Zn with ammonium chloride in aqueous MeOH.[1917]

Solid-supported Pd has been used for the reduction of nitro to amines using Et_3SiH or $NaBH_4$ in aqueous MeOH or using hydrazine in water.[1918] Nitro compounds are reduced to the corresponding amine by photoirradiation in the presence of the heterogeneous nanophotocatalyst TiO_2-P25.[1919] Aromatic nitro compounds were reduced to the aromatic amine using a 1,1,3,3-tetramethyldisiloxane (TMDS)/iron catalyst system.[1920] An In/TMDS system has been used for the reduction.[1921] Hydrazine hydrate with an Fe catalyst was used for the microwave-induced reduction of aromatic nitro compounds to aniline derivatives using flow conditions (Sec. 7.D).[1922] The Fe complex-catalyzed reduction of nitro compounds to amines with hydrazine hydrate has been reported.[1923]

Certain aromatic nitroso compounds (Ar—NO) can be obtained in good yields by irradiation of the corresponding nitro compounds in 0.1 M aqueous KCN with UV light.[1924] The photoinduced reduction of nitrobenzenes to primary amines in propan-2-ol was reported.[1925] The reaction has also been performed electrochemically.[1926]. Reductive alkylation of aromatic nitro compounds is possible. The reaction of nitrobenzene with allylic or benzyl halides in the presence of an excess of tin metal in methanol leads to the *N*,*N*-diallyl or *N*,*N*-dibenzyl aniline.[1927] A similar reaction occurs with nitrobenzene, allyl bromide, and In metal in aqueous acetonitrile.[1928]

OS **I**, 52, 240, 455, 485; **II**, 130, 160, 175, 254, 447, 471, 501, 617; **III**, 56, 59, 63, 69, 73, 82, 86, 239, 242, 453; **IV**, 31, 357; **V**, 30, 346, 552, 567, 829, 1067, 1130; **81**, 188.

19-50 Reduction of Nitro Compounds to Hydroxylamines

$$ArNO_2 \xrightarrow[H_2O]{Zn} ArNHOH$$

[1913] Jagadeesh, R.V.; Wienhöfer, G.; Westerhaus, F.A.; Surkus, A.-E.; Junge, H.; Junge, K.; Beller, M. *Chem. Eur. J.* ***2011***, *17*, 14375.
[1914] Chen, S.; Lu, G.; Cai, C. *New J. Chem.* ***2015***, 5360.
[1915] Reddy, P.L.; Tripathi, M.; Arundhathi, R.; Rawat, D.S. *Chem. Asian J.* ***2017***, *12*, 785.
[1916] Park, S.; Lee, I.S.; Park, J. *Org. Biomol. Chem.* ***2013***, *11*, 395.
[1917] Keenan, C.S.; Murphree, S.S. *Synth. Commun.* ***2017***, *47*, 1085.
[1918] Shil, A.K.; Sharma, D.; Guha, N.R.; Das, P. *Tetrahedron Lett.* ***2012***, *53*, 4858.
[1919] Zand, Z.; Kazemi, F.; Hosseini, S. *Tetrahedron Lett.* ***2014***, *55*, 338.
[1920] Pehlivan, L.; Métay, E.; Laval, S.; Dayoub, W.; Demonchaux, P.; Mignani, G.; Lemaire, M. *Tetrahedron* ***2011***, *67*, 1971.
[1921] Sakai, N.; Asama, S.; Konakahara, T.; Ogiwara, Y. *Synthesis* ***2015***, *47*, 3179.
[1922] Cantillo, D.; Baghbanzadeh, M.; Kappe, C.O. *Angew. Chem. Int. Ed.* ***2012***, *51*, 10190.
[1923] Jagadeesh, R.V.; Wienhöfer, G.; Westerhouas, F.A.; Surkus, A.-E.; Pohl, M.-M.; Junge, H.; Junge, K.; Beller, M. *Chem. Commun.* ***2011***, *47*, 10972.
[1924] Petersen, W.C.; Letsinger, R.L. *Tetrahedron Lett.* ***1971***, 2197; Vink, J.A.J.; Cornelisse, J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* ***1971***, *90*, 1333.
[1925] Huang, H.-H.; Chen, Y.-F.; Niu, G.-H.; Chuang, G.J. *Synlett.* ***2017***, *28*, 1191.
[1926] Lamoureux, C.; Moinet, C. *Bull. Soc. Chim. Fr.* ***1988***, 59.
[1927] Bieber, L.W.; da Costa, R.C.; da Silva, M.F. *Tetrahedron Lett.* ***2000***, *41*, 4827.
[1928] Kang, K.H.; Choi, K.I.; Koh, H.Y.; Kim, Y.; Chung, B.Y.; Cho, Y.S. *Synth. Commun.* ***2001***, *31*, 2277.

When aromatic nitro compounds are reduced with zinc and water under neutral conditions,[1929] hydroxylamines are formed. Among other reagents used for this purpose have been SmI_2,[1930] N_2H_4/Rh/C,[1931] and $KBH_4/BiCl_3$.[1932] Borane in THF reduces aliphatic nitro enolate anions to hydroxylamines.[1933] Nitro compounds have been reduced electrochemically to hydroxylamines, as well as to other products.[1934]

OS **I**, 445; **III**, 668; **IV**, 148; **VI**, 803; **VIII**, 16.

19-51 Reduction of Nitroso Compounds and Hydroxylamines to Amines

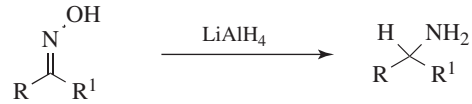
$$RNO \xrightarrow[HCl]{Zn} RNH_2$$

$$RNHOH \xrightarrow[HCl]{Zn} RNH_2$$

Nitroso compounds and hydroxylamines can be reduced to amines by the same reagents that reduce nitro compounds (**19-49**). Reaction with CuCl, and then phenylboronic acid (**12-27**), also reduces nitroso compounds to the amine.[1935] A hydroxylamine can be reduced to the amine with CS_2 in acetonitrile.[1936] Indium metal in EtOH/aqueous NH_4Cl reduces hydroxylamines to the amine.[1937] *N*-Nitroso compounds are similarly reduced to hydrazines, $R_2N{-}NO \rightarrow R_2N{-}NH_2$.[1938] Deoxygenation of amine *N*-oxides to give a tertiary amine by reaction with phenylboronic acid has been reported.[1939]

OS **I**, 511; **II**, 33, 202, 211, 418; **III**, 91; **IV**, 247. See also, OS **VIII**, 93.

19-52 Reduction of Oximes to Primary Amines or Aziridines



Both aldoximes and ketoximes can be reduced to primary amines with $LiAlH_4$. The reaction is slower than the similar reduction of ketones, so that, for example, PhCOCH=NOH gave 34% PhCHOHCH=NOH.[1940] Among other reducing agents that give this reduction[1941] are Zn/acetic acid, BH_3,[1942] $NaBH_3CN/TiCl_3$,[1943] polymethylhydrosiloxane (PMHS) with

[1929] See Entwistle, I.D.; Gilkerson, T.; Johnstone, R.A.W.; Telford, R.P. *Tetrahedron* ***1978***, *34*, 213.
[1930] Kende, A.S.; Mendoza, J.S. *Tetrahedron Lett.* ***1991***, *32*, 1699.
[1931] Oxley, P.W.; Adger, B.M.; Sasse, M.J.; Forth, M.A. *Org. Synth.* ***67***, 187.
[1932] Ren, P.D.-D.; Pan, X.-W.; Jin, Q.-H.; Yao, Z.-P. *Synth. Commun.* ***1997***, *27*, 3497.
[1933] Feuer, H.; Bartlett, R.S.; Vincent Jr., B.F.; Anderson, R.S. *J. Org. Chem.* ***1965***, *31*, 2880.
[1934] See Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 188–198; Lund, H. in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, ***1983***, pp. 285–313.
[1935] Yu, Y.; Srogl, J.; Liebeskind, L.S. *Org. Lett.* ***2004***, *6*, 2631.
[1936] Schwartz, M.A.; Gu, J.; Hu, X. *Tetrahedron Lett.* ***1992***, *33*, 1687.
[1937] Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* ***2003***, *5*, 1773.
[1938] See Lunn, G.; Sansone, E.B.; Keefer, L.K. *J. Org. Chem.* ***1984***, *49*, 3470.
[1939] Gupta, S.; Sureshbabu, P.; Singh, A.K.; Sabiah, S.; Kandasamy, J. *Tetrahedron Lett.* ***2017***, *58*, 909.
[1940] Felkin, H. *C.R. Acad. Sci.* ***1950***, *230*, 304.
[1941] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 845–846.
[1942] Feuer, H.; Braunstein, D.M. *J. Org. Chem.* ***1969***, *34*, 1817.
[1943] Leeds, J.P.; Kirst, H.A. *Synth. Commun.* ***1988***, *18*, 777.

Pd/C,[1944] and sodium and an alcohol.[1945] Catalytic hydrogenation is also effective.[1946] Reduction of oximes with In metal in acetic anhydride/acetic acid/THF leads to the acetamide.[1947]

The reduction has been performed enantioselectively with baker's yeast[1948] and with Ph_2SiH_2 and an optically active Rh-complex catalyst.[1949] Oxime *O*-ethers are reduced to the amine with modest enantioselectivity using a chiral boron compound.[1950]

When the reducing agent is DibalH, the product is a secondary amine, arising from a rearrangement: $RR'C{=}N{-}OH \rightarrow RNH{-}CH_2R'$.[1951] With certain oximes (e.g., those of the type $ArCH_2CR{=}NOH$), treatment with $LiAlH_4$ gives aziridines.[1952] Hydrazones, arylhydrazones, and semicarbazones can also be reduced to amines with various reducing agents, including Zn/HCl and H_2 and Raney nickel.

Oximes have been reduced in a different way, to give imines ($RR'C{=}NOH \rightarrow RR'C{=}NH$), which are generally unstable but which can be trapped to give useful products. Among reagents used for this purpose have been Bu_3P/SPh_2[1953] and $Ru_3(CO)_{12}$.[1954] Oximes can also be reduced to hydroxylamines (**19-42**). Nitrones have been reduced to imines using $AlCl_3{\bullet}6H_2O/KI$ followed by $Na_2S_2O_3/H_2O$.[1955]

OS **II**, 318; **III**, 513; **V**, 32, 83, 373, 376.

19-53 Reduction of Aliphatic Nitro Compounds to Oximes or Nitriles

$$RCH_2NO_2 \xrightarrow[HOAc]{Zn} RCH{=}NOH$$

Nitro compounds that contain an α hydrogen can be reduced to oximes with Zn dust in acetic acid[1956] or with other reagents, among them CS_2/NEt_3,[1957] $CrCl_2$,[1958] and (for α-nitro sulfones) $NaNO_2$.[1959] α-Nitro alkenes have been converted to oximes ($-C{=}C{-}NO_2 \rightarrow -CH{-}C{=}NOH$) with sodium hypophosphite, with In in aqueous $NH_4Cl/MeOH$,[1960] and with Pb/HOAc/DMF, as well as with certain other reagents.[1961] Primary aliphatic nitro

[1944] Chandrasekhar, S.; Reddy, M.V.; Chandraiah, L. *Synlett* ***2000***, 1351.
[1945] See Sugden, J.K.; Patel, J.J.B. *Chem. Ind. (London)* ***1972***, 683.
[1946] See Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 139–159.
[1947] Harrison, J.R.; Moody, C.J.; Pitts, M.R. *Synlett* ***2000***, 1601.
[1948] Gibbs, D.E.; Barnes, D. *Tetrahedron Lett.* ***1990***, *31*, 5555.
[1949] Brunner, H.; Becker, R.; Gauder, S. *Organometallics* ***1986***, *5*, 739; Takei, I.; Nishibayashi, Y.; Ishii, Y.; Mizobe, Y.; Uemura, S.; Hidai, M. *Chem. Commun.* ***2001***, 2360.
[1950] See Huang, X.; Ortiz-Marciales, M.; Huang, K.; Stepanenko, V.; Merced, F.G.; Ayala, A.M.; Correa, W.; De Jesús, M. *Org. Lett.* ***2007***, *9*, 1793.
[1951] Sasatani, S.; Miyazaki, T.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* ***1983***, *24*, 4711.
[1952] For a review, see Kotera, K.; Kitahonoki, K. *Org. Prep. Proceed.* ***1969***, *1*, 305. See Tatchell, A.R. *J. Chem. Soc., Perkin Trans. 1* ***1974***, 1294; Diab, Y.; Laurent, A.; Mison, P. *Tetrahedron Lett.* ***1974***, 1605.
[1953] Barton, D.H.R.; Motherwell, W.B.; Simon, E.S.; Zard, S.Z. *J. Chem. Soc., Chem. Commun.* ***1984***, 337.
[1954] Akazome, M.; Tsuji, Y.; Watanabe, Y. *Chem. Lett.* ***1990***, 635.
[1955] Boruah, M.; Konwar, D. *Synlett* ***2001***, 795.
[1956] Johnson, K.; Degering, E.F. *J. Am. Chem. Soc.* ***1939***, *61*, 3194.
[1957] Albanese, D.; Landini, D.; Penso, M. *Synthesis* ***1990***, 333.
[1958] Hanson, J.R. *Synthesis* ***1974***, 1 (pp. 7–8).
[1959] Zeilstra, J.J.; Engberts, J.B.F.N. *Synthesis* ***1974***, 49.
[1960] Yadav, J.S.; Subba Reddy, B.V.; Srinivas, R.; Ramalingam, T. *Synlett* ***2000***, 1447.
[1961] See Kabalka, G.W.; Pace, E.D.; Wadgaonkar, P.P. *Synth. Commun.* ***1990***, *20*, 2453; Sera, A.; Yamauchi, H.; Yamada, H.; Itoh, K. *Synlett* ***1990***, 477.

compounds can be reduced to aliphatic nitriles with *t*-BuN≡C/BuN═C═O.[1962] Secondary compounds give mostly ketones (e.g., nitrocyclohexane gave 45% cyclohexanone, 30% cyclohexanone oxime, and 19% *N*-cyclohexylhydroxylamine). Tertiary aliphatic nitro compounds do not react with this reagent (see also, **19-49**).

Nitro compounds are reduced to their corresponding oximes with visible light irradiation, a Ru photocatalyst, Hünig's base, $Mg(ClO_4)_2$ activation, in a MeCN solvent.[1963] Primary nitro compounds reacted with sodium dithionite to give the nitrile.[1964] Aryl nitro compounds with electron-withdrawing groups were reduced to arylhydroxyamines using a nitroreductase *Ba*NTR1.[1965] It is noted that the Cu-catalyzed hydrogenation of nitrocylohexane gave cyclohexanone oxime.[1966]

OS **IV**, 932.

19-54 Reduction of Azides to Primary Amines

$$RN_3 \xrightarrow{LiAlH_4} RNH_2$$

Azides are easily reduced to primary amines by $LiAlH_4$, as well as by a number of other reducing agents,[1967] including $NaBH_4$, $NaBH_4/LiCl$,[1968] $NaBH_4/CoCl_2/H_2O$,[1969] $NaBH_4/ZrCl_4$,[1970] H_2 and a catalyst, Mg or Ca in MeOH,[1971] In metal in EtOH,[1972] $Sm/NiCl_2$,[1973] Sm/I_2,[1974] $CeCl_3$,[1975] Zn/NH_4Cl/aqueous EtOH,[1976] and baker's yeast.[1977] Triethylsilane has been used for the radical reduction of azides to amines.[1978]

Aryl azides were reduced to aniline derivatives using ammonium formate and Cu nanoparticles.[1979] Alkyl and aryl azides were reduced to the amine using sodium thiophosphate in aqueous solutions.[1980] Azides were reduced by catalytic hydrogenation using a Pd nanoparticle catalyst.[1981] Organic azides were reduced to the corresponding

[1962] El Kaim, L.; Gacon, A. *Tetrahedron Lett.* ***1997***, *38*, 3391.
[1963] Cai, S.; Zhang, S.; Zhao, Y.; Wang, D.Z. *Org. Lett.* ***2013***, *15*, 2660.
[1964] Temelli, B.; Unaleroglu, C. *Synthesis* ***2014***, *46*, 1407.
[1965] Nguyen-Tran, H.-H.; Zheng, G.-W.; Qian, X.-H.; Xu, J.-H. *Chem. Commun.* ***2014***, *50*, 2861.
[1966] Zhang, Q.-Q.; Dong, J.; Liu, Y.-M.; Cao, Y.; He, H.-Y.; Wang, Y.-D. *Chem. Commun.* ***2017***, *53*, 2930.
[1967] For a review, see Scriven, E.F.V.; Turnbull, K. *Chem. Rev.* ***1988***, *88*, 297 (see pp. 321–327). For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 815–820.
[1968] Ram, S.R.; Chary, K.P.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 4495.
[1969] Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synthesis* ***2000***, 646.
[1970] Chary, K.P.; Ram, S.R.; Salahuddin, S.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 3559.
[1971] Maiti, S.N.; Spevak, P.; Narender Reddy, A.V. *Synth. Commun.* ***1988***, *18*, 1201.
[1972] Reddy, G.V.; Rao, G.V.; Iyengar, D.S. *Tetrahedron Lett.* ***1999***, *40*, 3937.
[1973] Wu, H.; Chen, R.; Zhang, Y. *Synth. Commun.* ***2002***, *32*, 189.
[1974] Huang, Y.; Zhang, Y.; Wang, Y. *Tetrahedron Lett.* ***1997***, *38*, 1065.
[1975] Bartoli, G.; Di Antonio, G.; Giovannini, R.; Giuli, S.; Lanari, S.; Paoletti, M.; Marcantoni, E. *J. Org. Chem.* ***2008***, *73*, 1919.
[1976] Lin, W.; Zhang, X.; He, Z.; Jin, Y.; Gong, L.; Mi, A. *Synth. Commun.* ***2002***, *32*, 3279.
[1977] Kamal, A.; Damayanthi, Y.; Reddy, B.S.N.; Lakminarayana, B.; Reddy, B.S.P. *Chem. Commun.* ***1997***, 1015; Baruah, M.; Boruah, A.; Prajapati, D.; Sandhu, J.S. *Synlett* ***1996***, 1193.
[1978] Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. *J. Org. Chem.* ***2006***, *71*, 5822.
[1979] Ahammed, S.; Saha, A.; Ranu, B.C. *J. Org. Chem.* ***2011***, *76*, 7235.
[1980] Norcliffe, J.L.; Conway, L.P.; Hodgson, D.R.W. *Tetrahedron Lett.* ***2011***, *52*, 2730.
[1981] Arai, N.; Onodera, N.; Ohkuma, T. *Tetrahedron Lett.* ***2016***, *57*, 4183. See Kara, B.Y.; Kılbaş, B.; Göksu, H. *New J. Chem.* ***2016***, 9550.

amines by reaction with NaI in the presence of acidic ion-exchange resin at 40 °C and 200 mbar pressure.[1982]

Reaction with PPh_3 leads to a phosphazide, $Ph_3P{=}N{-}N{=}N{-}R$, which loses nitrogen in what is called the *Staudinger reaction*:[1983] this is a method to prepare phosphazo compounds, but in this case leads to reduction. Diazirines have been prepared by a traceless Staudinger reaction.[1984] The reaction is diastereoselective.[1985] This reaction, combined with $RX \rightarrow RN_3$ (**10-42**), is an important way of converting alkyl halides RX to primary amines RNH_2; in some cases the two procedures have been combined into one laboratory step.[1986] Alkylation is possible, and the reaction of an alkyl azide with PMe_3, and then an excess of iodomethane leads to the *N*-methylated amine.[1987] Sulfonyl azides (RSO_2N_3) have been reduced to sulfonamides (RSO_2NH_2) by irradiation in isopropyl alcohol[1988] and with NaH.[1989]

OS **V**, 586; **VII**, 433.

19-55 Reduction of Miscellaneous Nitrogen Compounds

$$R{-}N{=}N{=}O \xrightarrow{LiAlH_4} R{-}NH{-}CH_3$$

$$R{-}N{=}C{=}S \xrightarrow{LiAlH_4} R{-}NH{-}CH_3$$

$$Ar{-}N{=}N{-}Ar \xrightarrow[Catalyst]{H_2} Ar{-}NH{-}NH{-}Ar$$

$$ArN_2^+Cl^- \xrightarrow{Na_2SO_3} ArNHNH_2$$

$$R_2N{-}NO \xrightarrow[Ni]{H_2} R_2NH$$

Isocyanates and isothiocyanates are reduced to methylamines on treatment with $LiAlH_4$. Azo compounds are not usually reduced by $LiAlH_4$[1990] (indeed these are the products from $LiAlH_4$ reduction of nitro compounds, **19-84**), but they can be reduced to hydrazo compounds by catalytic hydrogenation or with diimide[1991] (see **19-34**). Diazonium salts are reduced to hydrazines by sodium sulfite. This reaction probably has a nucleophilic mechanism.[1992] The initial product is a salt of hydrazinesulfonic acid, which is converted to the hydrazine by acid treatment. Diazonium salts can also be reduced to arenes (**19-73**). *N*-Nitrosoamines can be denitrosated to secondary amines by a number of reducing agents,

[1982] Suthagar, K.; Fairbanks, A.J. *Chem. Commun.* ***2017***, *53*, 713.
[1983] Staudinger, H.; Meyer, J. *Helv. Chim. Acta* ***1919***, *2*, 635. See Lin, F.L.; Hoyt, H.M.; van Halbeek, H.; Bergman, R.G.; Bertozzi, C.R. *J. Am. Chem. Soc.* ***2005***, *127*, 2686.
[1984] Ahad, A.A.; Jensen, S.M.; Jewett, J.C. *Org. Lett.* ***2013***, *15*, 5060.
[1985] Hu, L.; Wang, Y.; Li, B.; Du, D.-M.; Xu, J. *Tetrahedron* ***2007***, *63*, 9387.
[1986] See Koziara, A.; Osowska-Pacewicka, K.; Zawadzki, S.; Zwierzak, A. ***1987***, 487. The reactions **10-48**, **10-43**, and **19-50** have also been accomplished in one laboratory step: Koziara, A. *J. Chem. Res. (S)* ***1989***, 296.
[1987] Kato, H.; Ohmori, K.; Suzuki, K. *Synlett* ***2001***, 1003.
[1988] Reagen, M.T.; Nickon, A. *J. Am. Chem. Soc.* ***1968***, *90*, 4096.
[1989] Lee, Y.; Closson, W.D. *Tetrahedron Lett.* ***1974***, 381.
[1990] See Newbold, B.T. in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 601, 604–614.
[1991] See Ioffe, B.V.; Sergeeva, Z.I.; Dumpis, Yu.Ya. *J. Org. Chem. USSR* ***1969***, *5*, 1683.
[1992] Huisgen, R.; Lux, R. *Chem. Ber.* ***1960***, *93*, 540.

including H_2 and a catalyst,[1993] BF_3/THF/$NaHCO_3$,[1994] and $NaBH_4$/$TiCl_4$,[1995] as well as by hydrolysis.[1996]

A cyano group can be reduced to a methyl group (RCN → RCH_3) by treatment with a terpene, such as limonene [which acts as reducing agent, giving 4-methyl-(1-methyl-1-ethene)benzene] in the presence of Pd charcoal.[1997] Hydrogen gas (H_2) is also effective,[1998] although higher temperatures are required. The R group may be alkyl or aryl. Aryl nitro compounds are reduced to diaryl hydrazines with Al/KOH in methanol.[1999]

The reductive ring opening of aziridine-2-carboxylates by reaction with SmI_2 gave β-amino esters.[2000] Secondary and tertiary phosphine oxides were reduced to the corresponding phosphine by the Cu-catalyzed reaction with silanes.[2001] Phosphine oxides were also reduced using a Mg/TMSCl/1,3-dimethyl-2-imidazolidinone system.[2002]

OS **I**, 442; **III**, 475. Also see, OS **V**, 43.

D. Reactions in Which a Heteroatom Is Removed From the Substrate

19-56 Reduction of Silanes to Methylene Compounds

$$R{-}SiR'_3 \longrightarrow R{-}H$$

In certain cases, the C—Si bond of silanes can be converted to C—H. α-Silyl esters are reduced to esters with mercuric acetate and tetrabutylammonium fluoride, for example.[2003]

19-57 Reduction of Alkyl Halides

$$RX \longrightarrow RH$$

This type of reduction can be accomplished with many reducing agents.[2004] A powerful but highly useful reagent is $LiAlH_4$,[2005] which reduces almost all types of alkyl halide, including vinylic, bridgehead, and cyclopropyl halides.[2006] Reduction with $LiAlD_4$ serves to introduce deuterium into organic compounds. An even more powerful reducing agent, lithium triethylborohydride ($LiEt_3BH$; Super hydride), rapidly reduces primary, secondary, allylic, benzylic, and neopentyl halides, but not tertiary (these give elimination) or aryl

[1993] Enders, D.; Hassel, T.; Pieter, R.; Renger, B.; Seebach, D. *Synthesis* ***1976***, 548.
[1994] Jeyaraman, R.; Ravindran, T. *Tetrahedron Lett.* ***1990***, *31*, 2787.
[1995] Kano, S.; Tanaka, Y.; Sugino, E.; Shibuya, S.; Hibino, S. *Synthesis* ***1980***, 741.
[1996] Fridman, A.L.; Mukhametshin, F.M.; Novikov, S.S. *Russ. Chem. Rev.* ***1971***, *40*, 34 (pp. 41–42).
[1997] Kindler, K.; Lührs, K. *Chem. Ber.* ***1966***, *99*, 227; *Liebigs Ann. Chem.* ***1967***, *707*, 26.
[1998] See also, Brown, G.R.; Foubister, A.J. *Synthesis* ***1982***, 1036.
[1999] Khurana, J.M.; Singh, S. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 1893.
[2000] Zhao, W.; Lu, Z.; Wulff, W.D. *J. Org. Chem.* ***2014***, *79*, 10068.
[2001] Li, Y.; Das, S.; Zhou, S.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* ***2012***, *134*, 9727.
[2002] Kuroboshi, M.; Kita, T.; Aono, A.; Katagiri, T.; Kikuchi, S.; Yamane, S.; Kawakubo, H.; Tanaka, H. *Tetrahedron Lett.* ***2015***, *56*, 918.
[2003] Poliskie, G.M.; Mader, M.M.; van Well, R. *Tetrahedron Lett.* ***1999***, *40*, 589.
[2004] See Hudlicky, M. *Reductions in Organic Chemistry*, Ellis Horwood, Chichester, ***1984***, pp. 62–67, 181; Pinder, A.R. *Synthesis* ***1980***, 425. For a list of reagents, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 29–39.
[2005] See Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 101–294; Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides*, VCH, NY, ***1991***; Hajós, A. *Complex Hydrides*, Elsevier, NY, ***1979***.
[2006] Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* ***1982***, *47*, 276.

halides.[2007] A complex formed from lithium trimethoxyaluminum hydride $LiAlH(OMe)_3$ and CuI is also a powerful reagent that reduces primary, secondary, tertiary, allylic, vinylic, aryl, and neopentyl halides.[2008] Sodium borohydride ($NaBH_4$) is a milder reducing agent that reduces primary, secondary, and some tertiary[2009] halides in good yield, in a dipolar aprotic solvent such as Me_2SO, DMF, or sulfolane,[2010] at room temperature or above, without affecting other functional groups that would be reduced by $LiAlH_4$, for example, CO_2H, CO_2R, CN.[2011] A mixture of $NaBH_4$ and $InCl_3$ efficiently reduces secondary bromides.[2012] Borohydride exchange resin (BER) is also an effective reducing agent in the presence of metal catalysts such as $Ni(OAc)_2$.[2013] Heating *gem*-difluoromethylene derivatives with $LiAlH_4$ and $ZnCl_2$ as a catalyst led to dehydrodefluorination.[2014] The Pd-catalyzed reaction of vinyl bromides with $NaBH_4$/TMEDA gave the alkene.[2015]

Other reducing agents[2016] include Zn (with acid or base), $SnCl_2$, and Et_3SiH in the presence of an $AlCl_3$,[2017] an Ir,[2018] or an In[2019] catalyst. Diethyl phosphonate/Et_3N,[2020] phosphorus tris(dimethylamide) $(Me_2N)_3P$,[2021] and organotin hydrides R_nSnH_{4-n}[2022] (chiefly Bu_3SnH)[2023] are usually used in conjunction with a radical initiator such as AIBN[2024] or with transition metal salts such as $InCl_3$.[2025] A water-soluble organotin hydride, $(MeOCH_2CH_2OCH_2CH_2CH_2)_3SnH$, has been developed that reduces alkyl halides.[2026] Aluminum amalgam efficiently reduced an iodohydrin to the alcohol.[2027] The mono-dechlorination of trichloromethyl groups to give the *gem*-dichloromethyl group used Pt/C in DMA under a hydrogen atmosphere, but the mono-dechlorination of alkyl- and aryl-trichloromethyl groups also required the use of Bu_3SnH.[2028]

[2007] Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* ***1980***, *45*, 849; ***1983***, *48*, 3085.
[2008] Masamune, S.; Bates, G.S.; Georghiou, P.E. *J. Am. Chem. Soc.* ***1974***, *96*, 3686.
[2009] Hutchins, R.O.; Bertsch, R.J.; Hoke, D. *J. Org. Chem.* ***1971***, *36*, 1568.
[2010] Hutchins, R.O.; Kandasamy, D.; Dux III, F.; Maryanoff, C.A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* ***1978***, *43*, 2259.
[2011] See Bergbreiter, D.E.; Blanton, J.R. *J. Org. Chem.* ***1987***, *52*, 472.
[2012] Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* ***2002***, *124*, 906.
[2013] Yoon, N.M.; Lee, H.J.; Ahn, J.H.; Choi, J. *J. Org. Chem.* ***1994***, *59*, 4687.
[2014] Cheng, J.; Wu, J.; Cao, S. *Tetrahedron Lett.* ***2011***, *52*, 3481; Wu, J.-J.; Cheng, J.-H.; Zhang, J.; Shen, L.; Qian, X.-H.; Cao, S. *Tetrahedron* ***2011***, *67*, 285.
[2015] Chelucci, G. *Chem. Commun.* ***2014***, *50*, 4069.
[2016] See Kirwan, J.N.; Roberts, B.P.; Willis, C.R. *J. Chem. Soc., Perkin Trans. 1* ***1991***, 103; Hudlicky, M. *Reductions in Organic Chemistry*, Ellis Horwood, Chichester, ***1984***, pp. 62–67, 181; Pinder, A.R. *Synthesis* ***1980***, 425. For a list of reagents, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 29–39.
[2017] Doyle, M.P.; McOsker, C.C.; West, C.T. *J. Org. Chem.* ***1976***, *41*, 1393; Parnes, Z.N.; Romanova, V.S.; Vol'pin, M.E. *J. Org. Chem. USSR* ***1988***, *24*, 254.
[2018] Yang, J.; Brookhart, M. *J. Am. Chem. Soc.* ***2007***, *129*, 12656.
[2019] Miura, K.; Tomita, M.; Yamada, Y.; Hosomi, A. *J. Org. Chem.* ***2007***, *72*, 787.
[2020] Hirao, T.; Kohno, S.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 1881.
[2021] Downie, I.M.; Lee, J.B. *Tetrahedron Lett.* ***1968***, 4951.
[2022] Seyferth, D.; Yamazaki, H.; Alleston, D.L. *J. Org. Chem.* ***1963***, *28*, 703. For a novel trialkyltin hydride, see Gastaldi, S.; Stein, D. *Tetrahedron Lett.* ***2002***, *43*, 4309.
[2023] See Ingold, K.U.; Bowry, V.W. *J. Org. Chem.* ***2015***, *80*, 1321.
[2024] See Neumann, W.P. *Synthesis* ***1987***, 665; Kuivila, H.G. *Synthesis* ***1970***, 499; *Acc. Chem. Res.* ***1968***, *1*, 299; Uenishi, J.; Kawahama, R.; Shiga, Y.; Yonemitsu, O.; Tsuji, J. *Tetrahedron Lett.* ***1996***, *37*, 6759.
[2025] Hayashi, N.; Shibata, I.; Baba, A. *Org. Lett.* ***2004***, *6*, 4981.
[2026] Light, J.; Breslow, R. *Tetrahedron Lett.* ***1990***, *31*, 2957.
[2027] Wang, Y.-C.; Yan, T.-H. *Chem. Commun.* ***2000***, 545.
[2028] Sawama, Y.; Imanishi, T.; Nakatani, R.; Fujiwara, Y.; Monguchi, Y.; Sajiki, H. *Tetrahedron* ***2014***, *70*, 4540.

Reduction, especially of bromides and iodides, can also be effected by catalytic hydrogenation.[2029] Raney nickel by itself can reduce alkyl halides.[2030] Homogeneous, chiral transition metal complexes can be used for the asymmetric hydrogenation of halides.[2031]

Alkali metals such as Li[2032] or Na[2033] in *t*-BuOH or THF are good reducing agents for the removal of all halogen atoms in a polyhalo compound (including vinylic, allylic, geminal, and even bridgehead halogens). Zinc and ammonium chloride in alcohol facilitates dehalogenation with microwave irradiation.[2034] Nickel boride facilitates debromination.[2035] Propargylic halides can often be reduced with allylic rearrangement to give allenes.[2036] Reductive defluorination of C—F bonds in alkyl fluorides was accomplished using Sm(hexamethyldisilazane)$_2$.[2037] Bromonitroalkanes were reduced to the corresponding dehalogenated compounds using In metal and a Pd catalyst.[2038] Using a visible light-excited iridium catalyst induces reductive scission of the carbon–halogen bond of an organohalide to give the corresponding alkyl, alkenyl, and aryl radical that can undergo cyclization and hydrodehalogenation reactions.[2039] Alkyl iodides were heated with triethylborane, 4-*tert*-butylcatechol, air, and di-*tert*-butyl hyponitrite to give the deiodination reaction.[2040]

The choice of a reducing agent usually depends on what other functional groups are present, since each reducing agent reduces certain groups and not others. This type of selectivity is called *chemoselectivity*. A chemoselective reagent is one that reacts with one functional group (e.g., halide), but not another (e.g., C=O). For example, there are several reagents that reduce only the halogen of α-halo ketones, leaving the carbonyl group intact.[2041] Among them are decaborane with 10% Pd/C,[2042] Bi in aqueous THF,[2043] or In metal in water.[2044] Ionic liquids promote the selective debromination of α-bromo ketones.[2045] Debromination is also induced by In metal in a carboxylic acid.[2046] Finally, the halogen in α-haloimines has been reduced with $SnCl_2$/MeOH without reducing the C=N bond.[2047]

Tertiary alkyl, benzylic, and allylic halides are reduced by $NaBH_3CN/SnCl_2$,[2048] but these reagents do not react with primary or secondary alkyl or aryl halides. Sodium

[2029] Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***; Kantam, M.L.; Rahman, A.; Bandyopadhyay, T.; Haritha, Y. *Synth. Commun.* ***1999***, *29*, 691. See Ye, P.; Gellman, A.J. *J. Am. Chem. Soc.* ***2008***, *130*, 8518.

[2030] See Marquié, J.; Laporterie, A.; Dubac, J.; Roques, N. *Synlett* ***2001***, 493.

[2031] Ohkuma, T.; Tsutsumi, K.; Utsumi, N.; Arai, N.; Noyori, R.; Murata, K. *Org. Lett.* ***2007***, *9*, 255.

[2032] See Berkowitz, D.B. *Synthesis* ***1990***, 649.

[2033] See Gassman, P.G.; Marshall, J.L. *Org. Synth.* ***V***, 424.

[2034] Li, J.; Ye, D.; Liu, H.; Luo, X.; Jiang, H. *Synth. Commun.* ***2008***, *38*, 567.

[2035] Khurana, J.M.; Kandpal, B.M.; Kukreja, G.; Sharma, P. *Can. J. Chem.* ***2006***, *84*, 1019.

[2036] See Claesson, A.; Olsson, L. *J. Am. Chem. Soc.* ***1979***, *101*, 7302.

[2037] Janjetovic, M.; Träff, A.M.; Ankner, T.; Wettergren, J.; Hilmersson, G. *Chem. Commun.* ***2013***, *49*, 1826.

[2038] Acúrcio, R.C.; Soengas, R.G.; Silva, A.M.S. *Synlett* ***2014***, *25*, 1561.

[2039] Kim, H.; Lee, C. *Angew. Chem. Int. Ed.* ***2012***, *51*, 12303.

[2040] Povie, G.; Ford, L.; Pozzi, D.; Soulard, V.; Villa, G.; Renaud, P. *Angew. Chem. Int. Ed.* ***2016***, *55*, 11221.

[2041] See Noyori, R.; Hayakawa, Y. *Org. React.* ***1983***, *29*, 163.

[2042] Lee, S.H.; Jung, Y.J.; Cho, Y.J.; Yoon, C.-O.M.; Hwang, H.-J.; Yoon, C.M. *Synth. Commun.* ***2001***, *31*, 2251.

[2043] Ren, P.-D.; Hin, Q.-H.; Yao, Z.-P. *Synth. Commun.* ***1997***, *27*, 2577.

[2044] Park, L.; Keum, G.; Kang, S.B.; Kim, K.S.; Kim, Y. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 4462.

[2045] Ranu, B.C.; Chattopadhyay, K.; Jana, R. *Tetrahedron* ***2007***, *63*, 155.

[2046] Lee, S.H.; Cho, M.Y.; Nam, M.H.; Park, Y.S.; Yoo, B.W.; Lee, C.-W.; Yoon, C.M. *Synth. Commun.* ***2005***, *35*, 1335.

[2047] Aelterman, W.; Eeckhaut, A.; De Kimpe, N. *Synlett* ***2000***, 1283.

[2048] Kim, S.; Ko, J.S. *Synth. Commun.* ***1985***, *15*, 603.

cyanoborohydride, $NaBH_3CN$, in HMPA is another highly selective reagent, in this case for primary and secondary iodo and bromo groups.[2049] Most of the reducing agents mentioned reduce chlorides, bromides, and iodides, but organotin hydrides also reduce fluorides.[2050]

Alkyl halides, including fluorides and polyhalides, can be dehalogenated by initial reaction with Mg to give the Grignard reagent, followed by treatment with an acidic solvent such as ethanol or propan-2-ol.[2051] Vinyl halides can be reduced to the corresponding alkene in some cases.[2052] When vinyl dibromides such as $RCH{=}CBr_2$ are treated with $(MeO)_2P(=O)H$ and triethylamine, for example, the product is the vinyl bromide $RCH{=}CHBr$.[2053] Indium metal in ethanol accomplishes the same transformation.[2054] Similar reduction occurs when vinyl diiodides are treated with Zn/Cu in acetic acid.[2055]

Rearrangements have been found in the reduction of bicyclic tosylates with $LiAlH_4$, indicating that an S_N1-like mechanism can take place.[2056] There is evidence that $LiAlH_4$ and other metal hydrides can also reduce halides by an SET mechanism,[2057] especially those, such as vinylic,[2058] cyclopropyl,[2059] or bridgehead halides, that are resistant to nucleophilic substitution. Reduction of halides by $NaBH_4$ in 80% aqueous diglyme[2060] and by BH_3 in nitromethane[2061] takes place by an S_N1 mechanism. It is known that $NaBH_4$ in sulfolane reduces tertiary halides possessing a β hydrogen by an elimination-addition mechanism.[2062] The mechanism for reduction of alkyl halides is not always nucleophilic substitution. For example, reductions with organotin hydrides generally[2063] take place by free-radical mechanisms,[2064] as do those with $Fe(CO)_5$.

OS **I**, 357, 358, 548; **II**, 320, 393; **V**, 424; **VI**, 142, 376, 731; **VIII**, 82. See also, OS **VIII**, 583.

19-58 Reduction of Aryl Halides

$$ArX \xrightarrow{AlCl_3} ArH$$

Aryl halides can be dehalogenated by *Friedel-Crafts catalysts*. Iodine is the most easily cleaved. Dechlorination is seldom performed and defluorination apparently never. The

[2049] Hutchins, R.O.; Kandasamy, D.; Maryanoff, C.A.; Masilamani, D.; Maryanoff, B.E. *J. Org. Chem.* ***1977***, *42*, 82.
[2050] See Ohsawa, T.; Takagaki, T.; Haneda, A.; Oishi, T. *Tetrahedron Lett.* ***1981***, *22*, 2583. See also, Brandänge, S.; Dahlman, O.; Ölund, J. *Acta Chem. Scand. Ser. B* ***1983***, *37*, 141.
[2051] Bryce-Smith, D.; Wakefield, B.J.; Blues, E.T. *Proc. Chem. Soc.* ***1963***, 219.
[2052] See Curran, D.P. *Synthesis* ***1988***, 417, 489.
[2053] Abbas, S.; Hayes, C.J.; Worden, S. *Tetrahedron Lett.* ***2000***, *41*, 3215.
[2054] Ranu, B.C.; Samanta, S.; Guchhait, S.K. *J. Org. Chem.* ***2001***, *66*, 4102.
[2055] Kdota, I.; Ueno, H.; Ohno, A.; Yamamoto, Y. *Tetrahedron Lett.* ***2003***, *44*, 8645.
[2056] See Kraus, W.; Chassin, C. *Tetrahedron Lett.* ***1970***, 1443. See Omoto, M.; Kato, N.; Sogon, T.; Mori, A. *Tetrahedron Lett.* ***2001***, *42*, 939.
[2057] Ashby, E.C.; Deshpande, A.K. *J. Org. Chem.* ***1994***, *59*, 3798. See, however, Park, S.; Chung, S.; Newcomb, M. *J. Org. Chem.* ***1987***, *52*, 3275.
[2058] Chung, S. *J. Org. Chem.* ***1980***, *45*, 3513.
[2059] Hatem, J.; Waegell, B. *Tetrahedron* ***1990***, *46*, 2789.
[2060] Bell, H.M.; Brown, H.C. *J. Am. Chem. Soc.* ***1966***, *88*, 1473.
[2061] Matsumura, S.; Tokura, N. *Tetrahedron Lett.* ***1969***, 363.
[2062] Hutchins, R.O.; Bertsch, R.J.; Hoke, D. *J. Org. Chem.* ***1971***, *36*, 1568.
[2063] For an exception, see Carey, F.A.; Tramper, H.S. *Tetrahedron Lett.* ***1969***, 1645.
[2064] Tanner, D.D.; Singh, H.K. *J. Org. Chem.* ***1986***, *51*, 5182.

reaction is most successful when a reducing agent, say Br^- or I^-, is present to combine with the I^+ or Br^+ coming off.[2065] Except for deiodination, the reaction is seldom used for preparative purposes. Migration of halogen is also found,[2066] both intramolecular[2067] and intermolecular.[2068] The mechanism is probably the reverse of that of **11-10**.[2069] Debromination of aromatic rings having two attached amino groups was accomplished by refluxing in aniline containing acetic acid/HBr.[2070]

Removal of halogen from aromatic rings or heteroaromatic rings[2071] can also be accomplished by various reducing agents, among them Bu_3SnH,[2072] catalytic hydrogenolysis,[2073] catalytic transfer hydrogenolysis,[2074] Na/Hg in liquid NH_3,[2075] $LiAlH_4$,[2076] $NaBH_4$ and a catalyst,[2077] Pd/C,[2078] and Raney nickel in alkaline solution.[2079] The last method is effective for fluorine as well as for the other halogens. Aryl iodides are reduced with 4-DMAP methiodide salt.[2080] Not all these reagents operate by electrophilic substitution mechanisms. Some are nucleophilic substitutions and some are free-radical processes. Photochemical[2081] and electrochemical[2082] reduction are also known. Halogen can also be removed from aromatic rings indirectly by conversion to *Grignard reagents* (**12-37**) followed by hydrolysis (**11-38**).

Aryl fluorides were defluorinated by electrolysis in 0.2 M Bu_4NBF_4 and in the presence of $NaBH_4$.[2083] Aryl bromides were dibrominated using a large excess of KOH and a Co catalyst.[2084] The dehalogenation of aryl halides is possible under metal-free conditions, at 70–110 °C, in the presence of a catalytic amount of 1,10-phenanthroline and KO*t*-Bu.[2085] The Pd-catalyzed, silane-mediated hydrodehalogenation reaction of aryl halides

[2065] Pettit, G.R.; Piatak, D.M. *J. Org. Chem.* ***1960***, *25*, 721.
[2066] Olah, G.A.; Meidar, D.; Olah, J.A. *Nouv. J. Chim.*, ***1979***, *3*, 275.
[2067] Jacquesy, J.; Jouannetaud, M. *Tetrahedron Lett.* ***1982***, *23*, 1673.
[2068] Augustijn, G.J.P.; Kooyman, E.C.; Louw, R. *Recl. Trav. Chim. Pays-Bas* ***1963***, *82*, 965.
[2069] Choguill, H.S.; Ridd, J.H. *J. Chem. Soc.* ***1961***, 822; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, p. 1; Olah, G.A. in Olah, G.A. *Friedel-Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, pp. 36–38.
[2070] Choi, H.; Chi, D.Y. *J. Am. Chem. Soc.* ***2001***, *123*, 9202.
[2071] See Kinarivala, N.; Trippier, P.C. *Tetrahedron Lett.* ***2014***, *55*, 5386.
[2072] Maitra, U.; Sarma, K.D. *Tetrahedron Lett.* ***1994***, *35*, 7861.
[2073] See Subba Rao, Y.V.; Mukkanti, K.; Choudary, B.M. *J. Organomet. Chem.* ***1989***, *367*, C29. See also, Sajiki, H.; Kume, A.; Hattori, K.; Hirota, K. *Tetrahedron Lett.* ***2002***, *43*, 7247.
[2074] Anwer, M.K.; Spatola, A.F. *Tetrahedron Lett.* ***1985***, *26*, 1381.
[2075] Austin, E.; Alonso, R.A.; Rossi, R.A. *J. Chem. Res. (S)* ***1990***, 190.
[2076] Brown, H.C.; Chung, S.; Chung, F. *Tetrahedron Lett.* ***1979***, 2473. See Chung, F.; Filmore, K.L. *J. Chem. Soc., Chem. Commun.* ***1983***, 358; Beckwith, A.L.J.; Goh, S.H. *J. Chem. Soc., Chem. Commun.* ***1983***, 905. See also, Beckwith, A.L.J.; Goh, S.H. *J. Chem. Soc., Chem. Commun.* ***1983***, 907.
[2077] Narisada, M.; Horibe, I.; Watanabe, F.; Takeda, K. *J. Org. Chem.* ***1989***, *54*, 5308.
[2078] See Monguchi, Y.; Kume, A.; Hattori, K.; Maegawa, T.; Sajiki, H. *Tetrahedron* ***2006***, *62*, 7926. Also see Chen, J.; Zhang, Y.; Yang, L.; Zhang, X.; Liu, J.; Li, L.; Zhang, H. *Tetrahedron* ***2007***, *63*, 4266.
[2079] de Koning, A.J. *Org. Prep. Proced. Int.* ***1975***, *7*, 31.
[2080] Garnier, J.; Murphy, J.A.; Zhou, S.-Z.; Turner, A.T. *Synlett* ***2008***, 2127.
[2081] See Barltrop, J.A.; Bradbury, D. *J. Am. Chem. Soc.* ***1973***, *95*, 5085.
[2082] See Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 142–143. Also see, Bhuvaneswari, N.; Venkatachalam, C.S.; Balasubramanian, K.K. *Tetrahedron Lett.* ***1992***, *33*, 1499.
[2083] Wu, W.-B.; Li, M.-L.; Huang, J.-M. *Tetrahedron Lett.* ***2015***, *56*, 1520. For a similar dehalogenation that used Pd/AlO(OH) nanoparticles with $NaBH_4$, see Kara, B.Y.; Yazici, M.; Kilbas, B.; Goksu, H. *Tetrahedron* ***2016***, *72*, 5898.
[2084] Chan, K.S.; Liu, C.R.; Wong, K.L. *Tetrahedron Lett.* ***2015***, *56*, 2728.
[2085] Liu, W.; Hou, F. *Tetrahedron* ***2017***, *73*, 931.

was developed with greater scope with respect to substrate compatibility.[2086] The thermal hydro-dehalogenation of aryl halides or α-halo ketones was reported using a Ru catalyst and propan-2-ol.[2087]

The dehalogenation of functionalized aryl halides used Pd nanoparticles and tetramethyldisiloxane (TMDS) on water.[2088] Aryl bromides were hydro-dehalogenated by reaction with a composite of NaH and LiI.[2089]

OS **III**, 132, 475, 519; **V**, 149, 346, 998; **VI**, 82, 821.

19-59 Reduction of Alcohols:[2090] Hydrogenolysis

$$\mathrm{ROH + H_2} \xrightarrow{\text{Catalyst}} \mathrm{RH}$$

The hydroxyl groups of most alcohols can seldom be cleaved by catalytic hydrogenation; remember that alcohols are often used as solvents for hydrogenation of other compounds. However, benzyl-type alcohols undergo the reaction readily and have often been reduced.[2091] Diaryl and triarylcarbinols are similarly easy to reduce with $LiAlH_4/AlCl_3$,[2092] with $NaBH_4$ in F_3CCOOH,[2093] and with iodine, water, and red phosphorus (OS **I**, 224). Other reagents have been used,[2094] including Me_3SiCl/NaI,[2095] Et_3SiH/BF_3,[2096] $SmI_2/THF/HMPA$,[2097] and Sn/HCl. The reduction of secondary alcohols was accomplished using Ph_2SiClH and $InCl_3$.[2098] 1,3-Diols are especially susceptible to hydrogenolysis. Tertiary alcohols can be reduced by catalytic hydrogenolysis when the catalyst is Raney nickel.[2099] Allylic alcohols (and ethers and acetates) can be reduced (often with accompanying allylic rearrangement) with Zn amalgam and HCl, as well as with certain other reagents.[2100] Reagents that reduce the OH group of α-hydroxy ketones without affecting the C═O group include red phosphorus/iodine[2101] and Me_3SiI.[2102] Tertiary and secondary

[2086] Noonan, G.M.; Hayter, B.R.; Campbell, A.D.; Gorman, T.W.; Partridge, B.E.; Lamont, G.M. *Tetrahedron Lett.* ***2013***, *54*, 4518.
[2087] You, T.; Wang, Z.; Chen, J.; Xia, Y. *J. Org. Chem.* ***2017***, *82*, 1340.
[2088] Bhattacharjya, A.; Klumphu, P.; Lipshutz, B. *Org. Lett.* ***2015***, *17*, 1122.
[2089] Ong, D.Y.; Tejo, C.; Xu, K.; Hirao, H.; Chiba, S. *Angew. Chem. Int. Ed.* ***2017***, *56*, 1840.
[2090] For a review, see Müller, P. in Patai, S. *The Chemistry of Functional Groups*, Supplement E, pt. 1, Wiley, NY, ***1980***, pp. 515–522.
[2091] See Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 157–163, *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 449–468. For a review of the stereochemistry of hydrogenolysis, see Klabunovskii, E.I. *Russ. Chem. Rev.* ***1966***, *35*, 546.
[2092] Avendaño, C.; de Diego, C.; Elguero, J. *Monatsh. Chem.* ***1990***, *121*, 649.
[2093] See Gribble, G.W.; Nutaitis, C.F. *Org. Prep. Proced. Int.* ***1985***, *17*, 317. Also see, Nutaitis, C.F.; Bernardo, J.E. *Synth. Commun.* ***1990***, *20*, 487.
[2094] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 44–46.
[2095] Cain, G.A.; Holler, E.R. *Chem. Commun.* ***2001***, 1168.
[2096] See Wustrow, D.J.; Smith III, W.J.; Wise, L.D. *Tetrahedron Lett.* ***1994***, *35*, 61.
[2097] Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1989***, *30*, 2945.
[2098] Yasuda, M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. *J. Org. Chem.* ***2001***, *66*, 7741.
[2099] Krafft, M.E.; Crooks III, W.J. *J. Org. Chem.* ***1988***, *53*, 432. For another catalyst, see Parnes, Z.N.; Shaapuni, D.Kh.; Kalinkin, M.I.; Kursanov, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1974***, *23*, 1592.
[2100] See Elphimoff-Felkin, I.; Sarda, P. *Org. Synth.* ***VI***, 769; *Tetrahedron* ***1977***, *33*, 511. For another reagent, see Lee, J.; Alper, H. *Tetrahedron Lett.* ***1990***, *31*, 4101.
[2101] Ho, T.L.; Wong, C.M. *Synthesis* ***1975***, 161.
[2102] Ho, T.L. *Synth. Commun.* ***1979***, *9*, 665.

benzylic alcohols were reduced to alkanes by reaction with Et_3SiH and a tin complex catalyst.[2103]

Alcohols can also be reduced indirectly by conversion to a sulfonate and reduction of that compound (**19-63**). The two reactions can be carried out without isolation of the sulfonate if the alcohol is treated with pyridine/SO_3 in THF, followed by $LiAlH_4$.[2104] Another indirect reduction that can be done in one step involves treatment of the alcohol (primary, secondary, or benzylic) with NaI, Zn, and Me_3SiCl.[2105] In this case, the alcohol is first converted to the iodide, which is then reduced.

The mechanisms of most alcohol reductions are obscure.[2106] Hydrogenolysis of benzyl alcohols can give inversion or retention of configuration, depending on the catalyst.[2107] The mechanism of electroreduction of allylic alcohols in acidic aqueous media has been examined.[2108]

OS **I**, 224; **IV**, 25, 218, 482; **V**, 339; **VI**, 769.

19-60 Reduction of Phenolic and Other Hydroxyaryl Compounds

$$\mathrm{ArOH} \xrightarrow{\mathrm{Zn}} \mathrm{ArH}$$

Oxygenated compounds, such as phenols, phenolic esters, and ethers, can be reduced to the corresponding hydrocarbon.[2109] Phenols can be reduced by distillation over zinc dust or with HI and red phosphorus, but these methods are quite poor and are seldom feasible. Catalytic hydrogenation has also been used, but the corresponding cyclohexanol (see **19-36**) is a side product.[2110] Much better results have been obtained by conversion of phenols to certain esters or ethers and reduction of the latter. For example the reduction of $ArOSO_2CF_3$ with formic acid and a Pd catalyst gave ArH[2111] and ArOTs was reduced with $NaBH_4/NiCl_2$ to give ArH.[2112]

With a Pd/C catalyst, phenol derivatives are deoxygenated using Mg and MeO in the presence of ammonium acetate.[2113] Palladium on carbon also mediated hydrodexoygenation of phenol derivatives in the presence of diethylamine.[2114]

OS **VI**, 150. See also, OS **VII**, 476.

[2103] Tandiary, M.A.; Masui, Y.; Onaka, M. *Tetrahedron Lett.* ***2014***, *55*, 4160.
[2104] Corey, E.J.; Achiwa, K. *J. Org. Chem.* ***1969***, *34*, 3667.
[2105] Morita, T.; Okamoto, Y.; Sakurai, H. *Synthesis* ***1981***, 32.
[2106] See Garbisch Jr., E.W.; Schreader, L.; Frankel, J.J. *J. Am. Chem. Soc.* ***1967***, *89*, 4233; Mitsui, S.; Imaizumi, S.; Esashi, Y. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 2143.
[2107] Mitsui, S.; Imaizumi, S.; Esashi, Y. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 2143.
[2108] Shukun, H.; Yougun, S.; Jindong, Z.; Jian, S. *J. Org. Chem.* ***2001***, *66*, 4487.
[2109] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 44–52 ff.
[2110] Shuikin, N.I.; Erivanskaya, L.A. *Russ. Chem. Rev.* ***1960***, *29*, 309 (see pp. 313–315). See also, Bagnell, L.J.; Jeffery, E.A. *Aust. J. Chem.* ***1981***, *34*, 697.
[2111] Cacchi, S.; Ciattini, P.G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* ***1986***, *27*, 5541. See also, Cabri, W.; De Bernardinis, S.; Francalanci, F.; Penco, S. *J. Org. Chem.* ***1990***, *55*, 350.
[2112] Wang, F.; Chiba, K.; Tada, M. *J. Chem. Soc., Perkin Trans. 1* ***1992***, 1897.
[2113] Sajiki, H.; Mori, A.; Mizusaki, T.; Ikawa, T.; Maegawa, T.; Hirota, K. *Org. Lett.* ***2006***, *8*, 987.
[2114] Mori, A.; Mizusaki, T.; Ikawa, T.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Tetrahedron* ***2007***, *63*, 1270.

19-61 Replacement of OR or NR by Hydrogen: Hydrogenolysis

$$R{-}O{-}R' \xrightarrow{R, R' = \text{allyl, aryl, vinyl, benzylic}} R{-}H + R'{-}H$$

Simple ethers are not normally cleaved by reducing agents, although such cleavage has sometimes been reported.[2115] For example, THF treated with $LiAlH_4/AlCl_3$[2116] or with a mixture of $LiAlH(O\text{-}t\text{-}Bu)_3$ and Et_3B[2117] gave butan-1-ol; the latter reagent also cleaves methyl alkyl ethers.[2118] Certain types of ethers can be cleaved quite well by reducing agents.[2119] Among these are allyl aryl,[2120] vinyl aryl,[2121] benzylic ethers,[2091,2122] and anisole.[2123] 7-Oxobicyclo[2.2.1]heptanes can be reductively cleaved with DibalH and Ni catalysts.

The reaction of allyl aryl ethers with $NaBH_4$ and a Ru catalyst in aqueous *N*-methylformamide gave the phenol derivative as the major product.[2124] A Ni-catalyzed $NaBH_4$ hydrogenolysis for deallylation and debenzylation has been reported.[2125] The *p*-methoxybenzyl unit has been used as a protecting group for alcohols, and reaction with a Ag catalyst with 1,3,5-trimethoxybenzene facilitated deprotection via hydrogenolysis.[2126] The deprotection of benzyl-type ethers to give the alcohol used catalytic amounts of DDQ and *tert*-butyl nitrite under atmospheric pressure of O_2.[2127] Oxalyl chloride cleaved the PMB group from alkyl and aryl PMB ethers to give corresponding alcohols.[2128] cleavage of the *p*-methoxybenzyl protecting group of alcohols with *tert*-butyl bromide in acetonitrile at reflux gave the alcohol.[2129] The Rh-catalyzed reductive cleavage of the C^{aryl}—C bond of 1,1-biaryl methanols with H_2 gave a benzylic alcohol and the arene.[2130] The Ir-catalyzed reaction of aryl alkyl ethers gave the phenol derivative and an alkene when heated.[2131] The reaction of aryl ethers and aryl pivalates with $(MeO)_2MeSiH$ and a Ni catalyst gave C—O

[2115] Ranu, B.C.; Bhar, S. *Org. Prep. Proceed. Int.* ***1996***, *28*, 371.
[2116] Bailey, W.J.; Marktscheffel, F. *J. Org. Chem.* ***1960***, *25*, 1797.
[2117] Krishnamurthy, S.; Brown, H.C. *J. Org. Chem.* ***1979***, *44*, 3678.
[2118] For a review of ether reduction, see Müller, P. in Patai, S. *The Chemisry of Functional Groups*, Supplement E, pt. 1, Wiley, NY, ***1980***, pp. 522–528.
[2119] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1013–1019.
[2120] Rao, G.V.; Reddy, D.S.; Mohan, G.H.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 3565.
[2121] Tweedie, V.L.; Barron, B.G. *J. Org. Chem.* ***1960***, *25*, 2023. See also, Hutchins, R.O.; Learn, K. *J. Org. Chem.* ***1982***, *47*, 4380.
[2122] Shi, L.; Xia, W.J.; Zhang, F.M.; Tu, Y.Q. *Synlett* ***2002***, 1505. See also, Kelley, P.; Lin, S.; Edouard, G.; Day, M.W.; Agapie, T. *J. Am. Chem. Soc.* ***2012***, *134*, 5480; Sergeev, A.G.; Webb, J.D.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2012***, *134*, 20226; He, J.; Zhao, C.; Lercher, J.A. *J. Am. Chem. Soc.* ***2012***, *134*, 29768; Molinari, V.; Giordano, C.; Antonietti, M.; Esposito, D. *J. Am. Chem. Soc.* ***2014***, *136*, 1758.
[2123] Majetich, G.; Zhang, Y.; Wheless, K. *Tetrahedron Lett.* ***1994***, *35*, 8727.
[2124] Babler, J.H.; White, N.A.; Kowalski, E.; Jast, J.R. *Tetrahedron Lett.* ***2011***, *52*, 745.
[2125] Chouhan, M.; Kumar, K.; Sharma, R.; Grover, V.; Nair, V.A. *Tetrahedron Lett.* ***2013***, *54*, 4540.
[2126] Kern, N.; Dombray, T.; Blanc, A.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* ***2012***, *77*, 9227.
[2127] Shen, Z.; Sheng, L.; Zhang, X.; Mo, W.; Hu, B.; Sun, N.; Hu, X. *Tetrahedron Lett.* ***2013***, *54*, 1579. See Walsh, K.; Sneddon, H.F.; Moody, C.J. *Tetrahedron* ***2014***, *70*, 7380.
[2128] Ilangovan, A.; Anandhan, K.; Kaushik, M.P. *Tetrahedron Lett.* ***2015***, *56*, 1080.
[2129] Rival, N.; Albornoz Grados, A.; Schiavo, L.; Colobert, F.; Hanquet, G. *Tetrahedron Lett.* ***2015***, *56*, 6823.
[2130] Chen, K.; Li, H.; Lei, Z.-Q.; Li, Y.; Ye, W.-H.; Zhang, L.-S.; Sun, J.; Shi, Z.-J. *Angew. Chem. Int. Ed.* ***2012***, *51*, 9851.
[2131] Ren, Y.; Yan, M.; Wang, J.; Zhang, Z.C.; Yao, K. *Angew. Chem. Int. Ed.* ***2013***, *52*, 12674.

cleavage to form the arene.[2132] Unsaturated cyclic ethers were reduced with catalytic amounts of $B(C_6F_5)_3$ in the presence of an alkylsilane with ring cleavage to give the alkene alcohol.[2133] Reductive cleavage of the aryl C—O bonds of aryl alkyl ethers using $LiAlH_4$/KO*t*Bu gave the arene and an alcohol.[2134] The $NaBH_4$-promoted electrochemical cleavage of aryl C—O bonds in diaryl ethers gave phenols and arenes.[2135]

Acetals and ketals are resistant to $LiAlH_4$ and similar hydrides, and carbonyl groups are often converted to acetals or ketals for protection (**16-5**). However, a combination of $LiAlH_4$ and $AlCl_3$[2136] does reduce acetals and ketals, removing one group to give the mono ether.[2137] The actual reducing agents in this case are primarily chloroaluminum hydride (AlH_2Cl) and dichloroaluminum hydride ($AlHCl_2$), which are formed from the two reagents.[2138] This conversion can also be accomplished with DibalH,[2139] as well as with other reagents.[2140] Ortho esters are easily reduced to acetals by $LiAlH_4$ alone, offering a route to aldehydes, as these are easily prepared by hydrolysis of the acetals (**10-6**). Mixed ketals [R(OMe)OR′] can be demethoxylated (to give RHOR′) with $Bn_3SnCl/NaCHBH_3$ in the presence of AIBN.[2141]

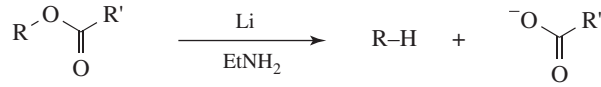
OS **III**, 693; **IV**, 798; **V**, 303. Also see, OS **III**, 742; **VII**, 386.

$$\mathrm{ArOR} \longrightarrow \mathrm{ArH}$$

In a few cases it is possible to remove an oxygen substituent directly from the aromatic ring. Treatment of an aryl mesylate (ArOMs) with a nickel catalyst in DMF, for example, leads to the deoxygenated product, Ar—H.[2142]

Primary alcohols were deoxygenated to the corresponding hydrocarbon first by reaction with $(PhO)_2P(O)Cl$ and then with $LiBHEt_3$ reduction of the first formed diphenyl phosphate esters.[2143] Alcohols have been first converted to alkyl triflates or alkyl iodides, after which the Cu-catalyzed reduction with tetramethyldisiloxane and CsF gave the deoxygenated hydrocarbon.[2144] The gold-catalyzed photochemical bromination of alcohols was combined with reductive dehalogenation via photoredox catalysis for a one-pot reductive deoxygenation protocol for primary alcohols.[2145]

19-62 Reductive Cleavage of Carboxylic Esters



[2132] Tobisu, M.; Yamakawa, K.; Shimasaki, T.; Chatani, N. *Chem. Commun.* ***2011***, *47*, 2946.
[2133] Mack, D.J.; Guo, B.; Njardarson, J.T. *Chem. Commun.* ***2012***, *48*, 7844.
[2134] Xu, H.; Yu, B.; Zhang, H.; Zhao, Y.; Yang, Z.; Xu, J.; Han, B.; Liu, Z *Chem. Commun.* ***2015***, *51*, 12212.
[2135] Wu, W.-B.; Huang, J.-M. *J. Org. Chem.* ***2014***, *79*, 10189.
[2136] See Rerick, M.N. in Augustine, R.L. *Reduction*, Marcel Dekker, NY, ***1968***, pp. 1–94.
[2137] Eliel, E.L.; Badding, V.G.; Rerick, M.N. *J. Am. Chem. Soc.* ***1962***, *84*, 2371.
[2138] See Diner, U.E.; Davis, H.A.; Brown, R.K. *Can. J. Chem.* ***1967***, *45*, 207.
[2139] See Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* ***1983***, 1593.
[2140] See Hojo, M.; Ushioda, N.; Hosomi, A. *Tetrahedron Lett.* ***2004***, *45*, 4499; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 931–942.
[2141] Srikrishna, A.; Viswajanani, R. *Synlett* ***1995***, 95.
[2142] Sasaki, K.; Kubo, T.; Sakai, M.; Kuroda, Y. *Chem. Lett.* ***1997***, 617.
[2143] Chowdhury, S.; Standaert, R.F. *J. Org. Chem.* ***2016***, *81*, 9957.
[2144] Dang, H.; Cox, N.; Lalic, G. *Angew. Chem. Int. Ed.* ***2014***, *53*, 752.
[2145] McCallum, T.; Slavko, E.; Morin, M.; Barriault, L. *Eur. J. Org. Chem.* ***2015***, 81.

The alkyl group R of certain carboxylic esters can be reduced to RH[2146] by treatment with lithium in ethylamine.[2147] The reaction is successful when R is a tertiary or a sterically hindered secondary alkyl group. A free-radical mechanism is likely.[2148] Similar reduction, also by a free-radical mechanism, has been reported with sodium in HMPA/*t*-BuOH.[2149] In the latter case, tertiary R groups give high yields of RH, but primary and secondary R are converted to a mixture of RH and ROH. Both of these methods provide an indirect method of accomplishing **19-59** for tertiary R.[2150] The same thing can be done for primary and secondary R by treating alkyl chloroformates, ROCOCl, with tri-*n*-propylsilane in the presence of *tert*-butylperoxide[2151] and by treating thiono ethers ROC(=S)W (where W can be OAr or other groups) with Ph_2SiH_2[2152] or Ph_3SiH[2153] and a free-radical initiator. Allylic acetates can be reduced with $NaBH_4$ and a Pd complex,[2154] and with SmI_2/Pd(0).[2155]

OS **VII**, 139.

19-63 Reduction of Tosylates and Similar Compounds: Hydrogenolysis

$$RCH_2OTs + LiAlH_4 \longrightarrow RCH_3$$

Tosylates and other sulfonates can be reduced[2156] with $LiAlH_4$,[2157] with $NaBH_4$ in a dipolar aprotic solvent,[2158] with $LiEt_3BH$, with *i*-Bu_2AlH (Dibal-H),[2159] or with Bu_3SnH/NaI.[2160] The Ni-catalyzed reduction of aryl tosylates proceeds in the presence of borane hydrides.[2161] The scope of the reaction seems to be similar to that of **19-57**. When the reagent is $LiAlH_4$, alkyl tosylates are reduced more rapidly than iodides or bromides if the solvent is Et_2O, but the order is reversed in diglyme.[2162] The reactivity difference is great enough that a tosylate function can be reduced in the presence of a halide and vice versa.

OS **VI**, 376, 762; **VIII**, 126. See also, OS **VII**, 66.

[2146] See Hartwig, W. *Tetrahedron* ***1983***, *39*, 2609.

[2147] Barrett, A.G.M.; Godfrey, C.R.A.; Hollinshead, D.M.; Prokopiou, P.A.; Barton, D.H.R.; Boar, R.B.; Joukhadar, L.; McGhie, J.F.; Misra, S.C. *J. Chem. Soc., Perkin Trans. 1* ***1981***, 1501. See Garst, M.E.; Dolby, L.J.; Esfandiari, S.; Fedoruk, N.A.; Chamberlain, N.C.; Avey, A.A. *J. Org. Chem.* ***2000***, *65*, 7098.

[2148] Barrett, A.G.M.; Prokopiou, P.A.; Barton, D.H.R.; Boar, R.B.; McGhie, J.F. *J. Chem. Soc., Chem. Commun.* ***1979***, 1173.

[2149] Deshayes, H.; Pete, J. *Can. J. Chem.* ***1984***, *62*, 2063.

[2150] Also see, Barton, D.H.R.; Crich, D. *J. Chem. Soc., Perkin Trans. 1* ***1986***, 1603.

[2151] Jackson, R.A.; Malek, F. *J. Chem. Soc., Perkin Trans. 1* ***1980***, 1207.

[2152] See Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.C. *Tetrahedron Lett.* ***1990***, *31*, 4681, and references cited therein. For similar methods, see Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 2578; Kirwan, J.N.; Roberts, B.P.; Willis, C.R. *Tetrahedron Lett.* ***1990***, *31*, 5093.

[2153] Oba, M.; Nishiyama, K. *Synthesis* ***1994***, 624.

[2154] Hutchins, R.O.; Learn, K.; Fulton, R.P. *Tetrahedron Lett.* ***1980***, *21*, 27. See also, Ipaktschi, J. *Chem. Ber.* ***1984***, *117*, 3320.

[2155] Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1986***, *27*, 601, 5237. See also, Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1989***, *30*, 2945.

[2156] For a list of substrate types and reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 46–52.

[2157] See Goodenough, K.M.; Moran, W.J.; Raubo, P.; Harrity, J.P.A. *J. Org. Chem.* ***2005***, *70*, 207.

[2158] Hutchins, R.O.; Hoke, D.; Keogh, J.; Koharski, D. *Tetrahedron Lett.* ***1969***, 3495.

[2159] Janssen, C.G.M.; Hendriks, A.H.M.; Godefroi, E.F. *Recl. Trav. Chim. Pays-Bas* ***1984***, *103*, 220.

[2160] Ueno, Y.; Tanaka, C.; Okawara, M. *Chem. Lett.* ***1983***, 795.

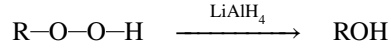
[2161] Kogan, V. *Tetrahedron Lett.* ***2006***, *47*, 7515.

[2162] Krishnamurthy, S. *J. Org. Chem.* ***1980***, *45*, 2550.

19-64 Hydrogenolysis of Esters (Barton-McCombie Reaction)

Alcohols can readily be converted to carbonate and thiocarbonate derivatives. Under radical conditions,[2163] using *azobis*-isobutyronitrile (AIBN, Sec. 14.A.i) and Bu_3SnH, the carbonate or thiocarbonate unit is reduced and replaced with hydrogen. The overall process is reduction of the ROH unit to RH and is called the *Barton-McCombie reaction.*[2164] Both $PhSiH_3$/AIBN[2165] and $PhSiH_2/BEt_3{\bullet}O_2$ can be used.[2166] This reaction can be catalytic in Bu_3SnH.[2167] Variations include reduction of ROCSNHPh derivatives using Ph_3SiH/BEt_3.[2168] Another variation used water as the hydrogen atom source when BMe_3 was used.[2169] Tetrabutylammonium peroxydisulfate and formate ion have been used.[2170]

19-65 Reduction of Hydroperoxides and Peroxides



Hydroperoxides can be reduced to alcohols with $LiAlH_4$ or Ph_3P[2171] or by catalytic hydrogenation. The hydroperoxide functional group is very susceptible to catalytic hydrogenation, as shown by the fact that a double bond may be present in the same molecule without being reduced.[2172] The reaction is an important step in a method for the oxidative decyanation of nitriles containing an α hydrogen.[2173] The nitrile is first converted to the α-hydroperoxy nitrile by treatment with base at −78 °C followed by O_2. The hydroperoxy nitrile is then reduced to the cyanohydrin, which is cleaved (the reverse of **16-51**) to the corresponding ketone. The method is not successful for the preparation of aldehydes (R′ = H). Peroxides are cleaved to 2 molar equivalents of alcohols by $LiAlH_4$, by Mg/MeOH,[2174] or by catalytic hydrogenation. Peroxides can be reduced to ethers with $P(OEt)_3$.[2175]

OS **VI**, 130.

[2163] Barton, D.H.R.; Jaszberenyi, J.Cs.; Tang, D. *Tetrahedron Lett.* ***1993***, *34*, 3381.

[2164] See Robins, M.J.; Wilson, J.S.; Hansske, F. *J. Am. Chem. Soc.* ***1983***, *105*, 4059; Lopez, R.M.; Hays, D.S.; Fu, G.C. *J. Am. Chem. Soc.* ***1997***, *119*, 6949; *The Merck Index*, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, ***2006***, p. ONR-6; Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis*, 2nd ed., Wiley-Interscience, New Jersey, ***2005***, pp. 68–69.

[2165] Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.Cs. *Tetrahedron* ***1993***, *49*, 2793.

[2166] Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.Cs. *Tetrahedron* ***1993***, *49*, 7193.

[2167] Lopez, R.M.; Hays, D.S.; Fu, G.C. *J. Am. Chem. Soc.* ***1997***, *119*, 6949.

[2168] Oba, M.; Nishiyama, K. *Tetrahedron* ***1994***, *50*, 10193.

[2169] Spiegel, D.A.; Wiberg, K.B.; Schacherer, L.N.; Medeiros, M.R.; Wood, J.L. *J. Am. Chem. Soc.* ***2005***, *127*, 12513.

[2170] Park, H.S.; Lee, H.Y.; Kim, Y.H. *Org. Lett.* ***2005***, *7*, 3187.

[2171] See Rowley, A.G. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 318–320.

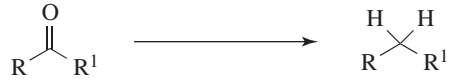
[2172] Rebeller, M.; Clément, G. *Bull. Soc. Chim. Fr.* ***1964***, 1302.

[2173] Freerksen, R.W.; Selikson, S.J.; Wroble, R.R.; Kyler, K.S.; Watt, D.S. *J. Org. Chem.* ***1983***, *48*, 4087.

[2174] Dai, P.; Dussault, P.H.; Trullinger, T.K. *J. Org. Chem.* ***2004***, *69*, 2851.

[2175] Horner, L.; Jurgeleit, W. *Liebigs Ann. Chem.* ***1955***, *591*, 138. See Rowley, A.G. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 320–322.

19-66 Reduction of Carbonyl to Methylene in Aldehydes and Ketones: Hydrogenolysis



There are various ways of reducing the C=O group of aldehydes and ketones to CH_2.[2176] Two old but still popular methods are the *Clemmensen reduction*[2177] and the *Wolff-Kishner reduction*. The Clemmensen reduction consists of heating the aldehyde or ketone with zinc amalgam, Zn/(Hg), and aqueous HCl.[2178] Ketones are reduced more often than aldehydes. In the Wolff-Kishner reduction,[2179] the aldehyde or ketone is heated with hydrazine hydrate and a base (usually NaOH or KOH). The *Huang-Minlon modification*[2180] of the Wolff-Kishner reduction, in which the reaction is carried out in refluxing diethylene glycol, has completely replaced the original procedure. A microwave-assisted Huang-Minlon procedure has been reported.[2181] The reaction can be carried out under more moderate conditions (room temperature) in DMSO with potassium *tert*-butoxide as base.[2182] A new modification of the reduction treats a ketone with hydrazine in toluene with microwave irradiation, and subsequent reaction with KOH with microwave irradiation completes the Wolff-Kishner reduction.[2183] The Wolff-Kishner reduction can also be applied to the semicarbazones of aldehydes or ketones.

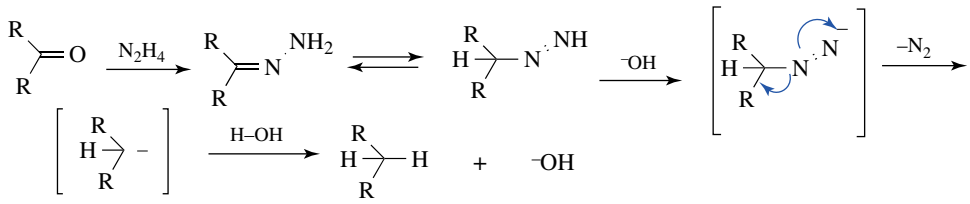
The Clemmensen reduction is usually easier to perform, but it fails for acid-sensitive and high molecular weight substrates. For these cases, the Wolff-Kishner reduction is quite useful. For high molecular weight substrates, a modified Clemmensen reduction, using activated zinc and gaseous HCl in an organic solvent, such as ether or acetic anhydride, has proved successful.[2184] The Clemmensen and Wolff-Kishner reductions are complementary, since the former uses acidic conditions and the latter basic conditions.

Both methods are fairly specific for aldehydes and ketones and can be carried out with many other functional groups present. However, certain types of aldehydes and ketones do not give normal reduction products. Under Clemmensen conditions,[2185] α-hydroxy ketones give either ketones (hydrogenolysis of the OH, **19-59**) or alkenes, and 1,3-diones usually undergo rearrangement (e.g., $MeCOCH_2COMe \rightarrow MeCOCHMe_2$).[2186] Neither method is suitable for α,β-unsaturated ketones, which give pyrazolines[2187] under Wolff-Kishner conditions. Under Clemmensen conditions, both groups of α,β-unsaturated ketones may be

[2176] See Reusch, W. in Augustine, R.L. *Reduction*, Marcel Dekker, NY, ***1968***, pp. 171–211.
[2177] See, however, Bailey, K.E.; Davis, B.R. *Aust. J. Chem.* ***1995***, *48*, 1827. Also see, Rosnati, V. *Tetrahedron Lett.* ***1992***, *33*, 4791.
[2178] See Vedejs, E. *Org. React.* ***1975***, *22*, 401. For a discussion of experimental conditions, see Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 1, Wiley, NY, ***1967***, pp. 1287–1289.
[2179] See Todd, D. *Org. React.* ***1948***, *4*, 378.
[2180] Huang-Minlon *J. Am. Chem. Soc.* ***1946***, *68*, 2487; ***1949***, *71*, 3301.
[2181] Jaisankar, P.; Pal, B.; Giri, V.S. *Synth. Commun.* ***2002***, *32*, 2569.
[2182] Cram, D.J.; Sahyun, M.R.V.; Knox, G.R. *J. Am. Chem. Soc.* ***1962***, *84*, 1734.
[2183] Gadhwal, S.; Baruah, M.; Sandhu, J.S. *Synlett* ***1999***, 1573.
[2184] Toda, M.; Hayashi, M.; Hirata, Y.; Yamamura, S. *Bull. Chem. Soc. Jpn.* ***1972***, *45*, 264.
[2185] See Buchanan, J.G.S.; Woodgate, P.D. *Q. Rev. Chem. Soc.* ***1969***, *23*, 522.
[2186] Galton, S.A.; Kalafer, M.; Beringer, F.M. *J. Org. Chem.* ***1970***, *35*, 1.
[2187] Pyrazolines can be converted to cyclopropanes; see **17-32**.

reduced or if only one group is reduced, it is the C=C bond.[2188] Sterically hindered ketones are resistant to both the Clemmensen and Huang-Minlon procedures, but can be reduced by vigorous treatment with anhydrous hydrazine.[2189] In the Clemmensen reduction, pinacols (**19-76**) are often side products.

The first step in the mechanism[2190] of the Wolff-Kishner reduction consists of formation of the hydrazone (**16-13**). It is this species that undergoes reduction in the presence of base, most likely in the following manner:



Not much is known about the mechanism of the Clemmensen reduction. Several mechanisms have been proposed,[2191] including one going through a zinc/carbene intermediate.[2192] One thing reasonably certain is that the corresponding alcohol is not an intermediate, since alcohols prepared in other ways fail to give the reaction. Note that the alcohol is not an intermediate in the Wolff-Kishner reduction either.

Other reagents have also been used to reduce the C=O of aldehydes and ketones to CH_2.[2193] Among these are Me_3SiCl followed by $Et_3SiH/TiCl_4$,[2194] $Ni(OAc)_2$ on borohydride-exchange resin,[2195] and, for aryl ketones (ArCOR and ArCOAr), $NaBH_3CN$ in THF/aqueous HCl,[2196] Ni/Al in H_2O,[2197] $HCOONH_4/Pd/C$,[2198] or trialkylsilanes in F_3CCOOH.[2199] Hydrogenation with a heterogeneous Cu/silica catalyst has been used.[2200] Silanes such as Et_3SiH and a triarylborane catalyst reduce aliphatic aldehydes to methyl, $-CHO \rightarrow -CH_3$.[2201] Zinc oxide/triethylsilane has been used,[2202] as has titanocene dichloride, $(C_5H_5)_2TiCl_2$.[2203] Most of these reagents also reduce aryl aldehydes (ArCHO) to methylbenzenes ($ArCH_3$).[2204] One carbonyl group of 1,2-diketones can be selectively

[2188] See Banerjee, A.K.; Alvárez, J.; Santana, M.; Carrasco, M.C. *Tetrahedron* ***1986***, *42*, 6615.
[2189] Barton, D.H.R.; Ives, D.A.J.; Thomas, B.R. *J. Chem. Soc.* ***1955***, 2056.
[2190] Szmant, H.H. *Angew. Chem. Int. Ed.* ***1968***, *7*, 120. Also see Taber, D.F.; Stachel, S.J. *Tetrahedron Lett.* ***1992***, *33*, 903.
[2191] See Di Vona, M.L.; Rosnati, V. *J. Org. Chem.* ***1991***, *56*, 4269.
[2192] Burdon, J.; Price, R.C. *J. Chem. Soc., Chem. Commun.* ***1986***, 893.
[2193] For a list, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 61–66.
[2194] Yato, M.; Homma, K.; Ishida, A. *Heterocycles* ***1995***, *41*, 17.
[2195] Bandgar, B.P.; Nikat, S.M.; Wadgaonkar, P.P. *Synth. Commun.* ***1995***, *25*, 863.
[2196] Pashkovsky, F.S.; Lokot, I.P.; Lakhvich, F.A. *Synlett* ***2001***, 1391.
[2197] Ishimoto, K.; Mitoma, Y.; Negashima, S.; Tashiro, H.; Prakash, G.K.S.; Olah, G.A.; Tahshiro, M. *Chem. Commun.* ***2003***, 514.
[2198] Ram, S.; Spicer, L.D. *Tetrahedron Lett.* ***1988***, *29*, 3741.
[2199] West, C.T.; Donnelly, S.J.; Kooistra, D.A.; Doyle, M.P. *J. Org. Chem.* ***1973***, *38*, 2675. See also, Olah, G.A.; Arvanaghi, M.; Ohannesian, L. *Synthesis* ***1986***, 770.
[2200] Zaccheria, F.; Ravasio, N.; Ercoli, M.; Allegrini, P. *Tetrahedron Lett.* ***2005***, *46*, 7743.
[2201] Gevorgyan, V.; Rubin, M.; Liu, J.-X.; Yamamoto, Y. *J. Org. Chem.* ***2001***, *66*, 1672.
[2202] Li, Z.; Deng, G.; Li, Y.-C. *Synlett* ***2008***, 3053.
[2203] van Tamelen, E.E.; Gladys, J.A. *J. Am. Chem. Soc.* ***1974***, *96*, 5290.
[2204] See Zahalka, H.A.; Alper, H. *Organometallics* ***1986***, *5*, 1909.

reduced by H_2S with an amine catalyst[2205] or by HI in refluxing acetic acid.[2206] One carbonyl group of quinones, such as anthracene-9,10-dione, can be reduced with Cu metal and sulfuric acid or with Sn and HCl.[2207] One carbonyl group of 1,3-diketones was selectively reduced by catalytic hydrogenolysis.[2208] Simply heating a ketone in supercritical propan-2-ol reduces the ketone to the methylene compound.[2209]

Heating carbonyl compounds with a cationic ruthenium hydride complex with a phenol ligand led to hydrogenolysis that gave the corresponding aliphatic product.[2210] The use of a Pd catalyst, polymethylhydrosiloxane (PMHS), aqueous KF, and a catalytic amount of an aromatic chloride gave the deoxygenation of benzylic carbonyl substrates.[2211] The hydrosilation of ketones, mediated by phosphonium cations, led to deoxygenation.[2212] The deoxygenation of aromatic ketones via transfer hydrogenolysis used Raney Ni in propan-2-ol.[2213] A silica-supported, chitosan-Schiff base Pd catalyst has also been used.[2214]

The reduction of α,β-unsaturated tosylhydrazones with $NaBH_3CN$, with $NaBH_4$/HOAc, or with catecholborane proceeds with migration of the double bond to the position formerly occupied by the carbonyl carbon, even if this removes the double bond from conjugation with an aromatic ring,[2215] to give the allylic aryl derivative. A cyclic mechanism is apparently involved, with loss of N_2. Another indirect method is conversion of the aldehyde or ketone to a dithioacetal or ketal, and desulfurization using Raney nickel or another reagent (**14-22**).

It is interesting to note that amines can be deaminated to give the corresponding methylene compounds with low-valent titanium ($TiCl_3$/Li/THF).[2216]

OS **I**, 60; **II**, 62, 499; **III**, 410, 444, 513, 786; **IV**, 203, 510; **V**, 533, 747; **VI**, 62, 293, 919; **VII**, 393. Also see, OS **IV**, 218; **VII**, 18.

19-67 Reduction of Carboxylic Acid Derivative Carbonyls to Methylene

$$\mathrm{RCOOR'} \xrightarrow[\mathrm{LiAlH_4}]{\mathrm{BF_3\text{-}etherate}} \mathrm{RCH_2OR'}$$

Carboxylic esters and lactones have been reduced to ethers, although 2 molar equivalents of alcohol are more commonly obtained (**19-42**). Reduction to ethers has been accomplished with a reagent prepared from BF_3-etherate and either $LiAlH_4$, $LiBH_4$, or $NaBH_4$,[2217] with trichlorosilane and UV light,[2218] and with catalytic hydrogenation. The reaction with the

[2205] Mayer, R.; Hiller, G.; Nitzschke, M.; Jentzsch, J. *Angew. Chem. Int. Ed.* ***1963***, *2*, 370.
[2206] Reusch, W.; LeMahieu, R. *J. Am. Chem. Soc.* ***1964***, *86*, 3068.
[2207] Meyer, K.H. *Org. Synth.* ***I***, 60; Macleod, L.C.; Allen, C.F.H. *Org. Synth.* ***II***, 62.
[2208] Cormier, R.A.; McCauley, M.D. *Synth. Commun.* ***1988***, *18*, 675.
[2209] Hatano, B.; Tagaya, H. *Tetrahedron Lett.* ***2003***, *44*, 6331.
[2210] Kalutharage, N.; Yi, C.S. *J. Am. Chem. Soc.* ***2015***, *137*, 11105.
[2211] Rahaim Jr., R.J.; Maleczka Jr., R.E. *Org. Lett.* ***2011***, *13*, 584.
[2212] Mehta, M.; Holthausen, M.H.; Mallov, I.; Pérez, M.; Qu, Z.-W.; Grimme, S.; Stephan, D.W. *Angew. Chem. Int. Ed.* ***2015***, *54*, 8250.
[2213] Zuidema, D.R.; Willimas, S.L.; Wert, K.J.; Bosma, K.J.; Smith, A.L.; Mebane, R.C. *Synth. Commun.* ***2010–2011***, *41*, 2927.
[2214] Gong, S.W.; He, H.F.; Zhao, Ch.Q.; Liu, L.J.; Chui, Q.X. *Synth. Commun.* ***2012***, *42*, 574.
[2215] See Greene, A.E. *Tetrahedron Lett.* ***1979***, 63.
[2216] Talukdar, S.; Banerji, A. *Synth. Commun.* ***1996***, *26*, 1051.
[2217] Ager, D.J.; Sutherland, I.O. *J. Chem. Soc., Chem. Commun.* ***1982***, 248. See also, Dias, J.R.; Pettit, G.R. *J. Org. Chem.* ***1971***, *36*, 3485.
[2218] Baldwin, S.W.; Haut, S.A. *J. Org. Chem.* ***1975***, *40*, 3885. See also, Kraus, G.A.; Frazier, K.A.; Roth, B.D.; Taschner, M.J.; Neuenschwander, K. *J. Org. Chem.* ***1981***, *46*, 2417.

BF_3 reagent apparently succeeds with secondary R′, but not with primary R′, which give **19-42**. Acyloxy groups are reduced by cleavage of the C—C=O bond, R(Ar)COO—C → C—H with an excess of Ph_2SiH_2 and di-*tert*-butyl peroxide.[2219] Esters are reduced to ethers using Et_3SiH and $TiCl_4$,[2220] BF_3,[2221] In(III) compounds,[2222] or $FeCl_3$.[2223] Lactones are converted to cyclic ethers[2224] by treatment with Cp_2TiCl_2 followed by Et_3SiH on Amberlyst 15.[2225] Esters and lactones reacted with hydrogen in the presence of a Ru/phosphine complex and aluminum triflate to give the corresponding ether via deoxygenation of the carbonyl moiety.[2226]

Thiono esters RCSOR′ can be reduced to ethers RCH_2OR' with Raney nickel (**14-27**).[2227] Reaction of thioesters such as R(C=S)SR with Ph_2SiH_2 and Ph_3SnH with BEt_3, followed by AIBN (Sec. 14.A.i) leads to reduction of the C=S unit to give an ether.[2228] Since the thiono esters can be prepared from carboxylic esters (**16-11**), this provides an indirect method for the conversion of carboxylic esters to ethers. Thiol esters (RCOSR′) have been reduced to thioethers (RCH_2SR').[2229]

See also, **19-69**, **19-62**.

Cyclic anhydrides are reduced with Zn/HOAc to give lactones, and are also reduced with hydrogen and Pt or $RuCl_2(Ph_3P)_3$,[2230] and with $NaBH_4$.[2231] With cyclic anhydrides, the reaction with $LiAlH_4$ can be controlled to give either diols or lactones,[2232] although diols are the more usual product. A BINOL/$LiAlH_4$/EtOH complex, however, gives smooth reduction to the lactone.[2233] With some reagents the reaction can be accomplished regioselectively, that is, only a specific one of the two C=O groups of an unsymmetrical anhydride is reduced.[2234] Open-chain anhydrides either are not reduced at all (e.g., with $LiAlH_4$ or $NaBH_4$) or give 2 molar equivalents of alcohol. $NaBH_4$ in THF, with dropwise addition of methanol, reduces open-chain anhydrides to 1 equivalent of primary alcohol and 1 equivalent of carboxylic acid.[2235] Acyl halides are reduced[2236] to alcohols by $LiAlH_4$ or $NaBH_4$, as well as by other metal hydrides (Table 19.2), but not by borane.

In general, reduction of amides to alcohols is difficult. More commonly the amide is reduced to an amine. An exception uses LiH_2NBH_3 to give the alcohol.[2237] Reduction with

[2219] Kim, J.-G.; Cho, D.H.; Jang, D.O. *Tetrahedron Lett.* ***2004***, *45*, 3031.
[2220] Yato, M.; Homma, K.; Ishida, A. *Tetrahedron* ***2001***, *57*, 5353.
[2221] Morra, N.A.; Pagenkopf, B.L. *Synthesis* ***2008***, 511.
[2222] Sakai, N.; Moriya, T.; Fujii, K.; Konakahara, T. *Synthesis* ***2008***, 3533.
[2223] Iwanami, K.; Seo, H.; Tobita, Y.; Oriyama, T. *Synthesis* ***2005***, 183.
[2224] See Pettit, G.R.; Kasturi, T.R.; Green, B.; Knight, J.C. *J. Org. Chem.* ***1961***, *26*, 4773; Edward, J.T.; Ferland, J.M. *Chem. Ind. (London)* ***1964***, 975.
[2225] Hansen, M.C.; Verdaguer, X.; Buchwald, S.L. *J. Org. Chem.* ***1998***, *63*, 2360.
[2226] Li, Y.; Topf, C.; Cui, X.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* ***2015***, *54*, 5196.
[2227] Baxter, S.L.; Bradshaw, J.S. *J. Org. Chem.* ***1981***, *46*, 831.
[2228] Jang, D.O.; Song, S.H. *Synlett* ***2000***, 811; Jang, D.O.; Song, S.H.; Cho, D.H. *Tetrahedron* ***1999***, *55*, 3479.
[2229] See Bublitz, D.E. *J. Org. Chem.* ***1967***, *32*, 1630.
[2230] Morand, P.; Kayser, M.M. *J. Chem. Soc., Chem. Commun.* ***1976***, 314. See also, Hara, Y.; Wada, K. *Chem. Lett.* ***1991***, 553.
[2231] Bailey, D.M.; Johnson, R.E. *J. Org. Chem.* ***1970***, *35*, 3574.
[2232] Bloomfield, J.J.; Lee, S.L. *J. Org. Chem.* ***1967***, *32*, 3919.
[2233] Matsuki, K.; Inoue, H.; Takeda, M. *Tetrahedron Lett.* ***1993***, *34*, 1167.
[2234] See Soucy, C.; Favreau, D.; Kayser, M.M. *J. Org. Chem.* ***1987***, *52*, 129.
[2235] Soai, K.; Yokoyama, S.; Mochida, K. *Synthesis* ***1987***, 647.
[2236] See Wheeler, O.H. in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***, pp. 231–251. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1263–1264.
[2237] Myers, A.G.; Yang, B.H.; Kopecky, D.J. *Tetrahedron Lett.* ***1996***, *37*, 3623.

sodium metal in propanol also gives the alcohol.[2238] Acyl imidazoles are also reduced to the corresponding alcohol with $NaBH_4$ in aqueous HCl.[2239]

There are no *Organic Syntheses* references, but see OS **II**, 526, for a related reaction. See OS **VI**, 482, for reduction to alcohols and OS **IV**, 271, for reduction of acyl halides.

19-68 Reduction of Amides to Amines

$$RCONH_2 \xrightarrow{LiAlH_4} RCH_2NH_2$$

Amides have been reduced to the amine, an alcohol or an aldehyde, depending on the steric demands of the amide and the nature of the reducing agent.[2240] A useful reagent is $LiAlH_4$, although the reaction is more difficult than the reduction of most other functional groups, and other groups are often reduced without disturbing an amide function. Although $NaBH_4$ by itself does not reduce amides, it does so in the presence of certain other reagents,[2241] including iodine.[2242] Lithium borohydride reduces acetamides.[2243] Substituted amides can be reduced with these powerful reagents; secondary amides are reduced to secondary amines and tertiary amides are reduced to tertiary amines. Borane[2244] and sodium in propan-1-ol[2245] are good reducing agents for all three types of amides. Lithium triethylborohydride produces the alcohol with most *N*,*N*-disubstituted amides, but not with unsubstituted or *N*-substituted amides.[2246] Sodium (dimethylamino)borohydride reduces unsubstituted and disubstituted amides but not monosubstituted amides.[2247]

With some $RCONR_2$, $LiAlH_4$ causes cleavage, and the aldehyde (**10-40**) or alcohol is obtained. Lactams are reduced to cyclic amines in high yields with $LiAlH_4$, although cleavage sometimes occurs here too. A mixture of $LiBHEt_3/Et_3SiH$ is also effective.[2248] Lactams are also reduced to cyclic amines with 9-BBN[2249] (**15-11**) or $LiBH_3NMe_2$.[2250] *Hantzsch esters* (see **19-37**, **16-15**) have been used for metal-free reduction of amides to amines.[2251] Selenoamides were reduced to the amine by SmI_2 with H_2O.[2252]

The reaction of secondary amides with 4 equivalents of Et_2SiH_2 and an Ir catalyst gave the amine, whereas the use of 2 equivalents gave the imine.[2253] The reaction of tertiary and *N*-phenyl secondary amides with tetramethyldisiloxane (TMDS) and $B(C_6F_5)_3$ as catalyst

[2238] Moody, H.M.; Kaptein, B.; Broxterman, Q.B.; Boesten, W.H.J.; Kamphuis, J. *Tetrahedron Lett.* ***1994***, *35*, 1777.
[2239] Sharma, R.; Voynov, G.H.; Ovaska, T.V.; Marquez, V.E. *Synlett* ***1995***, 839.
[2240] See Bailey, C.L.; Joh, A.Y.; Hurley, Z.Q.; Anderson, C.L.; Singaram, B. *J. Org. Chem.* ***2016***, *81*, 3619.
[2241] See Mandal, S.B.; Giri, V.S.; Pakrashi, S.C. *Synthesis* ***1987***, 1128; Akabori, S.; Takanohashi, Y. *Chem. Lett.* ***1990***, 251.
[2242] Prasad, A.S.B.; Kanth, J.V.B.; Periasamy, M. *Tetrahedron* ***1992***, *48*, 4623.
[2243] Tanaka, H.; Ogasawara, K. *Tetrahedron Lett.* ***2002***, *43*, 4417.
[2244] See Bonnat, M.; Hercourt, A.; Le Corre, M. *Synth. Commun.* ***1991***, *21*, 1579.
[2245] Bhandari, K.; Sharma, V.L.; Chatterjee, S.K. *Chem. Ind. (London)* ***1990***, 547.
[2246] Brown, H.C.; Kim, S.C. *Synthesis* ***1977***, 635.
[2247] Hutchins, R.O.; Learn, K.; El-Telbany, F.; Stercho, Y.P. *J. Org. Chem.* ***1984***, *49*, 2438.
[2248] Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreño, M.C.; García Ruano, J.L.G. *Tetrahedron Lett.* ***1994***, *35*, 2053.
[2249] Colllins, C.J.; Lanz, M.; Singaram, B. *Tetrahedron Lett.* ***1999***, *40*, 3673.
[2250] Flaniken, J.M.; Collins, C.J.; Lanz, M.; Singaram, B. *Org. Lett.* ***1999***, *1*, 799.
[2251] Barbe, G.; Charette, A.B. *J. Am. Chem. Soc.* ***2008***, *130*, 18.
[2252] Thurow, S.; Lenardão, E.J.; Just-Baringo, X.; Procter, D.J. *Org. Lett.* ***2017***, *19*, 50.
[2253] Cheng, C.; Brookhart, M. *J. Am. Chem. Soc.* ***2012***, *134*, 11304.

gave the amine.[2254] Activation of an amide by Tf_2O with $B(C_6F_5)_3$-catalyzed hydrosilylation using TMDS gave reduction of secondary amides to amines.[2255] The reaction of amides with Et_2Zn as catalyst using polymethylhydrosiloxane (PMHS) and a sub-stoichiometric amount of LiCl gave the amine.[2256] Primary amides were reduced to the corresponding amine using polymethylhydrosiloxane (PMHS)—$Ti(O\textit{i}\text{-}Pr)_4$.[2257] Reduction of aromatic or aliphatic secondary amides with InI_3 and TMDS (1,1,3,3-tetramethyldisiloxane) gave the corresponding secondary amines.[2258] The Ni-catalyzed[2259] or Ru-catalyzed[2260] reduction of amides with $PhSiH_3$ gave the amine. An *in situ* formation of an iron/*N*-heterocyclic carbene catalyst has been used for the hydrosilation of tertiary amides.[2261]

The transfer hydrogenation of aryl nitriles to the amine using a Ru catalyst has been reported.[2262] The Ru-catalyzed hydrogenation of functionalized α-phenoxy and related amides gave chiral alcohols with high enantioselectivity.[2263] Amides were reduced to amines by reaction with $LiAlH_4$/TMSCl.[2264] Two iron catalysts were used with $(EtO)_2MeSiH$ to reduce primary amides to amines.[2265] Lactams reacted with propan-2-ol, hydrogen, MsOH, and a Ru catalyst to give the cyclic amine.[2266] Zinc catalysts were used with $(EtO)_2MeSiH$ and secondary amides or with $Me_2HSi—O—SiHMe_2$ and tertiary amides to give the corresponding amine.[2267] A cationic Cu/pybox catalyst with TMDS led to reduction of secondary amides to the corresponding amine.[2268]

Amides can be reduced[2269] to amines by catalytic hydrogenation,[2270] but high temperatures and pressures are usually required. Ruthenium,[2271] Pt/V,[2272] or a Ru complex/Zn salt catalyst have been used for hydrogenation.[2273] Another reagent that reduces disubstituted

[2254] Chadwick, R.C.; Kardelis, V.; Lim, P.; Adronov, A. *J. Org. Chem.* ***2014***, *79*, 7728. See Blondiux, E.; Cantat, T. *Chem. Commun.* ***2014***, *50*, 9349.
[2255] Huang, P.-Q.; Lang, Q.-W.; Wang, Y.-R. *J. Org. Chem.* ***2016***, *81*, 4235.
[2256] Kovalenko, O.O.; Volkov, A.; Adolfsson, H. *Org. Lett.* ***2015***, *17*, 446.
[2257] Laval, S.; Dayoub, W.; Pehlivan, L.; Métay, E.; Favre-Réguillon, A.; Delbrayelle, D.; Mignani, G.; Lemaire, M. *Tetrahedron Lett.* ***2011***, *52*, 4072.
[2258] Sakai, N.; Takeoka, M.; Kumaki, T.; Asano, H.; Konakahara, T.; Ogiwara, Y. *Tetrahedron Lett.* ***2015***, *56*, 6448.
[2259] Simmons, B.J.; Hoffmann, M.; Hwang, J.; Jackl, M.K.; Garg, N.K. *Org. Lett.* ***2017***, *19*, 1910.
[2260] Li, B.; Sotais, J.-B.; Darcel, C. *Chem. Commun.* ***2013***, *49*, 3691.
[2261] Volkov, A.; Buitrago, E.; Adolfsson, H. *Eur. J. Org. Chem.* ***2013***, 2066.
[2262] Labes, R.; González-Calderón, D.; Battilocchio, C.; Mateos, C.; Cumming, G.R.; de Frutos, O.; Rincón, J.A.; Ley, S.V. *Synlett.* ***2017***, *28*, 2855.
[2263] Rasu, L.; John, J.M.; Stephenson, E.; Endean, R.; Kalapugama, S.; Clément, R.; Bergens, S.H. *J. Am. Chem. Soc.* ***2017***, *139*, 3065.
[2264] Ravinder, B.; Reddy, S.R.; Reddy, A.P.; Bandichhor, R. *Tetrahedron Lett.* ***2013***, *54*, 4908.
[2265] Das, S.; Wendt, B.; Möller, K.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* ***2012***, *51*, 1662.
[2266] Westhues, S.; Meuresch, M.; Klankermayer, J. *Angew. Chem. Int. Ed.* ***2016***, *55*, 12841.
[2267] Das, S.; Addis, D.; Junge, K.; Beller, M. *Chem. Eur. J.* ***2011***, *17*, 12186.
[2268] Das, S.; Join, B.; Junge, K.; Beller, M. *Chem. Commun.* ***2012***, *48*, 2683.
[2269] See Challis, B.C.; Challis, J.A. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 795–801; Gaylord, N.G. *Reduction with Complex Metal Hydrides*, Wiley, NY, ***1956***, p. 544. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 869–872.
[2270] See Magro, A.A.N.; Eastham, G.R.; Cole-Hamilton, D.J. *Chem. Commun.* ***2007***, 3154.
[2271] Coetzee, J.; Dodds, D.L.; Klankermayer, J.; Brosinski, S.; Leitner, W.; Slawin, A.M.Z.; Cole-Hamilton, D.J. *Chem. Eur. J.* ***2013***, *19*, 11039.
[2272] Mitsudome, T.; Miyagawa, K.; Maeno, Z.; Mizugaki, T.; Jitsukawa, K.; Yamasaki, J.; Kitagawa, Y.; Kaneda, K. *Angew. Chem. Int. Ed.* ***2017***, *56*, 9381.
[2273] Kita, Y.; Higuchi, T.; Mashima, K. *Chem. Commun.* ***2014***, *50*, 11213.

amides to amines is trichlorosilane.[2274] Other silanes, such as Et_3SiH, in the presence of a Re,[2275] Pt,[2276] In,[2277] Zn,[2278] or Ru[2279] catalyst, reduce amides to amines. Electrolytic reduction of carbamates to give an amine are possible.[2280]

Imides are generally reduced on both sides,[2281] although it is sometimes possible to stop with just one. Both cyclic and acyclic imides have been reduced in this manner, although with acyclic imides cleavage often takes place.[2282] It is noted that imides can be reduced to hydroxy lactams using different reagents, including $NaBH_4$.[2283]

OS **IV**, 339, 354, 564; **VI**, 382; **VII**, 41.

19-69 Reduction of Carboxylic Acids and Esters to Alkanes

$$RCOOR' \xrightarrow{(C_5H_5)_2TiCl_2} RCH_3 + R'OH$$

Titanocene dichloride reduces carboxylic esters in a different manner from that of **19-62**, **19-67**, or **19-42**. The products are the alkane RCH_3 and the alcohol R′OH. The mechanism probably involves an alkene intermediate. Aromatic acids can be reduced to methylbenzenes by a procedure involving refluxing first with trichlorosilane in MeCN, then with tripropylamine added, and finally with KOH and MeOH (after removal of the MeCN).[2284] Esters of aromatic acids are not reduced by this procedure, so an aromatic COOH group can be reduced in the presence of a COOR′ group.[2285] However, it is also possible to reduce aromatic ester groups, by a variation of the trichlorosilane procedure.[2286] Both *o*- and *p*-hydroxybenzoic acids and their esters have been reduced to cresols ($HOC_6H_4CH_3$) with Red-Al.[2287] Heating a 2-pyridylbenzyl ester with ammonium formate and a Ru catalyst leads to reduction of the CH_3COO unit to the alkane.[2288] Carboxylic acids can also be converted to alkanes, indirectly,[2289] by reduction of the corresponding tosylhydrazides ($RCONHNH_2$) with $LiAlH_4$ or borane.[2290]

OS **VI**, 747.

19-70 Hydrogenolysis of Nitriles

$$R{-}CN \longrightarrow R{-}H$$

[2274] Nagata, Y.; Dohmaru, T.; Tsurugi, J. *Chem. Lett.* ***1972***, 989. See also, Benkeser, R.A.; Li, G.S.; Mozdzen, E.C. *J. Organomet. Chem.* ***1979***, *178*, 21.
[2275] Igarashi, M.; Fuchikami, T. *Tetrahedron Lett.* ***2001***, *42*, 1945.
[2276] Hanada, S.; Motoyama, Y.; Nagashima, H. *Tetrahedron Lett.* ***2006***, *47*, 6173.
[2277] Sakai, N.; Fujii, K.; Konakahara, T. *Tetrahedron Lett.* ***2008***, *49*, 6873.
[2278] Das, S.; Addis, D.; Zhou, S.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* ***2010***, *132*, 1770.
[2279] Hanada, S.; Ishida, T.; Motoyama, Y.; Nagashima, H. *J. Org. Chem.* ***2007***, *72*, 7551.
[2280] Franco, D.; Duñach, E. *Tetrahedron Lett.* ***2000***, *41*, 7333.
[2281] See Akula, M.R.; Kabalka, G.W. *Org. Prep. Proceed. Int.* ***1999***, *31*, 214.
[2282] Witkop, B.; Patrick, J.B. *J. Am. Chem. Soc.* ***1952***, *74*, 3861.
[2283] See Issa, F.; Fischer, J.; Turner, P.; Coster, M.J. *J. Org. Chem.* ***2006***, *71*, 4703.
[2284] Benkeser, R.A.; Foley, K.M.; Gaul, J.M.; Li, G.S. *J. Am. Chem. Soc.* ***1970***, *92*, 3232.
[2285] Benkeser, R.A.; Ehler, D.F. *J. Org. Chem.* ***1973***, *38*, 3660.
[2286] Benkeser, R.A.; Mozdzen, E.C.; Muth, C.L. *J. Org. Chem.* ***1979***, *44*, 2185.
[2287] Cerny, M.; Málek, J. *Collect. Czech. Chem. Commun.* ***1970***, *35*, 2030.
[2288] Chatani, N.; Tatamidani, H.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* ***2001***, *123*, 4849.
[2289] See Le Deit, H.; Cron, S.; Le Corre, M. *Tetrahedron Lett.* ***1991***, *32*, 2759.
[2290] Attanasi, O.; Caglioti, L.; Gasparrini, F.; Misiti, D. *Tetrahedron* ***1975***, *31*, 341, and references cited therein.

This transformation is not common, but given the proliferation of nitriles in organic chemistry, it is potentially quite useful. In the presence of mercuric compounds, tertiary nitriles can be reduced to the hydrocarbon with sodium cyanoborohydride.[2291] *gem*-Dinitriles can be reduced to the corresponding mono-nitrile with SmI_2.[2292] Hydrosilanes facilitate reductive cleavage of nitriles in the presence of a Rh catalyst.[2293] The Ni-catalyzed decyanation of aryl and aliphatic cyanides using $(Me_2SiH)_2O$ gave the alkane.[2294] Decyanation of alkyl nitriles has been reported using Ni-catalyzed hydrogenation.[2295]

19-71 Reduction of the C—N Bond

$$RNH_2 \longrightarrow RH$$

Benzylic amines are particularly susceptible to hydrogenolysis by catalytic hydrogenation[2296] or dissolving metal reduction.[2297] The transition metal-catalyzed cleavage of C—N bonds has been reviewed.[2298] Note that the *Wolff-Kishner reduction* in **19-66** involved formation of a hydrazone and deprotonation by base that led to loss of nitrogen and reduction. Ceric ammonium nitrate in aqueous acetonitrile has also been shown to reductively cleave the *N*-benzyl group.[2299] Primary amines have been reduced to RH with hydroxylamine-*O*-sulfonic acid and aqueous NaOH to give the hydrocarbon, nitrogen gas, and the sulfate anion.[2300] It is postulated that R—N=N—H is an intermediate that decomposes to the carbocation. An indirect means of achieving the same result is the conversion of the primary amine to the sulfonamide $RNHSO_2R'$ (**16-96**) and subsequent treatment with NH_2OSO_2OH[2301] or NaOH and then NH_2Cl.[2302] Tosylaziridines derived from terminal alkenes are reduced to the corresponding primary tosylamine with polymethylhydrosiloxane/Pd/C.[2303] Aziridines can be reduced in the same way as epoxides (**19-39**).

The Ni-catalyzed cleavage of C—N bonds has been used to convert amides to esters.[2304] The reaction of *N*-tosylamines or *N*-benzylamines with electron-rich alkenes such as tetrakis(dimethylamino)ethene led to C—N bond cleavage and formation of the amine.[2305] The photochemical cleavage of the benzylic C—N bond in 3-(diethylamino)benzyl derivatives generates the amine.[2306] Tertiary amides with an *N*-isopropyl group were deprotected by heating in methanesulfonic acid.[2307]

[2291] Sassaman, M.B. *Tetrahedron* ***1996***, *52*, 10835.
[2292] Kang, H.-Y.; Hong, W.S.; Cho, Y.S.; Koh, H.Y. *Tetrahedron Lett.* ***1995***, *36*, 7661.
[2293] Tobisu, M.; Nakamura, R.; Kita, Y.; Chatani, N. *J. Am. Chem. Soc.* ***2009***, *131*, 3174.
[2294] Patra, T.; Agasti, S.; Maiti, A.; Maiti, D. *Chem. Commun.* ***2013***, *49*, 69.
[2295] Patra, T.; Agasti, S.; Modak, A.; Maiti, D. *Chem. Commun.* ***2013***, *49*, 8362.
[2296] Hartung, W.H.; Simonoff, R. *Org. React.* ***1953***, *7*, 263.
[2297] du Vigneaud, V.; Behrens, O.K. *J. Biol. Chem.* ***1937***, *117*, 27.
[2298] Ouyang, K.; Hao, W.; Zhang, W.-X.; Xi, Z. *Chem. Rev.* ***2015***, *115*, 1245.
[2299] Bull, S.D.; Davies, S.G.; Fenton, G.; Mulvaney, A.W.; Prasad, R.S.; Smith, A.D. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 3765.
[2300] Doldouras, G.A.; Kollonitsch, J. *J. Am. Chem. Soc.* ***1978***, *100*, 341.
[2301] Nickon, A.; Hill, R.H. *J. Am. Chem. Soc.* ***1964***, *86*, 1152.
[2302] Guziec Jr., F.S.; Wei, D. *J. Org. Chem.* ***1992***, *57*, 3772.
[2303] Chandrasekhar, S.; Ahmed, M. *Tetrahedron Lett.* ***1999***, *40*, 9325.
[2304] Hie, L.; Fine Nathel, N.F.; Shah, T.K.; Baker, E.L.; Hong, X.; Yang, Y.-F.; Liu, P.; Houk, K.N.; Garg, N.K. *Nature* ***2015***, *524*, 79.
[2305] See Murphy, J.A. *J. Org. Chem.* ***2014***, *79*, 3731.
[2306] Wang, P.; Devalankar, D.A.; Lu, W. *J. Org. Chem.* ***2016***, *81*, 6195.
[2307] Lorenc, C.; Reeves, J.T.; Busacca, C.A.; Senanayake, C.H. *Tetrahedron Lett.* ***2015***, *56*, 1280.

Other indirect methods involve reduction of *N*,*N*-ditosylates (Sec. 10.G.iii) with $NaBH_4$ in HMPA[2308] and modifications of the *Katritzky pyrylium-pyridinium method*.[2309] Allylic and benzylic amines[2091] can be reduced by catalytic hydrogenolysis. Aziridines can be reductively opened with SmI_2[2310] or with Bu_3SnH and AIBN.[2311] The C—N bond of enamines is reductively cleaved to give an alkene with alane (AlH_3),[2312] and with 9-BBN (**15-11**) or borane methyl sulfide (BMS).[2313] Since enamines can be prepared from ketones (**16-12**), this is a way of converting ketones to alkenes. In the latter case BMS gives retention of configuration [an (*E*) isomer gives the (*E*) product], while 9-BBN gives the other isomer.[2313] Diazo ketones are reduced to methyl ketones by HI:[2314]

$$RCOCHN_2 + HI \rightarrow RCOCH_3$$

Quaternary ammonium salts can be cleaved with $LiAlH_4$:

$$R_4N^+ + LiAlH_4 \rightarrow R_3N + R^-$$

as can quaternary phosphonium salts R_4P^+. Other reducing agents have also been used, for example, lithium triethylborohydride (which preferentially cleaves methyl groups)[2315] and Na in liquid ammonia. When quaternary salts are reduced with Na(Hg) in water, the reaction is known as the *Emde reduction*. However, this reagent is not applicable to the cleavage of ammonium salts with four *saturated* alkyl groups.

Nitro compounds, RNO_2, can be reduced to RH[2316] by sodium methylmercaptide, CH_3SNa, in an aprotic solvent[2317] or by Bu_3SnH.[2318] Both reactions have free-radical mechanisms.[2319] Tertiary nitro compounds can be reduced to RH by NaHTe.[2320] The nitro group of aromatic nitro compounds has been removed with sodium borohydride.[2321] Reduction of the C—N bond of aromatic amines with Li metal in THF generates the aryl compounds.[2322] Conversion of the aniline derivative to the methanesulfonamide and subsequent treatment with NaH and NH_2Cl gives the same result.[2323]

OS **III**, 148; **IV**, 508; **VIII**, 152.

[2308] Hutchins, R.O.; Cistone, F.; Goldsmith, B.; Heuman, P. *J. Org. Chem.* ***1975***, *40*, 2018.
[2309] See Katritzky, A.R.; Bravo-Borja, S.; El-Mowafy, A.M.; Lopez-Rodriguez, G. *J. Chem. Soc., Perkin Trans. 1* ***1984***, 1671.
[2310] Molander, G.A.; Stengel, P.J. *Tetrahedron* ***1997***, *53*, 8887.
[2311] Schwan, A.L.; Refvik, M.D. *Tetrahedron Lett.* ***1993***, *34*, 4901.
[2312] Coulter, J.M.; Lewis, J.W.; Lynch, P.P. *Tetrahedron* ***1968***, *24*, 4489.
[2313] Singaram, B.; Goralski, C.T.; Rangaishenvi, M.V.; Brown, H.C. *J. Am. Chem. Soc.* ***1989***, *111*, 384.
[2314] For example, see Pojer, P.M.; Ritchie, E.; Taylor, W.C. *Aust. J. Chem.* ***1968***, *21*, 1375.
[2315] Cooke Jr., M.P.; Parlman, R.M. *J. Org. Chem.* ***1975***, *40*, 531.
[2316] See Fessard, T.C.; Motoyoshi, H.; Carreira, E.M. *Angew. Chem. Int. Ed.* ***2007***, *46*, 2078.
[2317] See Kornblum, N.; Widmer, J.; Carlson, S.C. *J. Am. Chem. Soc.* ***1979***, *101*, 658.
[2318] See Ono, N. in Feuer, H.; Nielsen, A.T. *Nitro Compounds: Recent Advances in Synthesis and Chemistry*, VCH, NY, ***1990***, pp. 1–135 (pp. 1–45); Rosini, G.; Ballini, R. *Synthesis* ***1988***, 833 (see pp. 835–837). See Kamimura, A.; Ono, N. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 3629.
[2319] See Bowman, W.R.; Crosby, D.; Westlake, P.J. *J. Chem. Soc., Perkin Trans. 2* ***1991***, 73.
[2320] Suzuki, H.; Takaoka, K.; Osuka, A. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 1067.
[2321] See Kniel, P. *Helv. Chim. Acta* ***1968***, *51*, 371. For another method, see Ono, N.; Tamura, R.; Kaji, A. *J. Am. Chem. Soc.* ***1983***, *105*, 4017.
[2322] Azzena, U.; Dessanti, F.; Melloni, G.; Pisano, L. *Tetrahedron Lett.* ***1999***, *40*, 8291.
[2323] Wang, Y.; Guziec Jr., F.S. *J. Org. Chem.* ***2001***, *66*, 8293.

19-72 Reduction of Amine Oxides and Azoxy Compounds

Amine oxides[2324] and azoxy compounds (both alkyl and aryl)[2325] can be reduced practically quantitatively with triphenylphosphine.[2326] Other reducing agents have also been used, including $LiAlH_4$, $NaBH_4/LiCl$,[2327] H_2/Ni, PCl_3, Ga/H_2O,[2328] or $In/TiCl_4$.[2329] Indium metal with aqueous ammonium chloride in methanol gives good yields of pyridine from pyridine *N*-oxide.[2330] Similar results are obtained using ammonium formate and Raney nickel[2331] or ammonium formate and zinc.[2332] Sodium in ethanol, in a sealed tube, reduces pyridine *N*-oxide to pyridine.[2333] Similar reduction was accomplished with $Mo(CO)_6$ in ethanol.[2334] Indium(III) chloride has been used for the reduction of quinoline *N*-oxide to quinoline.[2335] Nitrile oxides[2336] ($R{-}C{\equiv}N^{+}{-}O^{-}$) can be reduced to nitriles with trialkylphosphines,[2337] and isocyanates (RNCO) to isocyanides (RNC) with Cl_3SiH/Et_3N.[2338]

Analogous to amino *N*-oxides, phosphine oxides ($R_3P{=}O$) are reduced to phosphines (R_3P). Treatment of a phosphine oxide with MeOTf followed by reduction with $LiAlH_4$[2339] or DibalH[2340] gives the phosphine. Chiral phosphine oxides are reduced to the phosphine with excellent enantioselectivity using PPh_3 and Cl_3SiH.[2341] Phosphine oxides were reduced to phosphines with an In catalyst and TMDS (1,1,3,3-tetramethyldisilazane).[2342] The TMSCl-promoted electroreduction of triphenylphosphine oxide to triphenylphosphine has been reported.[2343]

OS **IV**, 166. See also, OS **VIII**, 57.

[2324] See Albini, A.; Pietra, S. *Heterocyclic N-Oxides*, CRC Press, Boca Raton, FL, ***1991***, pp. 120–134; Katritzky, A.R.; Lagowski, J.M. *Chemistry of the Heterocyclic N-Oxides*, Academic Press, NY, ***1971***, pp. 166–231.

[2325] See Newbold, B.T. in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 602–603, 614–624.

[2326] See Rowley, A.G. in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 295–350.

[2327] Ram, S.R.; Chary, K.P.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 3511.

[2328] Han, J.H.; Choi, K.I.; Kim, J.H.; Yoo, B.W. *Synth. Commun.* ***2004***, *34*, 3197.

[2329] Yoo, B.W.; Choi, K.H.; Choi, K.I.; Kim, J.H. *Synth. Commun.* ***2003***, *33*, 4185.

[2330] Yadav, J.S.; Reddy, B.V.S.; Reddy, M.M. *Tetrahedron Lett.* ***2000***, *41*, 2663.

[2331] Balicki, R.; Maciejewski, G. *Synth. Commun.* ***2002***, *32*, 1681.

[2332] Balicki, R.; Cybulski, M.; Maciejewski, G. *Synth. Commun.* ***2003***, *33*, 4137.

[2333] Bjørsvik, H.-R.; Gambarotti, C.; Jensen, V.R.; González, R.R. *J. Org. Chem.* ***2005***, *70*, 3218.

[2334] Yoo, B.W.; Choi, J.W.; Yoon, C.M. *Tetrahedron Lett.* ***2006***, *47*, 125.

[2335] Ilias, Md.; Barman, D.C.; Prajapati, D.; Sandhu, J.S. *Tetrahedron Lett.* ***2002***, *43*, 1877.

[2336] See Torssell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH, NY, ***1988***, pp. 55–74; Grundmann, C. *Fortschr. Chem. Forsch.* ***1966***, *7*, 62.

[2337] Grundmann, C.; Frommeld, H.D. *J. Org. Chem.* ***1965***, *30*, 2077.

[2338] Baldwin, J.E.; Derome, A.E.; Riordan, P.D. *Tetrahedron* ***1983***, *39*, 2989.

[2339] Imamoto, T.; Kikuchi, S.-i.; Miura, T.; Wada, Y. *Org. Lett.* ***2001***, *3*, 87.

[2340] Lee, H.; Sabila, P.; Saha, A.; Sarvestani, M.; Shen, S.; Varsolona, R.; Wei, X.; Senanayake, C.H. *Org. Lett.* ***2005***, *7*, 4277.

[2341] Wu, H.-C.; Yu, J.-Q.; Spencer, J.B. *Org. Lett.* ***2004***, *6*, 4675.

[2342] Pehlivan, L.; Métay, E.; Delbrayelle, D.; Mignani, G.; Lemaire, M. *Tetrahedron* ***2012***, *68*, 3151.

[2343] Tanaka, T.; Yano, T.; Kobayashi, K.; Kamenoue, S.; Kuroboshi, M.; Kawakubo, H. *Synlett* ***2011***, *22*, 582; Kawakubo, H.; Kuroboshi, M.; Yano, T.; Kobayashi, K.; Kamenoue, S.; Akagi, T.; Tanaka, H. *Synthesis* ***2011***, *43*, 4091. See Li, P.; Wischert, R.; Métivier, P. *Angew. Chem. Int. Ed.* ***2017***, *56*, 15989.

19-73 Replacement of the Diazonium Group by Hydrogen

$$ArN_2^+ + H_3PO_2 \longrightarrow ArH$$

Reduction of a diazonium group (*dediazoniation*) provides an indirect method for the removal of an amino group from an aromatic ring.[2344] A common method uses hypophosphorus acid (H_3PO_2), although many other reducing agents[2345] have been used, including HMPA,[2346] thiophenol,[2347] and sodium stannite (Na_2SnO_2). Ethanol was the earliest reagent used, and it frequently gives good yields, but ethers (ArOEt) are frequent side products. When H_3PO_2 is used, 5–15 molar equivalents of this reagent are required per molar equivalent of substrate. Diazonium salts can be reduced in nonaqueous media by several methods, including treatment with Bu_3SnH or Et_3SiH in ethers or MeCN[2348] and by isolation as the BF_4^- salt and reduction of this with $NaBH_4$ in DMF.[2349] Aromatic amines can be deaminated ($ArNH_2 \rightarrow ArH$) in one laboratory step by treatment with an alkyl nitrite in DMF[2350] or boiling THF.[2351] The corresponding diazonium salt is an intermediate.

Not many investigations of the mechanism have been carried out. It is generally assumed that the reaction of diazonium salts with ethanol to produce ethers takes place by an ionic (S_N1) mechanism while the reduction to ArH proceeds by a free-radical process.[2352] The reduction with H_3PO_2 is also believed to have a free-radical mechanism.[2353] In the reduction with $NaBH_4$, an aryldiazene intermediate (ArN=NH) has been demonstrated,[2354] arising from nucleophilic attack by BH_4^- on the β nitrogen. Such diazenes can be obtained as moderately stable (half-life of several hours) species in solution.[2355] It is not entirely clear how the aryldiazene decomposes, but there are indications that either the aryl radical Ar• or the corresponding anion Ar^- may be involved.[2356]

The dediazoniation reaction is used for functionalization of aromatic rings, to remove an amino group after it has been used to direct one or more other groups to *ortho* and *para* positions. For example, the compound 1,3,5-tribromobenzene cannot be prepared by direct bromination of benzene because the bromo group is *ortho*/*para* directing; however, this compound is easily prepared by nitration of benzene, reduction to aniline, tribromination, and then treatment with HONO and finally H_2PO_2 gave 1,3,5-tribromobenzene. Many other compounds that would otherwise be difficult to prepare are easily synthesized with the

[2344] See Zollinger, H. in Patai, S.; Rappoport, Z. *The Chemistry of Functinal Groups*, Supplement C, pt. 1, Wiley, NY, ***1983***, pp. 603–669.
[2345] For lists of some of these, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 39–41; Tröndlin, F.; Rüchardt, C. *Chem. Ber.* ***1977***, *110*, 2494.
[2346] Shono, T.; Matsumura, Y.; Tsubata, K. *Chem. Lett.* ***1979***, 1051.
[2347] See Korzeniowski, S.H.; Blum, L.; Gokel, G.W. *J. Org. Chem.* ***1977***, *42*, 1469.
[2348] Nakayama, J.; Yoshida, M.; Simamura, O. *Tetrahedron* ***1970***, *26*, 4609.
[2349] Hendrickson, J.B. *J. Am. Chem. Soc.* ***1961***, *83*, 1251. See also, Threadgill, M.D.; Gledhill, A.P. *J. Chem. Soc., Perkin Trans. 1* ***1986***, 873.
[2350] Doyle, M.P.; Dellaria Jr., J.F.; Siegfried, B.; Bishop, S.W. *J. Org. Chem.* ***1977***, *42*, 3494.
[2351] Cadogan, J.I.G.; Molina, G.A. *J. Chem. Soc., Perkin Trans. 1* ***1973***, 541.
[2352] See Broxton, T.J.; Bunnett, J.F.; Paik, C.H. *J. Org. Chem.* ***1977***, *42*, 643.
[2353] See Levit, A.F.; Kiprianova, L.A.; Gragerov, I.P. *J. Org. Chem. USSR* ***1975***, *11*, 2395.
[2354] König, E.; Musso, H.; Záhorszky, U.I. *Angew. Chem. Int. Ed.* ***1972***, *11*, 45.
[2355] Smith III, M.R.; Hillhouse, G.L. *J. Am. Chem. Soc.* ***1988***, *110*, 4066.
[2356] See König, E.; Musso, H.; Záhorszky, U.I.; König, E.; Musso, H.; Záhorszky, U.I. *Angew. Chem. Int. Ed.* ***1972***, *11*, 45; Broxton, T.J.; McLeish, M.J. *Aust. J. Chem.* ***1983***, *36*, 1031.

aid of the dediazoniation reaction. Unwanted dediazoniation can be suppressed by using hexasulfonated calix[6]arenes (Sec. 3.C.ii).[2357]

OS **I**, 133, 415; **II**, 353, 592; **III**, 295; **IV**, 947; **VI**, 334.

19-74 Desulfurization

$$RSH \longrightarrow RH \quad RSR' \longrightarrow RH + R'H \quad RS(O)_nR' \longrightarrow RH + R'H$$

Thiols and thioethers,[2358] both alkyl and aryl, can be desulfurized by hydrogenolysis with Raney nickel.[2359] The hydrogen is usually not applied externally, since Raney nickel typically contains enough hydrogen for the reaction. Other sulfur compounds can be similarly desulfurized, including disulfides, thiono esters,[2360] thioamides, sulfoxides, and thioacetals.[2361] Reduction of thioacetals is an indirect way of accomplishing reduction of a carbonyl to a methylene group (**19-66**), and it can also give the alkene if a hydrogen atom is present.[2362] In most of the examples given, R can also be aryl. Other reagents[2363] have also been used.[2364] Reductive cleavage of sulfones and sulfonamides occurs with organobases such as bis(imidazolylidenes).[2365] The use of baker's yeast in the reduction of sulfur-containing compounds has been reviewed.[2366]

The desulfurization of heterocyclic thiols to give the sulfur-free heterocycle used Et_3SiH and Pd/C.[2367] Aryl and benzyl methyl sulfide were reduced with C—S cleavage to give the arene using $EtMe_2SiH$ and a Ni catalyst.[2368] Sulfides were reduced with Et_3SiH, using $B(C_6F_5)_3$ as a catalyst, and gave hydrodesulfurization of C—S bond.[2369] Aryl sulfides were reduced with C—S bond cleavage to give the arene using the Pd-catalyzed reaction with Et_3SiH and TMSCl.[2370]

Lithium aluminum hydride reduces most sulfur compounds with cleavage of the C—S bond, including thiols.[2371] Thioesters can be reduced with Ni_2B (from $NiBr_2/NaBH_4$).[2372] β-Ketosulfones are reduced with $TiCl_4/Zn$[2373] or $TiCl_4/Sm$.[2374] An important special case of

[2357] Shinkai, S.; Mori, S.; Araki, K.; Manabe, O. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 3679.
[2358] For a review of the reduction of thioethers, see Block, E. in Patai, S. *The Chemistry of Functional Groups*, Supplement E, pt. 1, Wiley, NY, ***1980***, pp. 585–600.
[2359] For reviews, see Belen'kii, L.I. in Belen'kii, L.I. *Chemistry of Organosulfur Compounds*, Ellis Horwood, Chichester, ***1990***, pp. 193–228; Pettit, G.R.; van Tamelen, E.E. *Org. React.* ***1962***, *12*, 356; Hauptmann, H.; Walter, W.F. *Chem. Rev.* ***1962***, *62*, 347.
[2360] See Baxter, S.L.; Bradshaw, J.S. *J. Org. Chem.* ***1981***, *46*, 831.
[2361] See Nakata, D.; Kusaka, C.; Tani, S.; Kunishima, M. *Tetrahedron Lett.* ***2001***, *42*, 415.
[2362] Fishman, J.; Torigoe, M.; Guzik, H. *J. Org. Chem.* ***1963***, *28*, 1443.
[2363] For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 53–60. See Luh, T.; Ni, Z. *Synthesis* ***1990***, 89; Becker, S.; Fort, Y.; Vanderesse, R.; Caubère, P. *J. Org. Chem.* ***1989***, *54*, 4848.
[2364] See Ikeshita, K.-i.; Kihara, N.; Ogawa, A. *Tetrahedron Lett.* ***2005***, *46*, 8773.
[2365] Schoenebeck, F.; Murphy, J.A.; Zhou, S.-z.; Uenoyama, Y.; Miclo, Y.; Tuttle, T. *J. Am. Chem. Soc.* ***2007***, *129*, 13368.
[2366] Deasy, R.E.; Maguire, A.R. *Eur. J. Org. Chem.* ***2014***, 3737.
[2367] Graham, T.H.; Liu, W.; Shen, D.-M. *Org. Lett.* ***2011***, *13*, 6232.
[2368] Barbero, N.; Martin, R. *Org. Lett.* ***2012***, *14*, 796.
[2369] Saito, K.; Kondo, K.; Akiyama, T. *Org. Lett.* ***2015***, *17*, 3366.
[2370] Matsumura, T.; Niwa, T.; Nakada, M. *Tetrahedron Lett.* ***2012***, *53*, 4313.
[2371] Smith, M.B.; Wolinsky, J. *J. Chem. Soc., Perkin Trans. 2* ***1998***, 1431.
[2372] Back, T.G.; Baron, D.L.; Yang, K. *J. Org. Chem.* ***1993***, *58*, 2407.
[2373] Guo, H.; Ye, S.; Wang, J.; Zhang, Y. *J. Chem. Res. (S)* ***1997***, 114.
[2374] Wang, J.; Zhang, Y. *Synth. Commun.* ***1996***, *26*, 1931.

RSR reduction is desulfurization of thiophene derivatives. This proceeds with concomitant reduction of the double bonds. Many compounds have been made by alkylation of thiophene to 1,5-dialkylthiophenes, followed by reduction to give the alkane. Thiophenes can also be desulfurized to alkenes ($RCH_2CH{=}CHCH_2R'$) with a nickel boride catalyst prepared from $NiCl_2$ and $NaBH_4$ in methanol.[2375] Only one SR group of a dithioacetal is reduced by treatment with borane/pyridine in trifluoroacetic acid or in CH_2Cl_2 in the presence of $AlCl_3$.[2376] Phenyl selenides RSePh can be reduced to RH with Ph_3SnH[2377] and with nickel boride.[2378] Cleavage of the C—Se bond can also be achieved with SmI_2.[2379]

The desulfurization reduction of 1,3-dithianes and 1,3-dithiolanes used *t*-BuOK/1,4-cyclohexadiene with photostimulation.[2380] Aryl thiols were desulfurized to the arene using molybdenum hexacarbonyl.[2381] The reduction of *cis*-*N*-triflylaziridines or *N*,*N*-dialkyltriflylamides used 10 equivalents of Red-Al in toluene at −40 to 0 °C to give deprotected parent aziridines or amides.[2382]

The exact mechanism of the Raney nickel reactions is still in doubt, although they are probably of the free-radical type.[2383] It has been shown that reduction of thiophene proceeds through butadiene and butene, not through butane-1-thiol or other sulfur compounds, that is the sulfur is removed before the double bonds are reduced. This was demonstrated by isolation of the alkenes and the failure to isolate any potential sulfur-containing intermediates.[2384]

OS **IV**, 638; **V**, 419; **VI**, 109, 581, 601. See also, OS **VII**, 124, 476.

$$ArSO_3H \xrightarrow[\text{dil. } H_2SO_4]{135\text{-}200\ ^\circ C} ArH + H_2SO_4$$

The cleavage of sulfo groups from aromatic rings is the reverse of **11-7**.[2385] By the principle of microscopic reversibility, the mechanism is also the reverse.[2386] Dilution is generally used, as the reversibility of sulfonation decreases with increasing H_2SO_4 concentration. The reaction permits the sulfo group to be used as a blocking group to direct *meta* and then to be removed. The sulfo group has also been replaced by nitro and halogen groups. Sulfo groups have also been removed from the ring by heating with an alkaline solution of Raney nickel.[2387] In another catalytic process, aromatic sulfonyl bromides or chlorides are converted to aryl bromides or chlorides, respectively, on heating with a Rh

[2375] Schut, J.; Engberts, J.B.F.N.; Wynberg, H. *Synth. Commun.* ***1972***, *2*, 415.
[2376] Kikugawa, Y. *J. Chem. Soc., Perkin Trans. 1* ***1984***, 609.
[2377] Clive, D.L.J.; Chittattu, G.; Wong, C.K. *J. Chem. Soc., Chem. Commun.* ***1978***, 41.
[2378] Back, T.G. *J. Chem. Soc., Chem. Commun.* ***1984***, 1417.
[2379] Ogawa, A.; Ohya, S.; Doi, M.; Sumino, Y.; Sonoda, N.; Hirao, T. *Tetrahedron Lett.* ***1998***, *39*, 6341.
[2380] Oksdath-Mansilla, G.; Argüello, J.E.; Peñéñory, A.B. *Tetrahedron Lett.* ***2013***, *54*, 1515.
[2381] Wang, Z.; Kuninobu, Y.; Kanai, M. *Synlett* ***2014***, *25*, 1869.
[2382] Miyamoto, K.; Hoque, Md.M.; Ogasa, S. *J. Org. Chem.* ***2012***, *77*, 8317.
[2383] For a review, see Bonner, W.A.; Grimm, R.A. in Kharasch, N.; Meyers, C.Y. *The Chemistry of Organic Sulfur Compounds*, Vol. 2, Pergamon, NY, ***1966***, pp. 35–71, 410–413. Also see Friend, C.M.; Roberts, J.T. *Acc. Chem. Res.* ***1988***, *21*, 394.
[2384] Owens, P.J.; Ahmberg, C.H. *Can. J. Chem.* ***1962***, *40*, 941.
[2385] See Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Wiley, NY, ***1968***, pp. 185–214; Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 349–355. See also, Krylov, E.N. *J. Org. Chem. USSR* ***1988***, *24*, 709.
[2386] See Kozlov, V.A.; Bagrovskaya, N.A. *J. Org. Chem. USSR* ***1989***, *25*, 1152.
[2387] Feigl, F. *Angew. Chem.* ***1961***, *73*, 113.

catalyst.[2388] This reaction is similar to the decarbonylation of aromatic acyl halides mentioned in **14-26**.

OS **I**, 388; **II**, 97; **III**, 262; **IV**, 364. Also see, OS **I**, 519; **II**, 128; **V**, 1070.

19-75 Reduction of Sulfonyl Halides and Sulfonic Acid Derivatives to Thiols or Disulfides

$$RSO_2Cl \xrightarrow{LiAlH_4} RSH$$

Thiols can be prepared by the reduction of sulfonyl halides[2389] with $LiAlH_4$. Usually, the reaction is carried out on aromatic sulfonyl chlorides. Zinc and acetic acid, and HI, also give the reduction. Sulfonic acids have been reduced to thiols with a mixture of triphenylphosphine and either I_2 or a diaryl disulfide.[2390]

Disulfides RSSR can also be produced.[2391] Other sulfonic acid derivatives can be converted to disulfides. Esters such as PhSAc are converted to disulfides PhS—SPh with the reagent Clayan and microwave irradiation.[2392] Thiobenzoate derivatives PhSBz are similarly converted to PhS—SPh with SmI_2.[2393] In a similar manner, RS—SO_3Na is converted to RS—SR when heated with Sm metal in water.[2394]

OS **I**, 504; **IV**, 695; **V**, 843.

$$2\ RSO_2Cl + Zn \longrightarrow (RSO_2)_2Zn \xrightarrow{H^+} 2\ RSO_2H$$

This reaction is done mostly on aromatic sulfonyl chlorides, but the reaction has also been applied to alkyl compounds. Zinc, sodium sulfite, hydrazine, sodium sulfide, and other reducing agents have been used. For reduction of sulfonyl chlorides to thiols, see **19-82**.

OS **I**, 7, 492; **IV**, 674.

19-76 Reduction of Sulfoxides and Sulfones

Sulfoxides can be reduced to sulfides by many reagents,[2395] including $LiAlH_4$, HI, Bu_3SnH,[2396] H_2/Pd/C,[2397] $NaBH_4/NiCl_2$,[2398] $NaBH_4/I_2$,[2399] $NaBH_4/CoCl_2$,[2400]

[2388] Blum, J.; Scharf, G. *J. Org. Chem.* ***1970***, *35*, 1895.
[2389] Wardell, J.L. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 216–220.
[2390] Oae, S.; Togo, H. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 3802; ***1984***, *57*, 232.
[2391] See Narayana, C.; Padmanabhan, S.; Kabalka, G.W. *Synlett* ***1991***, 125.
[2392] Meshram, H.M.; Bandyopadhyay, A.; Reddy, G.S.; Yadav, J.S. *Synth. Commun.* ***1999***, *29*, 2705.
[2393] Yoo, B.W.; Baek, H.S.; Keum, S.R.; Yoon, C.M.; Nam, G.S.; Kim, S.H.; Kim, J.H. *Synth. Commun.* ***2000***, *30*, 4317.
[2394] Wang, L.; Li, P.; Zhou, L. *Tetrahedron Lett.* ***2002***, *43*, 8141.
[2395] See Kukushkin, V.Yu. *Russ. Chem. Rev.* ***1990***, *59*, 844; Madesclaire, M. *Tetrahedron* ***1988***, *44*, 6537; Drabowicz, J.; Togo, H.; Mikolajczyk, M.; Oae, S. *Org. Prep. Proced. Int.* ***1984***, *16*, 171; Drabowicz, J.; Numata, T.; Oae, S. *Org. Prep. Proced. Int.* ***1977***, *9*, 63. See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***.
[2396] Kozuka, S.; Furumai, S.; Akasaka, T.; Oae, S. *Chem. Ind. (London)* ***1974***, 496.
[2397] Ogura, K.; Yamashita, M.; Tsuchihashi, G. *Synthesis* ***1975***, 385.
[2398] Khurana, J.M.; Ray, A.; Singh, S. *Tetrahedron Lett.* ***1998***, *39*, 3829.
[2399] Karimi, B.; Zareyee, D. *Synthesis* ***2003***, 335.
[2400] Yakabe, S.; Hirano, M.; Morimoto, T. *Synth. Commun.* ***2010–2011***, *41*, 2251.

catecholborane,[2401] BH_3 with a Mo catalyst,[2402] a Mo/In system,[2403] Ti compounds,[2404] and Sm/methanolic NH_4Cl with ultrasound.[2405] Sulfones, however, are usually more difficult to reduce, but they have been reduced to sulfides with DibalH.[2406] Both sulfoxides and sulfones can be reduced by heating with sulfur (which is oxidized to SO_2), although the reaction with sulfoxides proceeds at a lower temperature.

The reaction of sulfoxides with $SOCl_2$ and Ph_3P gave the corresponding sulfide.[2407] Deoxygenation of sulfoxides to the corresponding sulfides used $NaHSO_3$ in the presence of catalytic I_2.[2408] An oxo rhenium complex was used for the deoxygenation of aromatic and aliphatic sulfoxides.[2409] The Ru-catalyzed hydrogenation of sulfoxides gave the sulfide.[2410] Diarylsulfoxides were reduced to the sulfide using $PhSiH_3$ with a Re catalyst.[2411] The electrochemical deoxygenation of aromatic amides or aromatic and aliphatic sulfoxides to obtain the corresponding sulfide was reported.[2412] Sulfoxides were reduced to the sulfide using the Cp_2TiCl_2/Ga system.[2413] A $NbCl_5$/In system has also been used.[2414] Ascorbic acid and NBS has been used to reduce sulfoxides to sulfides.[2415] The ionic liquids [DMIm][$MoO_2(NCS)_4$], [RPy][$MoO_2(NCS)_4$], or [BMIm][$MoO_2(NCS)_4$] catalyzed the PPh_3 reduction of sulfoxides.[2416]

It has been shown by using substrate labeled with ^{35}S that sulfoxides simply give up the oxygen to the sulfur, but that the reaction with sulfones is more complex, since ~75% of the original radioactivity of the sulfone is lost.[2417] This indicates that most of the sulfur in the sulfide product comes in this case from the *reagent*. There is no direct general method for the reduction of sulfones to sulfoxides, but an indirect method has been reported.[2418] Selenoxides can be reduced to selenides with a number of reagents.[2419]

OS **IX**, 446.

E. Reduction With Cleavage

19-77 Dealkylation of Amines and Amides

$$R'_2N{-}R \longrightarrow R'_2N{-}H$$

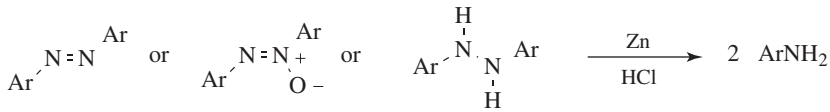
[2401] Harrison, D.J.; Tam, N.C.; Vogels, C.M.; Langler, R.F.; Baker, R.T.; Decken, A.; Westcott, S.A. *Tetrahedron Lett.* ***2004***, *45*, 8493.
[2402] Fernandes, A.C.; Romão, C.C. *Tetrahedron Lett.* ***2007***, *48*, 9176.
[2403] Yoo, B.W.; Song, M.S.; Park, M.C. *Synth. Commun.* ***2007***, *37*, 3089.
[2404] See Yoo, B.W.; Choi, K.H.; Kim, D.Y.; Choi, K.I.; Kim, J.H. *Synth. Commun.* ***2003***, 33, 53.
[2405] Yadav, J.S.; Subba Reddy, B.V.; Srinivas, C.; Srihari, P. *Synlett* ***2001***, 854.
[2406] Gardner, J.N.; Kaiser, S.; Krubiner, A.; Lucas, H. *Can. J. Chem.* ***1973***, *51*, 1419.
[2407] Jang, Y.; Kim, K.T.; Jeon, H.B. *J. Org. Chem.* ***2013***, *78*, 6328.
[2408] Abbasi, M.; Mohammadizadeh, M.R.; Moradi, Z. *Tetrahedron Lett.* ***2015***, *56*, 6610.
[2409] Sousa, S.C.A.; Bernardo, J.R.; Romão, C.C.; Fernandes, A.C. *Tetrahedron* ***2012***, *68*, 8194.
[2410] Mitsudome, T.; Takahashi, Y.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Angew. Chem. Int. Ed.* ***2014***, *53*, 8348.
[2411] Sousa, S.C.A.; Bernardo, J.R.; Wolff, M.; Machura, B.; Fernandes, A.C. *Eur. J. Org. Chem.* ***2014***, 1855.
[2412] Edinger, C.; Waldvogel, S.R. *Eur. J. Org. Chem.* ***2014***, 5144.
[2413] Yoo, B.W.; Min, S.K. *Synth. Commun.* ***2010–2011***, *41*, 2993.
[2414] Yoo, B.W.; Kim, H.M.; Kim, D. *Synth. Commun.* ***2013***, *43*, 2057.
[2415] Abbasi, M.; Mohammadizadeh, M.R.; Moradi, Z. *Bull. Chem. Soc. Jpn.* ***2016***, *89*, 405.
[2416] Bagherzadeh, M.; Ghazali-Esfahani, S. *New J. Chem.* ***2012***, 971; Bagherzadeh, M.; Ghazali-Esfahani, S. *Tetrahedron Lett.* ***2013***, *54*, 3765.
[2417] Kiso, S.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 1722. See also, Oae, S.; Nakai, M.; Tsuchida, Y.; Furukawa, N. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 445.
[2418] Still, I.W.J.; Ablenas, F.J. *J. Org. Chem.* ***1983***, *48*, 1617.
[2419] See Denis, J.N.; Krief, A. *J. Chem. Soc., Chem. Commun.* ***1980***, 544.

Certain amines can be dealkylated, usually under reductive conditions. Both *N*-allylamines and *N*,*N*-dialkyl allylamines are converted to the corresponding amine, $R_2N{-}H$, with DibalH/$NiCl_2$dppp[2420] and with $Pd(dba)_2$dppb.[2421] A mixture of $TiCl_3$ and Li converts *N*-benzylamines to the amine.[2422] In the case of *N*,*N*-dimethylamines, $RuCl_3$ and H_2O_2 demethylate the amine ($ArNMe_2 \rightarrow ArNHMe$).[2423] Tribenzylamines are dealkylated with ceric ammonium nitrate in aqueous acetonitrile to give the dibenzylamine.[2424] *N*-Benzyl indoles are cleaved to indoles with O_2, DMSO/KO*t*-Bu,[2425] or with tetrabutylammonium fluoride.[2426] *N*-Demethylation of alkaloids was reported using a Fe-mediated two-step procedure.[2427] *N*-Deallylation and *N*-debenzylation of amines occurs with alkali metals on silica.[2428]

The process is not limited to amines. Amides can also be dealkylated. *N*-Benzyl amides are debenzylated in the presence of NBS and AIBN.[2429] Scandium triflate removes *N*-*tert*-butyl from amides.[2430]

N-Alkyl sulfonamides are dealkylated with $PhI(OAc)_2$ and I_2 with ultrasound to give a primary sulfonamide.[2431] Similar results are obtained with H_5IO_6 and a Cr catalyst.[2432] *tert*-Butyl sulfonamides are cleaved to the primary sulfonamide with BCl_3.[2433]

19-78 Reduction of Azo, Azoxy, and Hydrazo Compounds to Amines



Azo, azoxy, and hydrazo compounds can all be reduced to amines.[2434] Metals (notably Zn) and acids, and $Na_2S_2O_4$, are frequently used as reducing agents, and Bu_3SnH with a Cu catalyst has been used.[2435] Borane reduces azo compounds to amines, although it does not reduce nitro compounds.[2436] $LiAlH_4$ does not reduce hydrazo compounds or azo compounds, although with the latter, hydrazo compounds are sometimes isolated. With azoxy compounds, $LiAlH_4$ gives only azo compounds (**19-72**). Note that azo compounds

[2420] Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* ***1998***, *39*, 4679.
[2421] Lemaire-Audoire, S.; Savignac, M.; Dupuis, C.; Genêt, J.-P. *Bull. Soc. Chim. Fr.* ***1995***, *132*, 1157; Lemaire-Audoire, S.; Savignac, M.; Genêt, J.-P.; Bernard, J.-M. *Tetrahedron Lett.* ***1995***, *36*, 1267.
[2422] Talukdar, S.; Banerji, A. *Synth. Commun.* ***1995***, *25*, 813.
[2423] Murahashi, S.-I.; Naota, T.; Miyaguchi, N.; Nakato, T. *Tetrahedron Lett.* ***1992***, *33*, 6991.
[2424] Bull, S.D.; Davies, S.G.; Mulvaney, A.W.; Prasad, R.S.; Smith, A.D.; Fenton, G. *Chem. Commun.* ***2000***, 337.
[2425] Haddach, A.A.; Kelleman, A.; Deaton-Rewoliwski, M.V. *Tetrahedron Lett.* ***2002***, *43*, 399.
[2426] Routier, S.; Saugé, L.; Ayerbe, N.; Couderet, G.; Mérour, J.-Y. *Tetrahedron Lett.* ***2002***, *43*, 589. For a related debenzylation see Meng, G.; He, Y.-P.; Chen, F.-E. *Synth. Commun.* ***2003***, *33*, 2593.
[2427] Kok, G.B.; Pye, C.C.; Singer, R.D.; Scammells, P.J. *J. Org. Chem.* ***2010***, *75*, 4806.
[2428] Nandi, P.; Dye, J.L.; Jackson, J.E. *Tetrahedron Lett.* ***2009***, *50*, 3864.
[2429] Baker, S.R.; Parsons, A.F.; Wilson, M. *Tetrahedron Lett.* ***1998***, *39*, 331.
[2430] Mahalingam, A.K.; Wu, X.; Alterman, M. *Tetrahedron Lett.* ***2006***, *47*, 3051.
[2431] Katohgi, M.; Togo, H. *Tetrahedron* ***2001***, *57*, 7481.
[2432] Xu, L.; Zhang, S.; Trudell, M.L. *Synlett* ***2004***, 1901.
[2433] Wan, Y.; Wu, X.; Kannan, M.A.; Alterman, M. *Tetrahedron Lett.* ***2003***, *44*, 4523.
[2434] See Newbold, B.T. in Patai, S. *The Chemistry of Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 629–637.
[2435] Tan, Z.; Qu, Z.; Chen, B.; Wang, J. *Tetrahedron* ***2000***, *56*, 7457.
[2436] Brown, H.C.; Subba Rao, B.C. *J. Am. Chem. Soc.* ***1960***, *82*, 681.

are reduced to the hydrazine by reaction with hydrazine hydrate in ethanol,[2437] or with Fe powder in ammonium chloride.[2438]

OS **I**, 49; **II**, 35, 39; **III**, 360; **X**, 327. Also see, OS **II**, 290.

19-79 Reduction of Disulfides to Thiols

$$\mathrm{RSSR} \xrightarrow[\mathrm{H^+}]{\mathrm{Zn}} 2\ \mathrm{RSH}$$

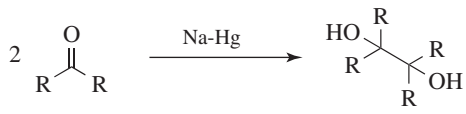
Disulfides can be reduced to thiols by mild reducing agents,[2439] such as Zn and dilute acid, In and NH_4Cl/EtOH,[2440] or Ph_3P and H_2O.[2441] The reaction can also be accomplished simply by heating with alkali.[2442] Among other reagents used have been $LiAlH_4$, $NaBH_4/ZrCl_4$,[2443] Mg/MeOH,[2444] and hydrazine or substituted hydrazines.[2445]

Aryl diselenides are similarly cleaved to selenols (ArSeH) with Cp_2TiH followed by $Ph_2I^+ X^-$.[2446]

OS **II**, 580. Also see, OS **IV**, 295.

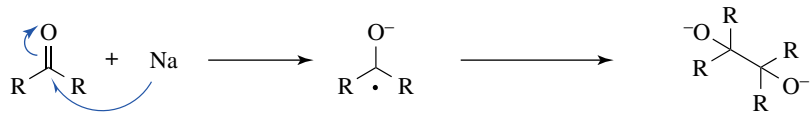
F. Reductive Coupling

19-80 Bimolecular Reduction of Aldehydes and Ketones to 1,2-Diols and Imines to 1,2-Diamines: Pinacol Coupling



1,2-Diols (pinacols) can be synthesized by reduction of aldehydes and ketones with active metals, such as Na, Mg, Ti,[2447] or Al.[2448] Aromatic ketones give better yields than aliphatic ones. The use of a Mg/MgI_2 mixture has been called the *Gomberg-Bachmann pinacol synthesis*.[2449] As with a number of other reactions involving Na, there is a direct electron transfer that converts the ketone or aldehyde to a ketyl, which dimerizes.

[2437] Zhang, C.-R.; Wang, Y.-L. *Synth. Commun.* ***2003***, *33*, 4205.
[2438] Mobinkhaledi, A.; Foroughhifar, N.; Jirandehi, H.F. *Monat. Chem.* ***2007***, *138*, 755.
[2439] Wardell, J.L. in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 220–229.
[2440] Reddy, G.V.S.; Rao, G.V.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 859.
[2441] Overman, L.E.; Smoot, J.; Overman, J.D. *Synthesis* ***1974***, 59.
[2442] See Danehy, J.P.; Hunter, W.E. *J. Org. Chem.* ***1967***, *32*, 2047.
[2443] Chary, K.P.; Rajaram, S.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 3905.
[2444] Sridhar, M.; Vadivel, S.K.; Bhalerao, U.T. *Synth. Commun.* ***1997***, *27*, 1347.
[2445] Maiti, S.N.; Spevak, P.; Singh, M.P.; Micetich, R.G.; Narender Reddy, A.V. *Synth. Commun.* ***1988***, *18*, 575.
[2446] Huang, X.; Wu, L.-L.; Xu, X.-H. *Synth. Commun.* ***2001***, *31*, 1871.
[2447] Hachiya, I.; Shimizu, M. *Tetrahedron Lett.* ***2014***, *55*, 2781.
[2448] See Fürstner, A.; Csuk, R.; Rohrer, C.; Weidmann, H. *J. Chem. Soc., Perkin Trans. 1* ***1988***, 1729. Also see Bian, Y.-J.; Liu, S.-M.; Li, J.-T.; Li, T.-S. *Synth. Commun.* ***2002***, *32*, 1169.
[2449] Gomberg, M.; Bachmann, W.E. *J. Am. Chem. Soc.* ***1927***, *49*, 236; *The Merck Index*, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, ***2006***, p. ONR-74; Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis*, 2nd ed., Wiley-Interscience, New Jersey, ***2005***, pp. 512–513. See Li, J.-T.; Chen, Y.-X.; Li, T.-S. *Synth. Commun.* ***2005***, *35*, 2831.



Other reagents have been used,[2450] including Sm,[2451] SmI_2,[2452] Pr,[2453] Yb,[2454] In with ultrasound,[2455] $InCl_3$ with Mg,[2456] $InCl_3$/Al in water,[2457] Al/$TiCl_3$,[2458] VCl_3/Zn in water,[2459] activated Mn,[2460] Zn,[2461] and a low-valent Ti reagent[2462] (see **19-80**). Unsymmetrical coupling between two different ketones has been accomplished using $TiCl_3$ in aqueous solution,[2463] and coupling of two different aldehydes has been achieved by the use of a V complex.[2464] Two aldehydes have also been coupled using Mg in water.[2465] Coupling leads to a mixture of *syn*- and *anti*-diols. "*Syn* selective" reagents are Cp_2TiCl_2/Mn,[2466] $TiCl_4$/Bu_4I,[2467] TiI_4,[2468] and $NbCl_3$.[2469] "*Anti* selective" coupling reactions are also known: Ti-salen,[2470] Mg with a $NiCl_2$ catalyst,[2471] and Sm/$SmCl_3$.[2472] Aryl aldehydes are coupled to give the bis(trimethylsilyl) ether using Mn, Me_3SiCl, and Cp_2TiCl_2.[2473]

Pinacol coupling has been reported using flow conditions (Sec. 7.D).[2474] A poly(ethylenedioxy)thiophene (PEDOT)-mediated pinacol rearrangement has been

[2450] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp.1111–1114.

[2451] Hélion, F.; Lannou, M.-I.; Namy, J.-L. *Tetrahedron Lett.* ***2003***, *44*, 5507. See Banik, B.K.; Banik, I.; Aounallah, N.; Castillo, M. *Tetrahedron Lett.* ***2005***, *46*, 7065.

[2452] Aspinall, H.C.; Greeves, N.; Valla, C. *Org. Lett.* ***2005***, *7*, 1919.

[2453] Drapo, J.R.; Priefer, R. *Synth. Commun.* ***2009***, *39*, 85.

[2454] Hou, Z.; Takamine, K.; Fujiwara, Y.; Taniguchi, K. *Chem. Lett.* ***1987***, 2061.

[2455] Lim, H.J.; Keum, G.; Kang, S.B.; Chung, B.Y.; Kim, Y. *Tetrahedron Lett.* ***1998***, *39*, 4367.

[2456] Mori, K.; Ohtaka, S.; Uemura, S. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 1497.

[2457] Wang, C.; Pan, Y.; Wu, A. *Tetrahedron* ***2007***, *63*, 429.

[2458] Li, J.-T.; Lin, Z.-P.; Qi, N.; Li, T.-S. *Synth. Commun.* ***2004***, *34*, 4339.

[2459] Xu, X.; Hirao, T. *J. Org. Chem.* ***2005***, *70*, 8594.

[2460] Rieke, R.D.; Kim, S.-H. *J. Org. Chem.* ***1998***, *63*, 5235. See Groth, U.; Jeske, M. *Synlett* ***2001***, 129.

[2461] Hekmatshoar, R.; Yavari, I.; Beheshtiha, Y.S.; Heravi, M.M. *Monat. Chem.* ***2001***, *132*, 689.

[2462] For a discussion of the mechanism, see Hashimoto, Y.; Mizuno, U.; Matsuoka, H.; Miyahara, T.; Takakura, M.; Yoshimoto, M.; Oshima, K.; Utimoto, K.; Matsubara, S. *J. Am. Chem. Soc.* ***2001***, *123*, 1503. See Duan, X.-F.; Feng, J.-X.; Zi, G.-F.; Zhang, Z.-B. *Synthesis* ***2009***, 277. Also see Kagayama, A.; Igarashi, K.; Mukaiyama, T. *Can. J. Chem.* ***2000***, *78*, 657.

[2463] Clerici, A.; Porta, O. *Tetrahedron* ***1983***, *39*, 1239. See Takahara, P.M.; Freudenberger, J.H.; Konradi, A.W.; Pedersen, S.F. *Tetrahedron Lett.* ***1989***, *30*, 7177.

[2464] Freudenberger, J.H.; Konradi, A.W.; Pedersen, S.F. *J. Am. Chem. Soc.* ***1989***, *111*, 8014.

[2465] Zhang, W.-C.; Li, C.-J. *J. Chem. Soc., Perkin Trans. 1* ***1998***, 3131.

[2466] Gansäuer, A.; Bauer, D. *Eur. J. Org. Chem.* ***1998***, 2673. Also see, Barden, M.C.; Schwartz, J. *J. Am. Chem. Soc.* ***1996***, *118*, 5484; Gansäuer, A. *Chem. Commun.* ***1997***, 457; Gansäuer, A. *Synlett* ***1997***, 363.

[2467] Tsuritani, T.; Ito, S.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* ***2000***, 65, 5066.

[2468] Hayakawa, R.; Shimizu, M. *Chem. Lett.* ***2000***, 724. For a *syn*-selective coupling with conjugated aldehydes see Shimizu, M.; Goto, H.; Hayakawa, R. *Org. Lett.* ***2002***, *4*, 4097.

[2469] Szymoniak, J.; Besançon, J.; Moïse, C. *Tetrahedron* ***1994***, *50*, 2841.

[2470] Chatterjee, A.; Bennur, T.H.; Joshi, N.N. *J. Org. Chem.* ***2003***, *68*, 5668.

[2471] Shi, L.; Fan, C.-A.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M. *Tetrahedron* ***2004***, *60*, 2851. See also Luanphaisarnnont, T.; Ndubaku, C.O.; Jamison, T.F. *Org. Lett.* ***2005***, *7*, 2937.

[2472] Matsukawa, S.; Hinakubo, Y. *Org. Lett.* ***2003***, *5*, 1221.

[2473] Dunlap, M.S.; Nicholas, K.M. *Synth. Commun.* ***1999***, *29*, 1097.

[2474] Sotto, N.; Cazorla, C.; Villette, C.; Billamboz, M.; Len, C. *J. Org. Chem.* ***2016***, *81*, 11065.

reported.[2475] A conjugated polymer poly-(*p*)-phenylene was used as a photoredox catalyst to promote pinacol coupling of aryl aldehydes with visible light to give the *vic*-diol.[2476] An Fe-catalyzed coupling reaction of aryl ketones has been reported, using a phenyltitanium reagent.[2477] Enantioselective pinacol couplings have been reported.[2478] A reversal of the pinacol coupling has been described.[2479]

Stereoselective pinacol coupling reactions are well known.[2480] Chiral additives with pinacol couplings lead to formation of a diol with moderate to good enantioselectivity.[2481] A crossed pinacol coupling was reported using Et_2Zn and, with a BINOL catalyst, gave good enantioselectivity.[2482] Enantioselective coupling was reported using a chiral salen/Mo complex.[2483] A combination of Mg and Me_3SiCl was also used to effect a crossed-pinacol.[2484] Chiral metal complexes in conjunction with a metal leads to diol formation with good enantioselectivity.[2485]

Intramolecular pinacol coupling reactions are known, giving cyclic 1,2-diols.[2486] Dialdehydes have been cyclized by reaction with $TiCl_3$ to give cyclic 1,2-diols in good yield.[2487] A variation of the pinacol coupling treats acyl nitriles with In metal and ultrasound to give a 1,2-diketone.[2488] Another variation couples acetals to give 1,2-diols.[2489]

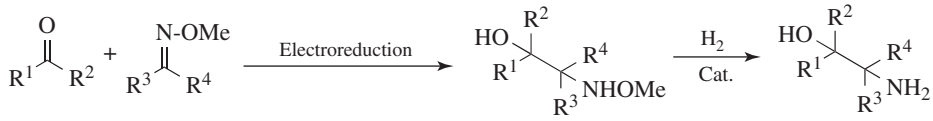
The photochemical dimerization of ketones to 1,2-diols is one of the most common photochemical reactions.[2490] The substrate, which is usually a diaryl or aryl alkyl ketone, is irradiated with UV light in the presence of a hydrogen donor, such as isopropyl alcohol, toluene, or an amine.[2491] In the case of benzophenone, irradiated in the presence of propan-2-ol, the ketone molecule initially undergoes $n \rightarrow \pi^*$ excitation, and the singlet species thus formed crosses to the T_1 state with high efficiency. The T_1 species abstracts hydrogen from the alcohol (Sec. 7.A.vii, category 4) and then dimerizes. The *i*-PrO• radical, which is formed by this process, reacts by atom transfer of H• to another molecule of ground-state benzophenone, producing acetone and a ketyl. This mechanism[2492] predicts that the quantum yield for the disappearance of benzophenone should be 2, since each quantum of light results in

[2475] Morton, M.D.; Smith, M.B. *Synlett* ***2011***, *22*, 2191.
[2476] Rouch, W.D.; Zhang, M.; McCulla, R.D. *Tetrahedron Lett.* ***2012***, *53*, 4942.
[2477] Hayashi, T.; Sasaki, K. *Chem. Lett.* ***2011***, *40*, 492.
[2478] Wen, J.; Liu, L.; Zhou, X.; Hu, R.; Xu, Y. *Tetrahedron: Asymmetry* ***2013***, *24*, 860.
[2479] Zalibera, M.; Nesvadba, P.; Gescheidt, G. *Org. Lett.* ***2013***, *15*, 4627; Tang, X.; Studer, A. *Org. Lett.* ***2016***, *18*, 4448.
[2480] For a review, see Chatterjee, A.; Joshi, N.N. *Tetrahedron* ***2006***, *62*, 12137.
[2481] Enders, D.; Ullrich, E.C. *Tetrahedron: Asymmetry* ***2000***, *11*, 3861.
[2482] Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* ***2003***, *125*, 2169.
[2483] Yang, H.; Wang, H.; Zhu, C. *J. Org. Chem.* ***2007***, *72*, 10029.
[2484] Maekawa, H.; Yamamoto, Y.; Shimada, H.; Yonemura, K.; Nishiguchi, I. *Tetrahedron Lett.* ***2004***, *45*, 3869.
[2485] See Takenaka, N.; Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* ***2004***, *126*, 13198.
[2486] See Handa, S.; Kachala, M.S.; Lowe, S.R. *Tetrahedron Lett.* ***2004***, *45*, 253.
[2487] McMurry, J.E.; Siemers, N.O. *Tetrahedron Lett.* ***1993***, *34*, 7891. See Raw, A.S.; Pedersen, S.F. *J. Org. Chem.* ***1991***, *56*, 830; Chiara, J.L.; Cabri, W.; Hanessian, S. *Tetrahedron Lett.* ***1991***, *32*, 1125.
[2488] Baek, H.S.; Lee, S.J.; Yoo, B.W.; Ko, J.J.; Kim, S.H.; Kim, J.H. *Tetrahedron Lett.* ***2000***, *41*, 8097.
[2489] Studer, A.; Curran, D.P. *Synlett* ***1996***, 255.
[2490] See Schönberg, A. *Preparative Organic Photochemistry*, Springer, NY, ***1968***, pp. 203–217; Neckers, D.C. *Mechanistic Organic Photochemistry*, Reinhold, NY, ***1967***, pp. 163–177; Turro, N.J. *Modern Molecular Photochemistry*, W.A. Benjamin, NY, ***1978***, pp. 363–385; Kan, R.O. *Organic Photochemisty*, McGraw-Hill, NY, ***1966***, pp. 222–229.
[2491] See Cohen, S.G.; Parola, A.; Parsons Jr., G.H. *Chem. Rev.* ***1973***, *73*, 141.
[2492] See Huyser, E.S.; Neckers, D.C. *J. Am. Chem. Soc.* ***1963***, *85*, 3641.

the conversion of 2 equivalents of benzophenone to a ketyl. Under favorable experimental conditions, the observed quantum yield does approach 2. Benzophenone abstracts hydrogen with very high efficiency. Other aromatic ketones are dimerized with lower quantum yields, and some (e.g., *p*-aminobenzophenone, *o*-methylacetophenone) cannot be dimerized at all in 2-propanol (although *p*-aminobenzophenone, for example, can be dimerized in cyclohexane[2493]). The reaction has also been carried out electrochemically.[2494]

A coupling reaction similar to pinacol coupling has been used with imines, which dimerize to give 1,2-diamines. A number of reagents have been used, including treatment with $TiCl_4$/Mg,[2495] In/aqueous EtOH,[2496] Zn/aqueous NaOH,[2497] or SmI_2.[2498]

Aldehydes are converted to 1,2-diamines by treatment with TMS_2NH, NaH, and Li metal in 5 M $LiClO_4$ in ether, with sonication.[2499] The reaction of an imine with Yb in THF/HMPA and then an aldehyde gives a 1,2-bis(imine).[2500] Aldehydes are coupled with *N*-sulfinyl imines to give *N*-sulfinyl amino alcohols in the presence of SmI_2.[2501] Hemi-aminals are coupled to give 1,2-diamines with TiI_4/Zn.[2502] Amides are converted to 1,2-diamines with Cp_2TiF_2 and $PhMeSiH_2$.[2503] Samarium(II) iodide was used to couple iminium salts, giving the 1,2-diamine.[2504] Ketones can be treated with Yb and then an imine to give amino alcohols.[2505] When electroreduction was used, it was possible to obtain cross products by coupling a ketone to an *O*-methyl oxime.[2506] The *N*-methoxyamino alcohol could then be reduced to the amino alcohol.[2506]



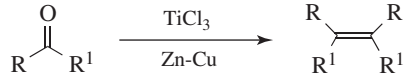
O-Methyl oxime ethers are coupled to give 1,2-diamines using Zn and $TiCl_4$.[2507] A photochemical coupling has also been reported.[2508]

An asymmetric aza-pinacol reaction has been developed using photoredox catalysis.[2509]

OS **I**, 459; **II**, 71; **X**, 312; **81**, 26.

[2493] Porter, G.; Suppan, P. *Proc. Chem. Soc.* ***1964***, 191.
[2494] Elinson, M.N.; Feducovich, S.K.; Dorofeev, A.S.; Vereshchagin, A.N.; Nikishin, G.I. *Tetrahedron* ***2000***, *56*, 9999. See Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 174–180; Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*, Springer, NY, ***1984***, pp. 137–140; Baizer, M.M. in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, ***1983***, pp. 639–689.
[2495] See Alexakis, A.; Aujard, I.; Mangeney, P. *Synlett* ***1998***, 873, 875.
[2496] Kalyanam, N.; Rao, G.V. *Tetrahedron Lett.* ***1993***, *34*, 1647.
[2497] Dutta, M.P.; Baruah, B.; Boruah, A.; Prajapati, D.; Sandu, J.S. *Synlett* ***1998***, 857.
[2498] Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* ***2004***, *6*, 4747.
[2499] Mojtahedi, M.M.; Saidi, M.R.; Shirzi, J.S.; Bolourtchian, M. *Synth. Commun.* ***2001***, *31*, 3587.
[2500] Jin, W.; Makioka, Y.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem.* ***2001***, *66*, 514.
[2501] Zhong, Y.-W.; Dong, Y.-Z.; Fang, K.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* ***2005***, *127*, 11956.
[2502] Yoshimura, N.; Mukaiyama, T. *Chem. Lett.* ***2001***, 1334.
[2503] Selvakumar, K.; Harrod, J.F. *Angew. Chem. Int. Ed.* ***2001***, *40*, 2129.
[2504] Kim, M.; Knettle, B.W.; Dahlén, A.; Hilmersson, G.; Flowers III, R.A. *Tetrahedron* ***2003***, *59*, 10397.
[2505] Su, W.; Yang, B. *Synth. Commun.* ***2003***, *33*, 2613.
[2506] Shono, T.; Kise, N.; Fujimoto, T. *Tetrahedron Lett.* ***1991***, *32*, 525.
[2507] Kise, N.; Ueda, N. *Tetrahedron Lett.* ***2001***, *42*, 2365.
[2508] Ortega, M.; Rodríguez, M.A.; Campos, P.J. *Tetrahedron* ***2004***, *60*, 6475.
[2509] Rono, L.J.; Yayla, H.G.; Wang, D.Y.; Armstrong, M.F.; Knowles, R.R. *J. Am. Chem. Soc.* ***2013***, *135*, 17735.

19-81 Bimolecular Reduction of Aldehydes or Ketones to Alkenes



Aldehydes and ketones, both aromatic and aliphatic (including cyclic ketones), can be converted in high yields to dimeric alkenes by treatment with low valent Ti,[2510] initially generated with $TiCl_3$ and a Zn/Cu couple.[2511] This is called the *McMurry reaction*.[2512] The reagent produced in this way is called a *low-valent titanium reagent*, and the reaction has also been accomplished[2513] with low-valent Ti reagents prepared in other ways, for example, from Mg and a $TiCl_3$/THF complex,[2514] from $TiCl_4$ and Zn or Mg,[2515] from $TiCl_3$ and $LiAlH_4$,[2516] and from $TiCl_3$ and K or Li[2517] (see **17-16**). Microwave irradiation has been used to facilitate the coupling.[2518] Unsymmetrical alkenes can be prepared from a mixture of two ketones in a cross-coupling reaction, if one is in excess.[2519] An aldehyde and a ketone were cross-coupled using $Yb(OTf)_3$, for example.[2520] The mechanism consists of initial coupling of two radical species to give a 1,2-dioxygen compound (a titanium pinacolate), which is then deoxygenated.[2521]

The reaction has been used to convert dialdehydes and diketones to cycloalkenes.[2522] Rings of 3–16 and 22 members have been closed in this way, as in the conversion of 2,2-dimethyl-1,3-diphenylpropane-1,3-dione to 1,2-diphenyl-3,3-dimethylcyclopropene.[2523] The same reaction on an ester with a distal keto moiety gives a cycloalkanone.[2524] Esters were coupled to diaryl ketones using $TiCl_4$/Zn to give α,α-diaryl α-hydroxy ketones.[2525] Indoles have been prepared form ortho-acyl amides with Ti(powder) and Me_3SiCl[2526] or with $TiCl_3/C_8K$.[2527]

OS **VII**, 1.

[2510] See Rele, S.; Chattopadhyay, S.; Nayak, S.K. *Tetrahedron Lett.* ***2001***, *42*, 9093.

[2511] McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. *J. Org. Chem.* ***1978***, *43*, 3255. For an optimized procedure, see McMurry, J.E.; Lectka, T.; Rico, J.G. *J. Org. Chem.* ***1989***, *54*, 3748.

[2512] See McMurry, J.E. *Chem. Rev.* ***1989***, *89*, 1513; *Acc. Chem. Res.* ***1983***, *16*, 405; Lenoir, D. *Synthesis* ***1989***, 883. For related reviews, see Kahn, B.E.; Rieke, R.D. *Chem. Rev.* ***1988***, *88*, 733; Pons, J.; Santelli, M. *Tetrahedron* ***1988***, *44*, 4295. See Duan, X.-F.; Zeng, J.; Lü, J.-W.; Zhang, Z.-B. *J. Org. Chem.* ***2006***, *71*, 9873.

[2513] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 305–308.

[2514] Tyrlik, S.; Wolochowicz, I. *Bull. Soc. Chim. Fr.* ***1973***, 2147.

[2515] Carroll, A.R.; Taylor, W.C. *Aust. J. Chem.* ***1990***, *43*, 1439.

[2516] Dams, R.; Malinowski, M.; Geise, H.J. *Bull. Soc. Chim. Belg.* ***1982***, *91*, 149, 311; Bottino, F.A.; Finocchiaro, P.; Libertini, E.; Reale, A.; Recca, A. *J. Chem. Soc., Perkin Trans. 2* ***1982***, 77. See, however, McMurry, J.E.; Fleming, M.P. *J. Org. Chem.* ***1976***, *41*, 896.

[2517] Rele, S.; Talukdar, S.; Banerji, A.; Chattopadhyay, S. *J. Org. Chem.* ***2001***, *66*, 2990.

[2518] Stuhr-Hansen, N. *Tetrahedron Lett.* ***2005***, *46*, 5491.

[2519] See Chisholm, M.H.; Klang, J.A. *J. Am. Chem. Soc.* ***1989***, *111*, 2324.

[2520] Curini, M.; Epifano, F.; Maltese, F.; Marcotullio, M.C. *Eur. J. Org. Chem.* ***2003***, 1631.

[2521] Dams, R.; Malinowski, M.; Westdorp, I.; Geise, H.Y. *J. Org. Chem.* ***1982***, *47*, 248. See Villiers, C.; Ephritikhine, M. *Angew. Chem. Int. Ed.* ***1997***, *36*, 2380; Stahl, M.; Pindur, U.; Frenking, G. *Angew. Chem. Int. Ed.* ***1997***, *36*, 2234.

[2522] McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. *J. Org. Chem.* ***1978***, *43*, 3255.

[2523] Baumstark, A.L.; McCloskey, C.J.; Witt, K.E. *J. Org. Chem.* ***1978***, *43*, 3609.

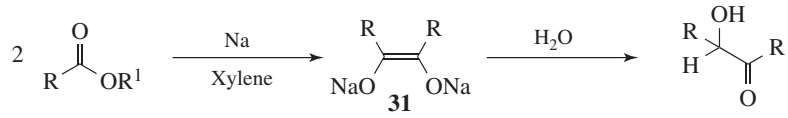
[2524] McMurry, J.E.; Miller, D.D. *J. Am. Chem. Soc.* ***1983***, *105*, 1660.

[2525] Kise, N.; Sakurai, T. *J. Org. Chem.* ***2015***, *80*, 3496.

[2526] Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* ***1995***, *117*, 4468.

[2527] Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* ***1994***, *59*, 5215.

19-82 Acyloin Ester Condensation



When carboxylic esters are heated with sodium in refluxing ether or benzene, a bimolecular reduction takes place to give a bis(alkoxide), **31**. After hydrolysis, the product is an α-hydroxy ketone (called an acyloin).[2528] The reaction, called the *acyloin ester condensation* (or just *acyloin condensation*),[2529] is quite successful when R is alkyl. Acyloins with long chains have been prepared in this way, for example, R = $C_{17}H_{35}$, but for high molecular weight esters, toluene or xylene is used as the solvent. Modifications to this procedure have been reported, including an ultrasound-promoted acyloin condensation in ether,[2530] which improved the yields of four-, five-, and six-membered rings, and Olah's procedure, which was also done in ether.[2531] Triazolium precatalysts in the presence of base were used for crossed acyloin condensation reactions of aliphatic and *ortho*-substituted aromatic aldehydes.[2532] The crossed acyloin condensation of aromatic aldehydes and acetaldehyde was catalyzed by *N*-heterocyclic carbenes.[2533]

The acyloin condensation has been used with great success, in xylene at reflux, to prepare cyclic acyloins from diesters.[2534] The yields are 50–60% for the preparation of 6- and 7-membered rings, 30–40% for 8- and 9-membered, and 60–95% for rings of 10–20 members. Even larger rings have been closed in this manner. Indeed, this is one of the best ways of closing rings of 10 members or more. The reaction has been used to close four-membered rings,[2535] although this is generally unsuccessful. For larger rings, the presence of double or triple bonds does not interfere.[2536] Even a benzene ring can be present, and many paracyclophane derivatives (**32**) with $n = 9$ or more have been synthesized in this manner.[2537] The acyloin condensation was used to prepare the first reported catenane[2538] (Sec. 3.D). This synthesis of a catenane was produced in low yield and relied on chance for threading the molecules before ring closure.

Yields in the acyloin condensation can be improved by running the reaction in the presence of chlorotrimethylsilane (Me_3SiCl), in which case the dianion **31** is converted to the bis(silyl) enol ether **33**, which can be isolated and subsequently hydrolyzed to the acyloin

[2528] See Bloomfield, J.J.; Owsley, D.C.; Nelke, J.M. *Org. React.* ***1976***, *23*, 259. For a list of reactions, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1313–1315.

[2529] Also see Daynard, T.S.; Eby, P.S.; Hutchinson, J.H. *Can. J. Chem.* ***1993***, *71*, 1022.

[2530] Fadel, A.; Canet, J,-L.; Salaün, J. *Synlett* ***1990***, 89.

[2531] Olah, G.A.; Wu, A. *Synthesis* ***1991***, 1177.

[2532] O'Toole, S.E.; Rose, C.A.; Gundala, S.; Zeitler, K.; Connon, S.J. *J. Org. Chem.* ***2011***, *76*, 347.

[2533] Jin, M.Y.; Kim, S.M.; Han, H.; Ryu, D.H.; Yang, J.W. *Org. Lett.* ***2011***, *13*, 880; Ramanjaneyulu, B.T.; Mahesh, S.; Anand, R.V. *Org. Lett.* ***2015***, *17*, 6.

[2534] See Finley, K.T. *Chem. Rev.* ***1964***, *64*, 573.

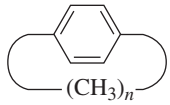
[2535] Bloomfield, J.J.; Irelan, J.R.S. *J. Org. Chem.* ***1966***, *31*, 2017.

[2536] Cram, D.J.; Gaston, L.K. *J. Am. Chem. Soc.* ***1960***, *82*, 6386.

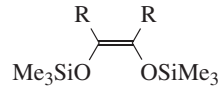
[2537] For a review, see Cram, D.J. *Rec. Chem. Prog.* ***1959***, *20*, 71.

[2538] For reviews of the synthesis of catenanes, see Sauvage, J. *Acc. Chem. Res.* ***1990***, *23*, 319; *Nouv. J. Chim.* ***1985***, *9*, 299; Dietrich-Buchecker, C.O.; Sauvage, J. *Chem. Rev.* ***1987***, *87*, 795.

with aqueous acid.[2539] This is now the standard way to conduct the acyloin condensation. Among other things, this method inhibits the *Dieckmann condensation*[2540] (**16-81**), which otherwise competes with the acyloin condensation when a five-, six-, or seven-membered ring can be closed. (Note that the ring formed by a Dieckmann condensation is always one carbon atom smaller than that formed by an acyloin condensation of the same substrate.) The Me_3SiCl method is especially good for the closing of four-membered rings.[2541]



32



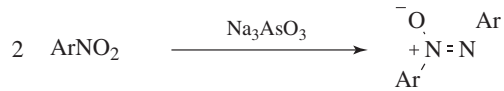
33

The mechanism is usually presumed to have a diketone (RCOCOR) as an intermediate,[2542] since small amounts of it are usually isolated as side products, and when it is resistant to reduction (e.g., *t*-Bu—COCO—*t*-Bu) it is the major product. A possible sequence involves formation of a ketyl and coupling. Subsequent loss of two alkoxide units to give a 1,2-diketone and final reaction with sodium to give **31**. A large surface area for the Na is usually required for good results in this coupling, consistent with a surface reaction. In order to form large rings, the two ends of the chain must approach each other even although this is conformationally unfavorable for long chains. However, it may be postulated that the two ends become attached to nearby sites on the surface[2543] of the Na. Although high dilution techniques are not always necessary, effective stirring (high speed stirrer at 2000–2500 rpm) is usually required to generate "sodium sand." Highly pure Na gives poorer results because the presence of a small percentage of K is important. Up to 50% potassium (1:1 Na/K)[2544] has been used in acyloin condensations.

In a related reaction, aromatic carboxylic acids were condensed to α-diketones (2ArCOOH → ArCOCOAr) on treatment with excess Li in dry THF in the presence of ultrasound.[2545] It is noted that the organocatalytic rearrangement of α-hydroxy acetals to α-alkoxy ketones proceeded with good enantioselectivity.[2546]

OS **II**, 114; **IV**, 840; **VI**, 167.

19-83 Reduction of Nitro Compounds to Azoxy Compounds



Azoxy compounds can be obtained from nitro compounds with certain reducing agents, notably sodium arsenite, sodium ethoxide, NaTeH,[2547] and glucose. The most probable

[2539] Schräpler, U.; Rühlmann, K. *Chem. Ber.* ***1964***, *97*, 1383. See Rühlmann, K. *Synthesis* ***1971***, 236.
[2540] Bloomfield, J.J. *Tetrahedron Lett.* ***1968***, 591.
[2541] Bloomfield, J.J.; Martin, R.A.; Nelke, J.M. *J. Chem. Soc., Chem. Commun.* ***1972***, 96.
[2542] Another mechanism has been proposed: Bloomfield, J.J.; Owsley, D.C.; Ainsworth, C.; Robertson, R.E. *J. Org. Chem.* ***1975***, *40*, 393.
[2543] For the preparation of high-surface sodium, see Makosza, M.; Grela, K. *Synlett* ***1997***, 267.
[2544] Vogel, I.A. *A Textbook of Practical Organic Chemistry*, 3rd ed, Wiley, NY, ***1966***, p. 856.
[2545] Karaman, R.; Fry, J.L. *Tetrahedron Lett.* ***1989***, *30*, 6267.
[2546] Wu, H.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* ***2017***, *56*, 5858.
[2547] Osuka, A.; Shimizu, H.; Suzuki, H. *Chem. Lett.* ***1983***, 1373. See Ohe, K.; Uemura, S.; Sugita, N.; Masuda, H.; Taga, T. *J. Org. Chem.* ***1989***, *54*, 4169.

mechanism with most reagents is that one molecule of nitro compound is reduced to a nitroso compound and another to a hydroxylamine (**19-50**), and these combine (**12-50**). The combination step is rapid compared to the reduction process.[2548] Nitroso compounds can be reduced to azoxy compounds with triethylphosphite or triphenylphosphine[2549] or with an alkaline aqueous solution of an alcohol.[2550]

OS **II**, 57.

19-84 Reduction of Nitro Compounds to Azo Compounds

$$2\ ArNO_2 \xrightarrow{LiAlH_4} Ar{-}N{=}N{-}Ar$$

Nitro compounds can be reduced to azo compounds with various reducing agents, of which $LiAlH_4$ and Zn and alkali are the most common. A combination of triethylammonium formate and lead in methanol is also effective.[2551] With many of these reagents, slight differences in conditions can lead either to the azo or azoxy (**19-83**) compound. When the reducing agent was $NaBH_4$,[2552] it was shown that azoxy compounds were intermediates. Nitroso compounds can be reduced to azo compounds with $LiAlH_4$. Dicarborane, with a catalytic amount of acetic acid, reduces aromatic nitro compounds to the amine.[2553]

Nitro compounds can be further reduced to hydrazo compounds with Zn and sodium hydroxide, with hydrazine hydrate and Raney nickel,[2554] or with $LiAlH_4$ mixed with a metal chloride such as $TiCl_4$ or VCl_3.[2555] The reduction has also been accomplished electrochemically.

OS **III**, 103.

G. Reactions in Which an Organic Substrate Is Both Oxidized and Reduced

Some reactions that belong in this category have been considered in earlier chapters. Among these are the *Tollens' condensation* (**16-43**), the benzil-benzilic acid rearrangement (**18-6**), and the *Wallach rearrangement* (**18-43**).

19-85 The Cannizzaro Reaction

$$2\ ArCHO \xrightarrow{NaOH} ArCH_2OH + ArCOO^-$$

Aromatic aldehydes, and aliphatic ones with no α hydrogen, give the *Cannizzaro reaction* when treated with NaOH or other strong bases.[2556] Reaction with triethylamine and

[2548] Ogata, Y.; Mibae, J. *J. Org. Chem.* ***1962***, *27*, 2048.
[2549] Bunyan, P.J.; Cadogan, J.I.G. *J. Chem. Soc.* ***1963***, 42.
[2550] See Hutton, J.; Waters, W.A. *J. Chem. Soc. B* ***1968***, 191. See also, Porta, F.; Pizzotti, M.; Cenini, S. *J. Organomet. Chem.* ***1981***, *222*, 279.
[2551] Srinavasa, G.R.; Abiraj, K.; Gowda, D.C. *Tetrahedron Lett.* ***2003***, *44*, 5835.
[2552] Hutchins, R.O.; Lamson, D.W.; Rufa, L.; Milewski, C.; Maryanoff, B. *J. Org. Chem.* ***1971***, *36*, 803.
[2553] Bae, J.W.; Cho, Y.J.; Lee, S.H.; Yoon, C.M. *Tetrahedron Lett.* ***2000***, *41*, 175.
[2554] Furst, A.; Moore, R.E. *J. Am. Chem. Soc.* ***1957***, *79*, 5492.
[2555] Olah, G.A. *J. Am. Chem. Soc.* ***1959***, *81*, 3165.
[2556] See Geissman, T.A. *Org. React.* ***1944***, *2*, 94.

$MgBr_2$ gave a room temperature Cannizzaro reaction.[2557] The reaction is mediated by organobases.[2558] In this reaction, one molecule of aldehyde oxidizes another to the acid and is itself reduced to the primary alcohol. Aldehydes with an α hydrogen do not give the reaction, because when these compounds are treated with base the aldol reaction (**16-34**) is much faster.[2559] Normally, the best yield of acid or alcohol is 50% each, but this can be altered in certain cases. Solvent-free reactions are known.[2560] On the other hand, high yields of alcohol can be obtained from almost any aldehyde by running the reaction in the presence of formaldehyde.[2561] In this case, the formaldehyde reduces the aldehyde to the alcohol and is itself oxidized to formic acid. In such a case, where the oxidant aldehyde differs from the reductant aldehyde, the reaction is called the *crossed-Cannizzaro reaction*.[2562] The *Tollens' condensation* (**16-43**) includes a crossed Cannizzaro reaction as its last step. A Cannizzaro reaction with 1,4-dialdehydes (note that α hydrogen atoms are present here) and a Rh catalyst gives ring closure to form a lactone, as in the closure of succinaldehyde (1,4-butanedial) to γ-butyrolactone [dihydrofuran-2(3*H*)-one].[2563] The lactone is derived from the hydroxy acid that would form and spontaneously cyclize from a normal Cannizzaro reaction. Chiral additives have been used, but with bis(oxazolidine) derivatives the reaction proceeded with poor enantioselectivity.[2564] Polyurethane nanomicelles and polymeric ionic solvents have been used for the Cannizzaro reaction.[2565] The asymmetric intramolecular Cannizzaro reaction of aryl and alkyl glyoxals with alcohols, with a Cu/sterically hindered trisoxazoline catalyst, gave the α-hydroxy ester.[2566] Cannizzaro-type reactions were catalyzed by lipase and done in water.[2567] α-Keto aldehydes undergo an internal Cannizzaro reaction, where the product is an α-hydroxy carboxylate.[2568] This product is also obtained on alkaline hydrolysis of compounds of the formula $RCOCHX_2$. Similar reactions have been performed on α-keto acetals[2569] and γ-keto aldehydes.

The mechanism[2570] of the Cannizzaro reaction[2571] involves a hydride shift (an example of mechanism type 2, Sec. 19.A). First, hydroxide adds to the C=O to give a tetrahedral intermediate, $RCHC(OH)O^-$, which may lose a proton in the basic solution to give the di-ion, $RCHC(O^-)_2$. The strong electron-donating character of O^- greatly facilitates the ability of the aldehyde hydrogen to leave with its electron pair. Hydride is transferred to

[2557] Abaee, M.S.; Sharifi, R.; Mojtahedi, M.M. *Org. Lett.* ***2005***, *7*, 5893.
[2558] Basavaiah, D.; Sharada, D.S.; Veerendhar, A. *Tetrahedron Lett.* ***2006***, *47*, 5771.
[2559] An exception is cyclopropanecarboxaldehyde: van der Maeden, F.P.B.; Steinberg, H.; de Boer, T.J. *Recl. Trav. Chim. Pays-Bas* ***1972***, *91*, 221.
[2560] Yoshizawa, K.; Toyota, S.; Toda, F. *Tetrahedron Lett.* ***2001***, *42*, 7983.
[2561] See Thakuria, J.A.; Baruah, M.; Sandhu, J.S. *Chem. Lett.* ***1999***, 995.
[2562] See Reddy, B.V.S.; Srinivas, R.; Yadav, J.S.; Ramalingam, T. *Synth. Commun.* ***2002***, *32*, 219.
[2563] Bergens, S.H.; Fairlie, D.P.; Bosnich, B. *Organometallics* ***1990***, *9*, 566.
[2564] Russell, A.E.; Miller, S.P.; Morken, J.P. *J. Org. Chem.* ***2000***, *65*, 8381.
[2565] Daemi, H.; Barikani, M.; Jahani, M. *New J. Chem.* ***2016***, 2121.
[2566] Wang, P.; Tao, W.-J.; Sun, X.-L.; Liao, S.; Tang, Y. *J. Am. Chem. Soc.* ***2013***, *135*, 16849.
[2567] Arora, B.; Pandey, P.S.; Gupta, M.N. *Tetrahedron Lett.* ***2014***, *55*, 3920.
[2568] Russell, G.A.; Mikol, G.J. *J. Am. Chem. Soc.* ***1966***, *88*, 6498; Prey, V.; Berbdk, H.; Steinbauer, E. *Monatsh. Chem.* ***1960***, *91*, 1196; ***1962***, *93*, 237.
[2569] Thompson, J.E. *J. Org. Chem.* ***1967***, *32*, 3947.
[2570] See Ashby, E.C.; Coleman III, D.T.; Gamasa, M.P. *J. Org. Chem.* ***1987***, *52*, 4079; Fuentes, A.; Marinas, J.M.; Sinisterra, J.V. *Tetrahedron Lett.* ***1987***, *28*, 2947.
[2571] See Swain, C.G.; Powell, A.L.; Sheppard, W.A.; Morgan, C.R. *J. Am. Chem. Soc.* ***1979***, *101*, 3576; Watt, C.I.F. *Adv. Phys. Org. Chem.* ***1988***, *24*, 57 (pp. 81–86).

another molecule of aldehyde. The hydride can come from the tetrahedral intermediate or the dianion. Evidence for this mechanism is: (i) the reaction can be first order in base and second order in substrate or, at higher base concentrations, second order in each; and (ii) when the reaction was run in D_2O, the recovered alcohol contained no α deuterium,[2572] indicating that the hydrogen comes from another equivalent of aldehyde and not from the medium.[2573]

An aza-Cannizzaro reaction is known.[2574]

OS **I**, 276; **II**, 590; **III**, 538; **IV**, 110.

19-86 The Tishchenko Reaction

$$2\ \mathrm{RCHO} \xrightarrow{\mathrm{Al(OEt)_3}} \mathrm{RCOOCH_2R}$$

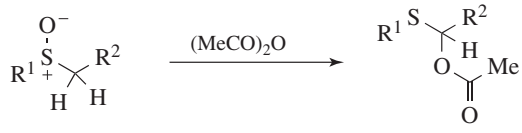
When aldehydes, with or without an α hydrogen, are treated with aluminum ethoxide, one molecule is oxidized and another reduced, as in **19-85**, but here they are found as the ester. The process is called the *Tishchenko reaction*.[2575] Crossed-Tishchenko reactions are also possible. With more strongly basic alkoxides, such as Mg or sodium alkoxides, aldehydes with an α hydrogen give the *aldol reaction*. Treatment of a dialdehyde, such as phthalic dicarboxaldehyde (phthalaldehyde) with CaO, leads to a lactone.[2576] Like **19-85**, this reaction has a mechanism that involves hydride transfer.[2577] The Tishchenko reaction can also be catalyzed[2578] by Ru complexes,[2579] organoactinides,[2580] and alkaline earth amides.[2581] Both CaO (noted above) and SrO have been used as catalysts.[2582] The bis Al(*O-i*-Pr)$_2$ derivative of catechol has also been used as a catalyst.[2583]

Selenide ions, generated *in situ* from Bu_2Se_2 and Bu_2Mg, catalyzed the Tishchenko reaction.[2584] The crossed Tishchenko reaction of two aldehydes, catalyzed by Ni with a NHC ligand, gave the corresponding ester.[2585] A *Tishchenko-aldol transfer reaction* was reported using β-hydroxy ketones and an aldehydes with an $AlMe_3$ catalyst, giving a mono acyl diol.[2586] Thiolate has been used the catalyze the crossed Tishchenko reaction.[2587]

OS **I**, 104.

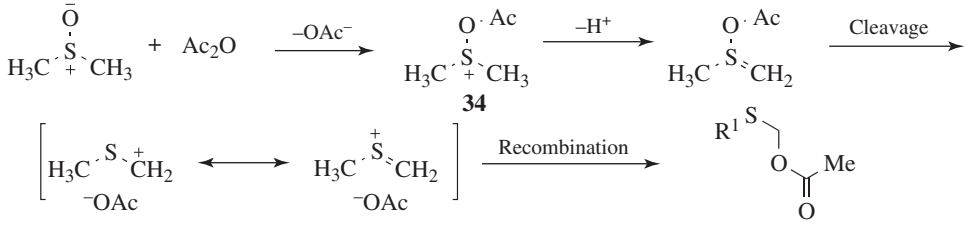
[2572] See Hauser, C.R.; Hamrick Jr., P.J.; Stewart, A.T. *J. Org. Chem.* ***1956***, *21*, 260.
[2573] See Swain, C.G.; Powell, A.L.; Lynch, T.J.; Alpha, S.R.; Dunlap, R.P. *J. Am. Chem. Soc.* ***1979***, *101*, 3584. See, however, Chung, S. *J. Chem. Soc., Chem. Commun.* ***1982***, 480.
[2574] Bandichhor, R. *Tetrahedron Lett.* ***2017***, *58*, 1891.
[2575] For a review, see Seki, T.; Nakajo, T.; Onaka, M. *Chem. Lett.* ***2006***, *35*, 824.
[2576] Seki, T.; Hattori, H. *Chem. Commun.* ***2001***, 2510.
[2577] See Saegusa, T.; Ueshima, T.; Kitagawa, S. *Bull. Chem. Soc. Jpn.* ***1969***, *42*, 248; Ogata, Y.; Kishi, I. *Tetrahedron* ***1969***, *25*, 929.
[2578] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1653–1655.
[2579] Ito, T.; Horino, H.; Koshiro, Y.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* ***1982***, *55*, 504.
[2580] Andrea, T.; Barnea, E.; Eisen, M.S. *J. Am. Chem. Soc.* ***2008***, *130*, 2454.
[2581] Crimmin, M.R.; Barrett, A.G.M.; Hill, M.S.; Procopiou, P.A. *Org. Lett.* ***2007***, *9*, 331.
[2582] Seki, T.; Akutsu, K.; Hattori, H. *Chem. Commun.* ***2001***, 1000.
[2583] Simpura, I.; Jevalainen, V. *Tetrahedron* ***2001***, *57*, 9867.
[2584] Curran, S.P.; Connon, S.J. *Org. Lett.* ***2012***, *14*, 1074.
[2585] Dzik, W.I.; Gooßen, L.J. *Angew. Chem. Int. Ed.* ***2011***, *50*, 11047.
[2586] Simpura, I.; Nevalainen, V. *Tetrahedron Lett.* ***2001***, *42*, 3905; Cavazzini, M.; Pozzi, G.; Quici, S.; Maillard, D.; Sinou, D. *Chem. Commun.* ***2001***, 1220.
[2587] Curran, S.P.; Connon, S.J. *Angew. Chem. Int. Ed.* ***2012***, *51*, 10866.

19-87 The Pummerer Rearrangement[2588]



When sulfoxides bearing an α hydrogen are treated with acetic anhydride, the product is an α-acetoxy sulfide. This is one example of *the Pummerer rearrangement*,[2589] in which the sulfur is reduced while an adjacent carbon is oxidized.[2590] The product is readily hydrolyzed (**10-6**) to the aldehyde R_2CHO.[2591] Besides acetic anhydride, other anhydrides and acyl halides give similar products. Inorganic acids, such as HCl, also give the reaction, and $RSOCH_2R'$ can be converted to $RSCHClR'$ in this way. Sulfoxides can also be converted to α-halo sulfides[2592] by other reagents, including sulfuryl chloride, NBS, and NCS. Enantioselective Pummerer rearrangements are known.[2593] Uncatalyzed thermal rearrangements are also known.[2594]

A four-step mechanism[2595] has been proposed for the reaction between acetic anhydride and DMSO.[2596]



For DMSO and acetic anhydride, the final step is intermolecular, as shown by ^{18}O isotopic labeling studies.[2597] With other substrates, however, this step can be inter- or intramolecular, depending on the structure of the sulfoxide.[2598] Depending on the substrate and reagent, any of the first three steps can be rate determining. In the case of DMSO treated with $(F_3CCO)_2O$, the intermediate corresponding to **34**[2599] could be isolated at low

[2588] See Bur, S.K.; Padwa, A. *Chem. Rev.* ***2004***, *104*, 2401.
[2589] For a review, see Feldman, K.S. *Tetrahedron* ***2006***, *62*, 5003. Also see Smith, L.H.S.; Coote, S.C.; Sneddon, H.F.; Procter, D.J. *Angew. Chem. Int. Ed.* ***2010***, *49*, 5832.
[2590] See De Lucchi, O.; Miotti, U.; Modena, G. *Org. React.* ***1991***, *40*, 157.
[2591] See Sugihara, H.; Tanikaga, R.; Kaji, A. *Synthesis* ***1978***, 881.
[2592] See Dilworth, B.M.; McKervey, M.A. *Tetrahedron* ***1986***, *42*, 3731.
[2593] See Kita, Y.; Shibata, N.; Kawano, N.; Tohjo, T.; Fujimori, C.; Matsumoto, K. *Tetrahedron Lett.* ***1995***, *36*, 115.
[2594] Wladislaw, B.; Marzorati, L.; Biaggio, F.C. *J. Org. Chem.* ***1993***, *58*, 6132.
[2595] See Patil, M.; Loerbroks, C.; Thiel, W. *Org. Lett.* ***2013***, *15*, 1682.
[2596] See Kita, Y.; Shibata, N.; Yoshida, N.; Fukui, S.; Fujimori, C. *Tetrahedron Lett.* ***1994***, *35*, 2569.
[2597] Oae, S.; Kitao, T.; Kawamura, S.; Kitaoka, Y. *Tetrahedron* ***1963***, *19*, 817.
[2598] See Itoh, O.; Numata, T.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 266; Oae, S.; Itoh, O.; Numata, T.; Yoshimura, T. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 270.
[2599] See Marino, J.P. *Top. Sulfur Chem.* ***1976***, *1*, 1.

temperature, and on warming gave the expected product.[2600] There is much other evidence for this mechanism.[2601]

Methiothiomethyl esters were prepared from carboxylic acids via a microwave-assisted Pummerer rearrangement with DMSO.[2602] A Cu-catalyzed Pummerer-type reaction has been reported.[2603] A sila-Pummerer rearrangement has been reported.[2604] A seleno-Pummerer reaction gave O, Se acetals.[2605]

19-88 The Willgerodt Reaction

$$ArCOCH_3 \xrightarrow{(NH_4)_2S_x} ArCH_2CONH_2 + ArCH_2COO^- NH_4^+$$

In the *Willgerodt reaction*, a straight- or branched-chain aryl alkyl ketone is converted to the amide and/or the ammonium salt of the acid by heating with ammonium polysulfide.[2606] The carbonyl group of the product is always at the end of the chain. Thus $ArCOCH_2CH_3$ gives the amide and the salt of $ArCH_2CH_2CO_2H$, and $ArCOCH_2CH_2CH_3$ gives derivatives of $ArCH_2CH_2CH_2CO_2H$. However, yields sharply decrease with increasing length of chain. The reaction has also been carried out on vinylic and ethynyl aromatic compounds and on aliphatic ketones, but yields are usually lower in these cases. Unlike the *Pummerer rearrangement* (**19-87**), which involves transposition of an oxygen from S to C, the Willgerodt reaction involves oxygen migration *and* oxidation of the organic species. The use of sulfur and a dry primary or secondary amine (or ammonia) as the reagent is called the *Kindler modification* of the Willgerodt reaction.[2607] The product in this case is $Ar(CH_2)_nCSNR_2$,[2608] which can be hydrolyzed to the acid. Particularly good results are obtained with morpholine as the amine. For volatile amines, the HCl salts can be used instead, with NaOAc in DMF at 100 °C.[2609] The Kindler modification has also been applied to aliphatic ketones.[2610] Thioamides have been prepared from ketones in a base-catalyzed reaction.[2611]

Alkyl aryl ketones can be converted to aryl acetic acid derivatives in an entirely different manner. The reaction consists of treatment of the substrate with silver nitrate and I_2 or Br_2.[2612]

[2600] Sharma, A.K.; Swern, D. *Tetrahedron Lett.* ***1974***, 1503.

[2601] See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 154–156; Oae, S.; Numata, T. *Isot. Org. Chem.* ***1980***, *5*, 45 (p. 48); Wolfe, S.; Kazmaier, P.M. *Can. J. Chem.* ***1979***, *57*, 2388, 2397; Russell, G.A.; Mikol, G.J. *Mech. Mol. Migr.* ***1968***, *1*, 157.

[2602] McCarthy, A.; Spatney, R.; Manpadi, M.; Myers, B.J.; Zimmerman, J.R. *Tetrahedron Lett.* ***2012***, *53*, 4782.

[2603] Saha, P.; Ray, S.K.; Singh, V.K. *Tetrahedron Lett.* ***2017***, *58*, 1765.

[2604] Kirpichenko, S.V.; Suslova, E.N.; Albanov, A.I.; Shainyan, B.A. *Tetrahedron Lett.* ***1999***, *40*, 185; Mikina, M.; Mikołajczyk, M. *Tetrahedron Lett.* ***2014***, *55*, 3954.

[2605] Urabe, D.; Yamaguchi, H.; Someya, A.; Inoue, M. *Org. Lett.* ***2012***, *14*, 3842.

[2606] For a review, see Brown, E.V. *Synthesis* ***1975***, 358.

[2607] See Mayer, R. in Oae, S. *The Organic Chemistry of Sulfur*, Plenum, NY, ***1977***, pp. 58–63; Lundstedt, T.; Carlson, R.; Shabana, R. *Acta Chem. Scand. Ser. B* ***1987***, *41*, 157, and other papers in this series. See also, Kanyonyo, M.R.; Gozzo, A.; Lambert, D.M.; Lesieur, D.; Poupaert, J.H. *Bull. Soc. Chim. Belg.* ***1997***, *106*, 39.

[2608] See Asinger, F.; Offermanns, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 907.

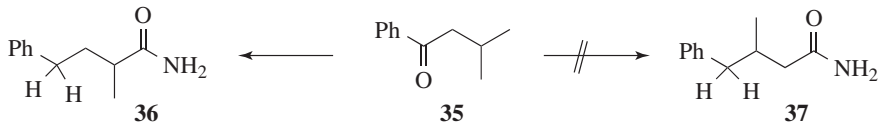
[2609] Amupitan, J.O. *Synthesis* ***1983***, 730.

[2610] See Dutron-Woitrin, F.; Merényi, R.; Viehe, H.G. *Synthesis* ***1985***, 77.

[2611] For a review, see Poupaert, J.H.; Bouinidane, K.; Renard, M.; Lambert, D.; Isa, M. *Org. Prep. Proceed. Int.* ***2001***, *33*, 335.

[2612] Higgins, S.D.; Thomas, C.B. *J. Chem. Soc., Perkin Trans. 1* ***1982***, 235. See also, Higgins, S.D.; Thomas, C.B. *J. Chem. Soc., Perkin Trans. 1* ***1983***, 1483.

The mechanism of the Willgerodt reaction is not completely known, but some conceivable mechanisms can be excluded. Thus, one might suppose that the alkyl group becomes completely detached from the ring, and then attacks it with its other end. However, this possibility is ruled out by experiments results. When isobutyl phenyl ketone (**35**) is subjected to the Willgerodt reaction, the product is **36**, not **37**; **37** would arise if the end carbon of the ketone became bonded to the ring in the product.[2613]



36 **35** **37**

This mechanism also excludes a cyclic intermediate similar to that of the *Claisen rearrangement* (**18-33**). Another important fact is that the reaction is successful for singly branched side chains, such as **35**, but not for doubly branched side chains, as in $PhCOCMe_3$.[2613] Still another piece of evidence is that compounds oxygenated along the chain give the same products; thus $PhCOCH_2CH_3$, $PhCH_2COMe$, and $PhCH_2CH_2CHO$ all give $PhCH_2CH_2CONH_2$.[2614] All these facts point to a mechanism consisting of consecutive oxidations and reductions along the chain, although just what form these take is not certain. Initial reduction to the hydrocarbon can be ruled out, since alkylbenzenes do not give the reaction. In certain cases, imines[2615] or enamines[2616] have been isolated from primary and secondary amines, respectively, and these have been shown to give the normal products, leading to the suggestion that they may be reaction intermediates.

[2613] King, J.A.; McMillan, F.H. *J. Am. Chem. Soc.* ***1946***, *68*, 632.
[2614] See Asinger, F.; Saus, A.; Mayer, A. *Monatsh. Chem.* ***1967***, *98*, 825.
[2615] Asinger, F.; Halcour, K. *Monatsh. Chem.* ***1964***, *95*, 24. See also, Nakova, E.P.; Tolkachev, O.N.; Evstigneeva, R.P. *J. Org. Chem. USSR* ***1975***, *11*, 2660.
[2616] Mayer, R. in Janssen, M.J. *Organosulfur Chemistry*, Wiley, NY, ***1967***, pp. 229–232.

APPENDIX A

The Literature of Organic Chemistry

All discoveries in the laboratory must be published if the information is to be made available to the scientific community. A new experimental result that is not published is useless to the chemical community. Traditionally, the total body of chemical knowledge (called *the literature*) is located on the combined shelves of all the chemical libraries in the world. Nowadays, books remain on library shelves, but many, if not most, chemical journals are available online. As e-books are increasingly available, books are increasingly available online or for personal electronic reading devices. Anyone who wishes to learn the answer to a chemical question will need to access the chemical literature, both books and original articles in journals. Perhaps the most expedient method of searching a question is to "Google™" it, but extreme caution must be exercised to evaluate the source of the information, since there is little or no control of what may be posted on the internet. The answers to simple questions are quickly obtained by this method, but the answers for more complex questions should be confirmed by examining the original journal references (see below) and/or by using multiple sources.

The expressions "is known," "has been done," etc., usually means "has been published." The contents of the scientific literature may appear formidably large, but the process of extracting information from the literature of organic chemistry is usually manageable. This appendix examines both the print literature of organic chemistry[1] and, within reasonable limits, electronic forms of the literature.

It is quite clear that the literature can be divided into two broad categories: primary sources and secondary sources. A *primary source* publishes the original results of laboratory investigations, usually in scientific journals but also in patents. Books, indexes, and other publications that cover material that has previously been published in primary sources are called *secondary sources*. Electronic search engines that use primary sources as a database are also considered to be secondary sources. It is because of the excellence of the secondary sources in organic chemistry (especially *Chemical Abstracts*, *SciFinder*) that literature searching is comparatively straightforward.

[1] See Williams, S. *College Teaching* ***2005***, *53*, 137; Kennedy, M.M. *Educational Researcher* ***2007***, *36*, 139; www.chemistryguide.org; Gallagher, G.J.; Adams, D.L. *J. Chem. Educ.* ***2002***, *79*, 1368. Also see Wolman, Y. *Chemical Information*, 2nd ed., Wiley, NY, ***1988***; Maizell, R.E. *How to Find Chemical Information*, 2nd ed., Wiley, NY, 1987; Antony, A. *Guide to Basic Information Sources in Chemistry,* Jeffrey Norton Publishers, NY, ***1979***; Bottle, R.T. *Use of the Chemical Literature*, Butterworth, London, ***1979***; Woodburn, H.M. *Using the Chemical Literature*, Marcel Dekker, NY, ***1974***. For a three-part article on the literature of organic chemistry, see Hancock, J.E.H. *J. Chem. Educ.* ***1968***, *45*, 193, 260, 336.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

A. PRIMARY SOURCES

A.i. Journals

From the mid-nineteenth century onwards, nearly all new work in organic chemistry (except for that disclosed in patents) has been published in journals. There are many journals that publish chemical papers, in many countries, and in many languages. Nowadays, a high percentage of the journals are published in English, but not all. Some printed journals cover all fields of science, some are restricted to chemistry, some to organic chemistry, and some are still more specialized. Most journals are now available in electronic form.[2] The actual article is usually offered as both an html file and a PDF file, often with links to the cited references. The concept of "pure" organic chemistry is not as useful nowadays because organic chemistry is important in many areas, and multi-disciplinary research often includes organic chemistry. Literature that is important to an organic chemist is found in journals and patents that focus on bioorganic, organometallic, materials science, polymer science, separation science, medicinal chemistry, pharmaceutical sciences, and medicine, to name a few. The reader is therefore cautioned that the journals listed in this section have organic chemistry as their primary focus, but are by no means the only sources of information concerning organic chemistry. The literature is vast and many journals are published weekly and some semi-monthly.

Ordinary papers, usually referred to as full papers, may include full experimental details as part of the paper itself. With the increase in the volume of chemical literature, and especially with the proliferation of electronic journals, many journals now place full experimental details into "Supplemental Information." For journals published by the American Chemical Society, a URL link is provided for each article that contains the supplemental information: experimental details, spectral data, visual reproductions of spectral data, X-ray crystallographic data, etc. Other publishers offer similar links. Such details are the mainstay of modern research, providing a guide to what has been done, and the experimental details allow one to repeat that work, assuming the reader has the expertise in the laboratory, at the same level as the authors of the work. Once a paper is accepted, the online version (such as American Chemical Society ASAP papers) can be found before the print version or the full electronic version that contains the page numbers appear.

In addition to full papers, there are two other types of publications in which original work is reported: *notes* and *communications*. A note is a brief paper, often without a summary (nearly all papers are published with summaries or abstracts prepared by the author). Otherwise, a note is similar to a paper.[3] Some journals specialize in publishing only notes. Communications (also called *letters*) are also brief and usually without summaries (some journals now publish summaries along with their communications), and there are journals that publish only communications or letters.

Communications differ from notes and papers in three respects:

1. They are brief, not because the work is of small scope, but because they are condensed. Usually they include only the most important experimental details or none at all.

[2] For examples of the contents of an academic electronic library see http://lib.uconn.edu/ or http://www.chem.ox.ac.uk/cheminfo/ejournals.html. Also see eJournal Locator.

[3] In some journals notes are called "short communications," an unfortunate practice, because they are not communications as that term is defined in this text.

2. They are of often of immediate significance. Journals that publish communications make every effort to have them appear as soon as possible after they are received. With modern computer technology, communications can often be published in a matter of weeks.
3. Communications are preliminary reports, and the material in them may be republished as papers at a later date, in contrast to the material in papers and notes, which cannot be republished.

The number of journals is in flux, as is the languages of publication. The six prominent traditional European journals (*Chemische Berichte*, *Liebigs Annalen der Chemie*, *Bulletin de la Société Chimique de France*, *Bulletin des Sociétés Chimique Belges*, *Recueil des Travaux Chimiques des Pays-Bas*, and *Gazzetta Chimica Italiana*) were discontinued. In their place is the *European Journal of Organic Chemistry*, published in English. Many of the articles published in other languages have summaries printed in English also. Important papers were published in German and French for over 200 years, and these were generally not available in translation, so that the organic chemist was required to have at least a reading knowledge of these languages. Before about 1920, more than half of the important chemical papers were in these languages. In recent years, however, fewer papers in French or German have appeared without an English translation, and computer technology often allows relatively rapid translation of many languages. It can be argued that a reading knowledge of French and German (especially German) is critical for the older literature. Many, if not most, chemistry departments have modified their language requirements, or dropped them altogether. However, it should be realized that the original literature is never obsolete. Nineteenth century journals with primary literature are found in most chemical libraries and are still consulted, although they are often not available electronically and the archive section of modern university libraries must be consulted. With the rise of Japan and China in the scientific community, journals are published in Japanese and Chinese. However, work by Chinese and Japanese scientists regularly appears in English-language journals.

Table A.1 presents a list of important current journals that publish original papers[4] and communications in organic chemistry. Some of them also publish review articles, book reviews, and other material.

For some years, the American Chemical Society journals, including *J. Am. Chem. Soc.* and *J. Org. Chem.*, provided supplementary material for some of their papers on microfilm or microfiche. As noted above, this material is now available online, and for older literature is available from the Microforms and Back Issues Office at the ACS Washington office, either on microfiche or as a photocopy. These newer methods have not yet succeeded in substantially reducing the total volume of the world's primary chemical literature since many new journals have appeared, and the yearly page count for most journals has doubled or tripled.

A.ii. Patents

In many countries, including the United States, it is possible to patent a new compound or a new method for making a known compound (either laboratory or industrial procedures). It comes as a surprise to many to learn that a substantial proportion of the patents granted have been chemical patents. Chemical patents are part of the chemical literature, and both U.S.

[4] In Table A.1 notes are counted as papers.

TABLE A.1 A list of the more important *current* journals that currently publish original papers in organic chemistry, listed in alphabetical order of *Chemical Abstracts* abbreviations, which are given. Also given are the year of founding, number of issues per year as of 2018, and whether the journal primarily publishes papers (P), communications (C), or both

No.	Name, year of founding and abbreviation	Papers or communications	Issues per year
1	Angewandte Chemie (1887) *Angew. Chem.*	C[5]	12
2	Angewandte Chemie International Edition (1962) *Angew. Chem. Int. Ed.*	C[5]	48
3	Australian Journal of Chemistry (1948) *Aust. J. Chem.*	P	12
4	Bioorganic Chemistry (1971) *Bioorg. Chem.*	P	4
5	Bioorganic & Medicinal Chemistry Letters (1991) *Bioorg. Med. Chem. Lett.*	C	12
6	Bulletin of the Chemical Society of Japan (1926) *Bull. Chem. Soc. Jpn.*	P	12
7	Canadian Journal of Chemistry (1929) *Can. J. Chem.*	P, C	12
8	Carbohydrate Research (1965) *Carbohydr. Res.*	P, C	22
9	Chemistry, a European Journal (1995) *Chem. Eur. J.*	P	24
10	Chemistry, an Asian Journal (2006) *Chem. Asian J.*	P	24
11	Chemistry and Industry (London) (1923) *Chem. Ind. (London)*	C	24
12	Chemistry Letters (1972) *Chem. Lett.*	C	12
13	Chimia (1947) *Chimia*	C	12
14	ChemPlusChem *ChemPlusChem*	P	12
15	Doklady Chemistry (1922) *Dokl. Chem.*	C	12
16	European Journal of Organic Chemistry (1998) *Eur. J. Org. Chem.*	P	12
17	Helvetica Chimica Acta (1918) *Helv. Chim. Acta*	P	8
18	Heteroatom Chemistry (1990) *Heteroat. Chem.*	P	6
19	Heterocycles (1973) *Heterocycles*	C	12
20	Indian Journal of Chemistry (Section B) *Ind. J. Chem. B*	P	12
21	International Journal of Chemical Kinetics (1969) *Int. J. Chem. Kinet.*	P	12

[5] These journals also publish review articles regularly.

TABLE A.1 (*Continued*)

No.	Name, year of founding and abbreviation	Papers or communications	Issues per year
22	Israel Journal of Chemistry (1963) *Isr. J. Chem.*	P	4
23	Journal of the American Chemical Society (1879) *J. Am. Chem. Soc.*	P, C	52
24	Journal of Carbohydrate Chemistry (1981) *J. Carbohydr. Chem.*	P, C	6
25	Journal of Chemical Research, Synopses (1977) *J. Chem. Res. Synop.*	P	12
26	Chemical Communications (1965) *Chem. Commun.*	C	24
27	Journal of Combinatorial Chemistry (2000) *J. Comb. Chem.*	P, C	6
28	Journal of Computational Chemistry (1979) *J. Comput. Chem.*	P	16
29	Journal of Fluorine Chemistry (1971) *J. Fluorine Chem.*	P, C	12
30	Journal of Heterocyclic Chemistry (1964) *J. Heterocycl. Chem.*	P, C	12
31	Journal of the Indian Chemical Society (1924) *J. Indian Chem. Soc.*	P	12
32	Journal of Lipid Research (1959) *J. Lipid Res.*	P	12
33	Journal of Medicinal Chemistry (1958) *J. Med. Chem.*	P, C	12
34	Journal of Molecular Structure (1967) *J. Mol. Struct.*	P, C	16
35	Journal of Organometallic Chemistry (1963) *J. Organomet. Chem.*	P, C	48
36	Journal of Organic Chemistry (1936) *J. Org. Chem.*	P, C	26
37	Journal of Photochemistry and Photobiology, A: Chemistry (1972) *J. Photochem. Photobiol A*	P	12
38	Journal of Physical Organic Chemistry (1988) *J. Phys. Org. Chem.*	P	12
39	Journal of Polymer Science Part A (1962) *J. Polym. Sci. A*	P	24
40	Journal für Praktische Chemie (1834) *J. Prakt. Chem.*	P	6
41	Macromolecules (1968) *Macromolecules*	P, C	26
42	Liebigs Annalen der Chemie (1832) *Liebigs Ann. Chem.*	P	12
43	Mendeleev Communications (1991) *Mendeleev Commun.*	C	8

(*continued*)

TABLE A.1 (*Continued*)

No.	Name, year of founding and abbreviation	Papers or communications	Issues per year
44	Monatshefte für Chemie (1870) *Monatsh. Chem.*	P	12
45	New Journal of Chemistry (1977) *New J. Chem.*	P	11
46	Organometallics (1982) *Organometallics*	P, C	12
47	Organic and Biomolecular Chemistry (2003) *Org. Biomol. Chem.*	P	24
48	Organic Letters (1999) *Org. Lett.*	C	12
49	Organic Mass Spectrometry (1968) *Org. Mass Spectrom.*	PC	12
50	Organic Preparations and Procedures International (1969)[5] *Org. Prep. Proced. Int.*	P	6
51	Organic Process Research & Development (1997) *Org. Process Res. Dev.*	P	6
52	Photochemistry and Photobiology (1962) *Photochem. Photobiol.*	P	12
53	Polish Journal of Chemistry (1921)[6] *Pol. J. Chem.*	P, C	12
54	Pure and Applied Chemistry (1960) *Pure Appl. Chem.*	P[7]	12
55	Research on Chemical Intermediates (1973)[8] *Res. Chem. Intermed.*	P	6
56	Russian Journal of Organic Chemistry (1984) *Russ. J. Org. Chem.*	P, C	12
57	Sulfur Letters (1982) *Sulfur Lett.*	C	6
58	Synlett (1989) *Synlett*	C	12
59	Synthetic Communications (1971) *Synth. Commun.*	C	22
60	Synthesis (1969)[5] *Synthesis*	P	12
61	Tetrahedron (1958)[5] *Tetrahedron*	P	52
62	Tetrahedron: Asymmetry (1990–2017) *Tetrahedron: Asymmetry*	PC	12
63	Tetrahedron Letters (1959) *Tetrahedron Lett.*	C	52

[6] Before 1978 this journal was called *Roczniki Chemii (Rocz. Chem.)*.
[7] *Pure Appl. Chem.* publishes IUPAC reports and lectures given at IUPAC meetings.
[8] Before 1989 this journal was called *Reviews of Chemical Intermediates*, abbreviated as *Rev. Chem. Intermed.*

and foreign patents were regularly abstracted by *Chemical Abstracts* and now *SciFinder*. In addition to learning about the contents of patents from this source, chemists may consult the *Official Gazette* of the U.S. Patent Office,[9] published weekly and available in many libraries, which lists the titles of all the patents issued that week. Bound volumes of all U.S. patents are kept in a number of large libraries, including the New York Public Library, which also has an extensive collection of foreign patents. Patents are available via *SciFinder* (formerly, *CAS Online*).

Although patents are often very useful to the laboratory chemist, and no literature search is complete that neglects relevant patents, as a rule they are not as reliable as papers. There are two reasons for this:

1. It is in the interest of the inventor to claim as much as possible. The patent may show, for example, that a reaction was actually carried with ethanol and with propan-1-ol, but will claim all primary alcohols, and perhaps even secondary and tertiary alcohols, glycols, and phenols. An investigator repeating the reaction on an alcohol that the inventor did not use may find that the reaction gives no yield at all. In general, it is safest to duplicate the actual examples given, of which most chemical patents contain one or more.
2. Although legally a patent gives an inventor a monopoly, any alleged infringements must be protected in court, and this may cost a good deal of money. Therefore some patents are written so that certain essential details are concealed or entirely omitted. A patent is supposed to be a full disclosure, but patent attorneys are generally skilled in the art of writing patents, and procedures given are not always sufficient to duplicate the results.

It is important to state that the above statements do not apply to all chemical patents: many make full disclosures and claim only what was actually done. It must also be pointed out that it is not always possible to duplicate the work reported in every paper in a journal due to the use of proprietary catalysts or equipment not available to the public, and it is not uncommon for the patent owner to buy up what is literally the world's supply of a key ingredient. It is noted, however, that some work is not published or patented but rather maintained within the company as a trade secret. Such work is, of course, not available to the public.

B. SECONDARY SOURCES

Journal articles and patents contain virtually all of the original work in organic chemistry. However, if this were all, if there were no indexes, abstracts, review articles, and other secondary sources, the literature would be unusable. It is so vast that no one could hope to find anything in particular. Fortunately, the secondary sources are excellent. There are various kinds and the classification shown here is somewhat arbitrary.

B.i. Listings of Titles

The profusion of original papers is vast, but publications usually provide a Table of Contents with a graphical abstract that allows one to scan the contents rather quickly.

[9] https://www.uspto.gov/learning-and-resources/official-gazette/

Chemical Abstracts was available online as *CAS Online*, but this service has been supplanted by *SciFinder* (see Appendix A, D.iii). University libraries and companies pay the appropriate fees so access to the journals is usually quite easy if one is affiliated with these organizations. Search engines allow one to quickly scan an enormous amount of literature from office or home. However, the number of pertinent "hits" can be enormous, depending on the scan parameters, In other words, the search may return several hundred thousand or even millions of "hits," and for the most part only 5–20 of the returned items will be surveyed. In addition, most browsers have online searching capabilities via various search engines, and simply typing in an author, a topic, a chemical, or a few key words can lead to important articles or information. "Google® searching"[10] is commonly employed for a "quick and dirty" search, but, as noted above, the source of much information is not clear and one is strongly urged to use one of the established scientific search engines for a proper search. The more important online technology will be discussed below.

Other resources[11] include *Specialty Citation Indexes Science Citation Index Expanded*™, *Web of Science*®, *Science Citation Index*®, *ISI Proceedings*℠, *Reaction Citation Index*™, and the *Derwent Innovations Index*℠. The discussion will begin with the older print versions for chemical searches.

A print-version "title" publication covering the whole of chemistry is *Current Contents Physical, Chemical & Earth Sciences*,[12] which began in 1967 and appears weekly, contains the contents pages of all issues of about 800 journals in chemistry, physics, earth sciences, mathematics, and allied sciences. Each issue contains an index of important words taken from the titles of the papers listed in that issue, and an author index, which, however, lists only the first-named author of each paper. The author's address is also given, so that one may write for reprints. An online service is available and is a multi-disciplinary Web resource.[13]

B.ii. Abstracts

This section is largely devoted to using the printed *Chemical Abstracts*. With *SciFinder* and *Reaxys*, it is likely that many if not most readers will have no need of this section. However, the section remains for those who may need to access and use the more arcane search methods. If nothing else, this section is a reminder that there are alternative search methods that may be of value.

Listings of titles are valuable, as far as they go, but they do not tell what is in the paper, beyond the implications carried by the titles. Most current journals contain a graphic abstract as well as a title and a brief print description of the research. The graphical abstract is extremely useful for scanning the literature presented in a journal, and both the print and graphical abstracts are available online for most journals.

From the earliest days of organic chemistry, abstracts of papers have been widely available. A publication entirely devoted to abstracts covering the whole field of chemistry was *Chemical Abstracts* (*CA*), which was published until 2010. Abstracts are now available online via *SciFinder*. Although now out of print, knowledge of *Chemical Abstracts* may be important to properly do a literature search that includes older literature, although with

[10] www.google.com/

[11] See http://scientific.thomson.com/products/categories/citation/

[12] Title pages of organic chemistry journals are also carried by *Current Contents Life Sciences*, which is a similar publication covering biochemistry and medicine.

[13] http://www.ovid.com/site/catalog/databases/862.jsp

modern computer searching such a statement may be out of date. *Chemical Abstracts* appeared weekly, printing abstracts in English of virtually every paper containing original work in pure or applied chemistry published anywhere in the world.[14] The abstracts appeared in 80 sections, with sections 21 to 34 devoted to organic chemistry, under such headings as "Alicyclic Compounds," "Alkaloids," "Physical Organic Chemistry," "Heterocyclic Compounds (One Heteroatom)," etc. Each abstract of a paper had a heading that gave (i) the abstract number;[15] (ii) the title of the paper; (iii) the authors' names as given in the paper; (iv) the authors' address; (v) the abbreviated name of the journal (see Table A.1);[16] (vi) the year, volume, issue, and page numbers; and (vii) the language of the paper. In earlier years *CA* gave the language only if it differed from the language of the journal title. Abstracts of patents showed the abstract number, title, inventor and company (if any), patent number, patent class number, date patent issued, country of priority, patent application number, date patent applied for, and number of pages in the patent. The body of the abstract contained a concise summary of the information in the paper. For many common journals the author's summary (if there is one) was used in *CA* as it appeared in the original paper, with perhaps some editing and additional information. Each issue of *CA* contained an author index, a patent index, and an index of keywords taken from the titles and the texts or contexts of the abstracts. The patent index listed all patents in order of number. The same compound or method is often patented in several countries. *CA* abstracted only the first patent, but listed the patent numbers of the duplicated patents in the patent index along with all previous patent numbers that correspond to it. Before 1981 there were separate Patent Number Indexes and Patent Concordances (the latter began in 1963).

Chemical Abstracts is useful as a repository of chemical information, a place for finding out what was done in the past. This value stems from the excellent indexes, which enable the chemist in most cases to ascertain quickly where information is located. From the time of its founding in 1907 until 1961, *CA* published annual indexes. After 1962 there were two volumes published each year, and a separate index was issued for each volume. Beginning in 1972 the subject index was issued in two parts, a chemical substance index and a general subject index, which included all entries that are not the names of single chemical substances. However, the indexes to each volume were essentially superseded by each collective index. The first collective indexes were ten-year (decennial) indexes, but the volume of information made five-year indexes necessary from 1956. Collective indexes so far published are shown in Table A.2.

As noted above, the print form of Chemical Abstracts has been superseded by *SciFinder* (see Appendix A, D.iii).

Beginning with the *Eighth Collective Index* period, *CA* has published an *Index Guide*. This publication gave structural formulas and/or alternate names for thousands of compounds, as well as many other cross-references. It was designed to help the user find *CA* references to subjects of interest in the general subject, formula, and chemical substance indexes efficiently and rapidly. Each collective index contained its own *Index Guide*. The *Index Guide* was necessary because the *CA* general subject index was a "controlled index," meaning it restricted its entries only to certain terms.

For example, anyone looking for the term "refraction" in the printed general subject index would not find the term. The *Index Guide* included this term, and directed the reader

[14] For a guide to the use of *CA*, see Schulz, H. *From CA to CAS ONLINE*, VCH, NY, ***1988***.

[15] Began in 1967. See AppendixA/B.ii.

[16] These abbreviations are changed from time to time. Therefore the reader may notice inconsistencies.

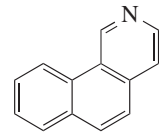
TABLE A.2 *CA* collective indexes

Collective Index	General Subject Index	Chemical Substance Index	Author Index	Formula Index	Patent Index
1	1907–1916		1907–1916		
2	1917–1926		1917–1926		1907–1936
3	1927–1936		1927–1936	1920–1946	
4	1937–1946		1937–1946		1937–1946
5	1947–1956		1947–1956	1947–1956	1947–1956
6	1957–1961		1957–1961	1957–1961	1957–1961
7	1962–1966		1962–1966	1962–1966	1962–1966
8	1967–1971		1967–1971	1967–1971	1967–1971
9	1972–1976	1972–1976	1972–1976	1972–1976	1972–1976
10	1977–1981	1977–1981	1977–1981	1977–1981	1977–1981
11	1982–1986	1982–1986	1982–1986	1982–1986	1982–1986
12	1987–1991	1987–1991	1987–1991	1987–1991	1987–1991
13	1992–1996	1992–1996	1992–1996	1992–1996	1992–1996
14	1997–2001	1997–2001	1997–2001	1997–2001	1997–2001
15	2002–2006	2002–2006	2002–2006	2002–2006	2002–2006

Note that Volumes 146–167 are published, but Collective Volumes are unavailable.

to "Electromagnetic wave, refraction of," "Sound and ultrasound, refraction of," and other terms, all of which *were* found in the general subject index. Similarly, the chemical substance index usually listed a compound only under one name, the approved *CA* name. Trivial and other names were found in the *Index Guide*. For example, the term "methyl carbonate" is not in the chemical substance index, but the *Index Guide* does have this term, and directs the reader to the chemical substance index under the headings "carbonic acid, esters, dimethyl ester" (for Me_2CO_3) and "carbonic acid, esters, monomethyl ester" (for $MeHCO_3$). Furthermore, the *Index Guide* gives terms related to the chosen term, helping users to broaden a search. For example, one who looks for "Atomic orbital" in the *Index Guide* will find the terms "Energy Level," "Molecular orbital," "Atomic integral," and "Exchange, quantum mechanical, integrals for," all of which are controlled index terms.

Each index (annual, semiannual, or collective) also provided an index of ring systems. This valuable index enables the user to ascertain immediately if any ring system appears in the corresponding subject or chemical substance index and under what names.



Benz(*h*)isoquinoline

For example, someone wishing to determine whether any compounds containing the benz(*h*)isoquinoline ring system are reported in the 1982–1986 collective index would locate, under the heading "3-ring systems," the listing **6**,**6**,**6** (since the compound has three rings of six members each), and would find the sublisting C_5N–C_6–C_6 (since one ring contains five carbons and a nitrogen while the others are all carbon), under which is listed the name benz(*h*)isoquinoline, as well as the names of 30 other C_5N–C_6–C_6 systems. A search of the chemical substance index under these names will give all references to these ring systems that appeared in *CA* from 1982 to 1986.

However, this method of search is now probably outdated. Nowadays, the drawing tools of *SciFinder* (see Appendix A, D.iii) or *Reaxys* (Appendix A, D.vi) are used to *draw* this structure and then perform the search.

Before 1967, *CA* used a two-column page, with each column separately numbered. A row of letters from *a* to *h* appeared down the center of the page for the guidance of the user. Thus an entry 7337*b* refers to the *b* section of column 7337. In early years superscript numbers, e.g., 4327^5, were used in a similar manner. In very early years these numbers were not printed on the page at all, though they are given in the decennial indexes, so that the user needed to mentally divide the page into nine parts. Beginning with 1967, abstracts were individually numbered and column numbers were discarded. Therefore, beginning with 1967, index entries give the abstract number rather than the column number. The abstract numbers are followed by a letter that serves as a check character to prevent miscopying errors in computer handling. To use the *CA* general subject, chemical substance, and formula indexes intelligently requires practice, and the student should become familiar with representative volumes of these indexes and with the introductory sections to them, as well as with the *Index Guides*.

In the *CA* formula indexes formulas were listed in order of: (i) number of carbon atoms; (ii) number of hydrogen atoms; (iii) other elements in alphabetic order. Thus, all C_3 compounds are listed before any C_4 compound, all C_5H_7 compounds before any C_5H_8 compound, $C_7H_{11}Br$ before $C_7H_{11}N$, $C_9H_6N_4S$ before C_9H_6O, etc. Deuterium and tritium are represented by D and T and treated alphabetically, e.g., C_2H_5DO after C_2H_5Cl and before C_2H_5F or C_2H_6.

Since 1965, *CA* has assigned a Registry Number[17] to each unique chemical substance. This is a number of the form [766-51-8] (which is 2-chloroanisole) and which remains invariant, no matter what names are used in the literature. More than 137 million numbers have already been assigned and thousands are added each week. Registry Numbers are primarily for computer use, but chemical suppliers use CAS registry numbers to identify chemicals that are available for sale.

There were a number of earlier abstracting publications now defunct. The most important were *Chemisches Zentralblatt* and *British Abstracts*.

B.iii. Beilstein

This publication has been so important to organic chemistry that it deserves a section by itself. Beilstein's *Handbuch der Organischen Chemie*, usually referred to just as *Beilstein*, lists all the known organic compounds reported in the literature during its period of coverage. The print version will be described first, as it is particularly important for older literature. Although the online version may be used most often, a working knowledge of the print version remains an important tool in a chemist's literature arsenal.

For each compound in *Beilstein*, the following data are given: all names; the molecular formula; the structural formula; all methods of preparation (briefly, e.g., "by refluxing 1-butanol with NaBr and sulfuric acid"); physical constants such as melting point, refractive index, etc.; other physical properties; chemical properties including reactions; occurrence in nature (i.e., which species it was isolated from); biological properties, if any; derivatives with melting points; analytical data; and any other information that has been reported in the literature.[18] Equally importantly, for every piece of information, a reference is given to the

[17] See http://www.cas.org/expertise/cascontent/registry/regsys.html

[18] For a discussion of how data are processed for inclusion in Beilstein, see Luckenbach, R.; Ecker, R.; Sunkel, J. *Angew. Chem. Int. Ed. Engl.* ***1981***, *20*, 841 [*Angew. Chem. 93*, 876].

original literature. Furthermore, the data in *Beilstein* have been critically evaluated. That is, all information is carefully researched and documented, and duplicate and erroneous results are eliminated. Some compounds are discussed in two or three lines and others require several pages.

The print editions are invaluable for searching older literature, but, even today, they provide valuable data for many compounds that are used every day. A discussion of using *Beilstein* is therefore essential.

The first three editions of *Beilstein* are obsolete. The fourth edition (*vierte Auflage*), fifth supplement edition, covers the literature from 1960 through 1979. In this edition, the earliest work is covered in *das Hauptwerk* (the basic work), which consists of 27 volumes. The compounds are arranged in order of a system too elaborate to discuss fully here.[19] The compounds are divided into three divisions that are further subdivided into "systems":

Division	Volumes	System numbers
I. Acyclic Compounds	1–4	1–499
II. Carbocyclic Compounds	5–16	450–2359
III. Heterocyclic Compounds	17–27	2360–4720

Das Hauptwerk is still the basis of Beilstein and has not been superseded. The later literature is covered by supplements that have been arranged to parallel *das Hauptwerk*. The same system is used, so that the compounds are treated in the same order. The first supplement (*erstes Ergänzungswerk*) covers 1910–1919; the second supplement (*zweites Ergänzungwerk*) covers 1920–1929; the third supplement (*drittes Ergänzungswerk*) covers 1930–1949; the fourth supplement (*viertes Ergänzungswerk*) covers 1950–1959, and the fifth supplement covers 1960–1979. Like *das Hauptwerk*, each supplement contains 27 volumes,[20] except that supplements 3 and 4 are combined for vols. 17 to 27, so that for these volumes the combined third and fourth supplement covers the years 1930–1959.

Each supplement has been divided into volumes in the same way as *das Hauptwerk*, and, for example, compounds found in vol. 3, system number 199, of *das Hauptwerk* will also be found in vol. 3, system number 199, of each supplement. To make cross-referencing even easier, each supplement gives, for each compound, the page numbers at which the same compound can be found in the earlier books. Thus, on page 554 of vol. 6 of the fourth supplement, under the listing "phenetole" are found the symbols (H 140; E I 80; E II 142; E III 545) indicating that earlier information on phenetole is given on page 140 of vol. 6 of *das Hauptwerk*, on page 80 of the first, page 142 of the second, and page 545 of the third supplement. Furthermore, each page of the supplements contains, at the top center, the corresponding page numbers of *das Hauptwerk*. Since the same systematic order is followed in all six series, location of a compound in any one series gives its location in the other five. If a compound is found, for example, in vol. 5 of *das Hauptwerk*, one only has to note the page number and scan vol. 5 of each supplement until that number appears in

[19] For descriptions of the Beilstein system and directions for using it, see Sunkel, J.; Hoffmann, E.; Luckenbach, R. *J. Chem. Educ.* ***1981***, *58*, 982; Luckenbach, R. *CHEMTECH* ***1979***, 612. The Beilstein Institute has also published two English-language guides to the system. One, available free, is *How to Use Beilstein*, Beilstein Institute, Frankfurt/Main, ***1979***. The other is by Weissbach, O. *A Manual for the Use of Beilstein's Handbuch der Organischen Chemie*, Springer, NY, ***1976***. An older work, which many students will find easier to follow, is by Huntress, E.H. *A Brief Introduction to the Use of Beilstein's Handbuch der Organischen Chemie,* 2nd ed., Wiley, NY, ***1938***.

[20] In some cases, to keep the system parallel and to avoid books that are too big or too small, volumes are issued in two or more parts, and, in other cases, two volumes are bound as one.

the top center of the page (the same number often covers several pages). Of course, many compounds are found in only one, two, three, four, or five of the series, since no work may have been published on that compound during a particular period covered.

From *das Hauptwerk* to the fourth supplement, *Beilstein* is in German, but it is not difficult to read since most of the words are the names of compounds. Also, a *Beilstein* German–English Dictionary, available free from the publisher, is in many libraries. For the fifth supplement (covering 1960–1979), and which is in English, publication of Division III began before the earlier divisions. Volumes 17 to 22 (totaling 70 separate parts exclusive of index volumes) of this supplement have been published, as well as a combined index for volumes 17–19. This index covers only the fifth supplement. The subject portion of this index, which lists compound names only, gives these names in English.

Volumes 28 and 29 of *Beilstein* are subject and formula indexes, respectively. The most recent complete edition of these volumes is part of the second supplement and covers only *das Hauptwerk* and the first two supplements (though complete indexes covering *das Hauptwerk* and the first four supplements have been announced to appear in the next few years). For vol. 1 there is a cumulative subject and a cumulative formula index, which combine *das Hauptwerk* and the first four supplements.[21] Similar index volumes, covering all four supplements, have been issued for the other volumes, 2 to 27. Some of these are combined, e.g., 2–3, 12–14, and 23–25. For English-speaking chemists (and probably for many German-speaking chemists) the formula indexes are more convenient. Of course (except for the fifth supplement indexes), one must still know some German, because most formula listings contain the names of many isomers. If a compound is found only in *das Hauptwerk*, the index listing is merely the volume and page numbers, e.g., **1**, 501. Roman numbers are used to indicate the supplements, for example, **26**, 15, I 5, II 7. Thus the subject and formula indexes lead at once to locations in *das Hauptwerk* and the first four supplements. The *Beilstein* formula indexes are constructed the same way as the *CA* indexes (see Appendix A, B.ii).

There is also a fourth division of *Beilstein* (systems 4721 to 4877) that covers natural products of uncertain structure: rubbers, sugars, etc. These are treated in vols. 30 and 31, which do not go beyond 1935 and which are covered in the collective indexes. These volumes will not be updated. All such compounds are now included in the regular *Beilstein* volumes.

In recent years, *Beilstein* was available online, with the useful search engine *CrossFire*. However, this database is now incorporated into *Reaxys* (see Appendix A, D.vi).

B.iv. Tables of Information

In addition to *Beilstein*, there are many other print reference works in organic chemistry that are essentially compilations of data. These books are very useful and often save the research worker a great deal of time. In this section we discuss some of the more important of such works.

1. The sixth edition of *Heilbron's Dictionary of Organic Compounds*, J. Buckingham, Ed., 9 vols., Chapman and Hall, London, ***1996***, contains brief listings of more

[21] Most page number entries in the combined indexes contain a letter, e.g., $CHBr_2Cl$ 67f, II 33a, III 87d, IV, 81. These letters tell where on the page to find the compound and are useful because the names given in the index are not necessarily those used in the earlier series. The letter "a" means the compound is the first on its page, "b" is the second, etc. No letters are given for the fourth supplement.

than 150 000 organic compounds, giving names, structural formulas, physical properties, and derivatives, with references. Additional data concerning occurrence, biological activity, and toxicity hazard information are also given for many entries. The arrangement is alphabetical. The dictionary contains indexes of names, formulas, heteroatoms, and *CA* Registry Numbers. Annual supplements, with cumulative indexes, have appeared since 1983. A similar work, devoted to organometallic compounds, is the 2nd edition of the *Dictionary of Organometallic Compounds*, 6 vols. in its 5th Supplement, published by Chapman and Hall in ***1989***. Another, *Dictionary of Steroids*, 2 vols., 1991, is also published by Chapman and Hall.

2. A multi-volume compendium of physical data is *Zahlenwerte und Funktionen aus Physik, Chemie, Astronomie, Geophysik, und Technik*, 6th ed., by H. Landolt and R. Börnstein, Springer, Berlin, ***1950***. There is also a "New Series," for which the volumes are given the English title *Numerical Data and Functional Relationships in Science and Technology*, as well as the German title. This compendium, which is not yet complete, lists a great deal of data, some of which are of interest to organic chemists, e.g., indexes of refraction, heats of combustion, optical rotations, and spectral data. Literature references are given for all data.
3. *The Handbook of Chemistry and Physics*, CRC Press, Boca Raton, FL (called the "rubber handbook"), which is revised annually (99th ed., ***2018***; Ruble, J., ed.), is a valuable repository of data that can be quickly found. For organic chemists an important table is *Physical Constants of Organic Compounds*, which lists names, formulas, color, solubility, and physical properties of thousands of compounds. However, there are many other useful tables. A similar work is *Lange's Handbook of Chemistry*, 17th ed., McGraw-Hill, New York, ***2016***; Speight, J., ed. Another such handbook, but restricted to data of interest to organic chemists, is *Dean's Handbook of Organic Chemistry*, 2nd ed., McGraw-Hill, New York, ***2003***. This book also contains a long table of *Physical Constants of Organic Compounds* and has much other information, including tables of thermodynamic properties, spectral peaks, pK_a values, bond distances, and dipole moments.
4. A list of most of the known natural compounds, e.g., terpenes, alkaloids, carbohydrates, to which structures have been assigned, along with structural formulas, melting points, optical rotations, and references, is provided in T.K. Devon and A.J. Scott, *Handbook of Naturally Occurring Compounds*, 3 vols., Academic Press, New York, ***1972***.
5. R.R. Dreisbach, *Physical Properties of Chemical Compounds*, Advances in Chemistry Series nos. 15, 22, 29, American Chemical Society, Washington, ***1955–1961***, lists many physical properties of more than 1000 organic compounds.
6. Physical properties of thousands of organometallic compounds, with references, are collected in five large compendia: the *Dictionary of Organometallic Compounds*, mentioned earlier in this list under item 1, above; M. Dub, *Organometallic Compounds*, 2nd ed., 3 vols. with supplements and index, Springer, New York, ***1966–1975***; N. Hagihara, M. Kumada, and R. Okawara, *Handbook of Organometallic Compounds*, W.A. Benjamin, New York, ***1968***; and H.C. Kaufman, *Handbook of Organometallic Compounds*, Van Nostrand, Princeton, NJ, ***1961***; *Comprehensive Organometallic Chemistry II*, 14 vols., Pergamon, ***1995***.
7. The *Merck Index*, 14th ed., Merck and Company, Rahway, NJ, ***2006***, is a good source of information about chemicals of medicinal importance. The newest *Merck Index* is

available online from the Royal Society of Chemistry.[22] Many drugs are given three types of name: chemical *name* (which is the name an organic chemist would give it; of course, there may well be more than one); *generic name*, which must be placed on all containers of the drug; and *trade names,* which are different for each company that markets the drug. For example, the generic name for 1-(4-chlorobenzhydryl)-4-methylpiperazine is chlorcyclazine. Among the trade names for this drug, which is an antihistamine, are Trihistan, Perazyl, and Alergicide. The *Merck Index* is especially valuable because it gives all known names of all three types for each compound and the names are cross-indexed. Also given, for each compound, are the structural formula, *CA* preferred name and Registry Number, physical properties, medicinal and other uses, toxicity indications, and references to methods of synthesis. There are indexes of formulas and Registry Numbers, and miscellaneous tables. The *Merck Index* also includes a lengthy list of organic name reactions, with references.

8. There are two publications that list properties of azeotropic mixtures. J. Timmermans, *The Physico-chemical Constants of Binary Systems in Concentrated Solutions*, 4 vols., Interscience, New York, ***1959–1960***, is by far the more comprehensive. The other is *Azeotropic Data*, 2 vols., Advances in Chemistry Series no. 6 and no. 35, American Chemical Society, Washington, ***1952***, ***1962***.
9. Thousands of dipole moments, with references, are collected in V.A.L. McClellan, *Tables of Experimental Dipole Moments*, vol. 1, W.H. Freeman, San Francisco, CA, ***1963***; vol. 2, Rahara Enterprises, El Cerrita, CA, ***1974***.
10. *Tables of Interatomic Distances and Configurations in Molecules and Ions*, London Chemical Society Special publication no. 11, ***1958***, and its supplement, Special publication no. 18, ***1965***, include bond distances and angles for hundreds of compounds, along with references.
11. The *Ring Systems Handbook*, published in 1988 by the Chemical Abstracts Service, provides the names and formulas of ring and cage systems that have been published in *CA*. The ring systems are listed under a system essentially the same as that used for the *CA* index of ring systems (see Appendix A, B.i, Appendix A, B.ii). Each entry gives the *CA* index name and Registry Number for that ring system. In many cases a *CA* reference is also given. There is a separate *Formula Index* (for the parent ring systems) and a *Ring Name Index*. Cumulative supplements are issued twice a year. The *Ring Systems Handbook* supersedes earlier publications called *The Parent Compound Handbook* and *The Ring Index*.
12. Spectra Data. The Sadtler Research Laboratories published large collections of IR, UV, NMR, and other spectra, in loose-leaf form. Indexes are available. An usable online site is available that has extensive spectral data, known as Spectral Database for Organic Compounds, SDBS, managed by the National Institute of Advanced Industrial Science and Technology (AIST), Japan. See http://sdbs.db.aist.go.jp/sdbs/cgi-bin/cre_index.cgi
13. Infrared, UV, NMR, Raman, and mass spectral data, as well as melting-point, boiling-point, solubility, density, and other data for more than 30 000 organic compounds are collected in the *CRC Handbook of Data on Organic Compounds*, 2nd ed., 9 vols., CRC Press, Boca Raton, FL, ***1988***, edited by R.C. Weast and J.G. Grasselli. It differs from the Sadtler collection in that the data are given in tabular

[22] https://www.rsc.org/merck-index?e=1

form (lists of peaks) rather than reproduction of the actual spectra, but this book has the advantage that all the spectral and physical data for a given compound appear in one place. References are given to the Sadtler and other collections of spectra. Volumes 7 to 9 contain indexes of spectral peaks for IR, UV, NMR, ^{13}C NMR, mass, and Raman spectra, as well as indexes of other names, molecular formulas, molecular weights, and physical constants. Annual updates began appearing in 1990 (the first one is called volume 10).

14. The *Aldrich Library of Infrared Spectra*, 3rd ed., Aldrich Chemical Company, Milwaukee, WI, ***1981*** (C. Pouchert), contains more than 12 000 IR spectra so arranged that the user could readily see the change that takes place in a given spectrum when a slight change is made in the structure of a molecule. The same company also publishes the *Aldrich Library of FT-IR Spectra* and the *Aldrich Library of NMR Spectra*, both also by C. Pouchert. A similar volume, which has IR and Raman spectra of about 1000 compounds, is *Raman/Infrared Atlas of Organic Compounds*, 2nd ed., VCH, New York, ***1989***, by B. Schrader.
15. An extensive list of visible and UV peaks is given in *Organic Electronic Spectral Data*, Wiley, New York. Twenty-six volumes have appeared so far, covering the literature through 1984.
16. A collection of 500 ^{13}C NMR spectra is found in L.F. Johnson and W.C. Jankowski, *Carbon-13 NMR Spectra*, Wiley, New York, ***1972***.

C. REVIEWS

A review article is an intensive survey of a rather narrow field. For example, the titles of some recent reviews are "Frustrated Lewis Pairs Catalyzed Asymmetric Metal-Free Hydrogenations and Hydrosilylations,"[23] and "Green and Sustainable Solvents in Chemical Processes."[24] A good review article is of enormous value, because it is a thorough survey of all the work done in the field under discussion. Review articles are printed in review journals and in certain books. The most important review journals in organic chemistry (though most are not exclusively devoted to organic chemistry) are shown in Table A.3. Some of the journals listed in Table A.1 also publish occasional review articles.

There are several open-ended serial publications that are similar in content to the review journals but are published irregularly (seldom more often than once a year) and are hardbound. Some of these publish reviews in all fields of chemistry; some cover only organic chemistry; some specialize further. The coverage is indicated by the titles. Table A.4 shows some of the more important such publications, with their *CA* abbreviations.

Another publication is the *Index of Reviews in Organic Chemistry*, complied by D.A. Lewis, Chemical Society, London, a classified listing of review articles. Classified lists of review articles on organometallic chemistry are found in articles by Smith and Walton[25] and by Bruce.[26] A similar list for heterocyclic chemistry is found in articles by A. Katritzky and others.[27] See also the discussion of the *Index of Scientific Reviews* in sec. Appendix A, D.iv.

[23] Meng, W.; Feng, X.; Du, H. *Acc. Chem. Res.* ***2018***, *51*, 191.
[24] Clarke, C.J.; Tu, W.-C.; Levers, O.; Bröhl, A.; Hallett, J.P. *Chem. Rev.* ***2018***, *118*, 747.
[25] Smith, J.D.; Walton, D.R.M. *Adv. Organomet. Chem.* ***1975***, *13*, 453.
[26] Bruce, M.I. *Adv. Organomet. Chem.* ***1972***, *10*, 273; ***1973***, *11*, 447; ***1974***, *12*, 380.
[27] Belen'kii, L.I. *Adv. Heterocycl. Chem.* ***1988***, *44*, 269; Katritzky, A.R.; Jones, P.M. *Adv. Heterocycl. Chem.* ***1979***, *25*, 303; Katritzky, A.R.; Weeds, S.M. *Adv. Heterocycl. Chem.* ***1966***, *7*, 225.

TABLE A.3 Review journals, with year of founding and issues per year

Journal (year of founding)	Abbreviation	Issues per year
Accounts of Chemical Research (1968)	*Acc. Chem. Res.*	12
Aldrichimica Acta (1968)	*Aldrichim. Acta*	4
Angewandte Chemie (1888) and its English translation	*Angewandte Chemie (1888)*	12
Angewandte Chemie, International Edition (1962)	*Angew. Chem. Int. Ed.*	12
Chemical Reviews (1924)	*Chem. Rev.*	8
Chemical Society Reviews (1947)[28]	*Chem. Soc. Rev.*	4
Heterocycles (1973)	*Heterocycles (1973)*	12
Natural Product Reports (1984)	*Nat. Prod. Rep.*	6
Organic Preparations and Procedures International (1969)	*Org. Prep. Proced. Int.*	6
Soviet Scientific Reviews, Section B, Chemistry Reviews (1979) Irreg.	*Sov. Sci. Rev. Sect B Chem. Rev.*	
Sulfur Reports (1980)	*Sulfur Rep.*	6
Synlett (1989)	*Synlett*	12
Synthesis (1969)	*Synthesis*	12
Tetrahedron (1958)	*Tetrahedron*	52
Topics in Current Chemistry (1949)[29]	*Top. Curr. Chem.*	Irreg.
Uspekhi Khimii (1932) and its English translation	*Usp. Khim.*	12
Russian Chemical Reviews (1960)	*Russ. Chem. Rev.*	12

C.i. Annual Reviews

The review articles discussed in Table A.3 are each devoted to a narrow topic covering the work done in that area over a period of years. An annual review is a publication that covers a broad area but limits the period covered, usually to 1 or 2 years.

1. The oldest annual review publication still publishing is *Annual Reports on the Progress of Chemistry*, published by the Royal Society of Chemistry (formerly the Chemical Society), which began in 1905 and which covers the whole field of chemistry. Since 1967 it has been divided into sections. Organic chemistry is found in Section B.
2. Because the number of papers in chemistry has become so large, the Royal Society of Chemistry publishes annual review-type volumes of smaller scope, called *Specialist Periodical Reports*. Among those of interest to organic chemists are *Carbohydrate Chemistry* (vol. 22 covers 1988), *Photochemistry* (vol. 21 covers 1988–1989), and *General and Synthetic Methods*, (vol. 12 covers 1987).
3. *Organic Reaction Mechanisms*, published by Wiley, New York, is an annual survey that covers the latest developments in the field of mechanisms. The first volume, covering 1965, appeared in 1966.
4. There are two annual reviews devoted to progress in organic synthesis. Theilheimer, *Synthetic Methods of Organic Chemistry*, S. Karger, Verlag, Basel, is an annual

[28] Successor to *Quarterly Reviews* (abbreviated as *Q. Rev., Chem. Soc.*).
[29] Formerly called *Fortschritte der Chemischen Forschung* (abbreviated as *Fortschr. Chem. Forsch.*).

TABLE A.4 Irregularly published serial publications

Title	Abbreviation
Advances in Carbocation Chemistry	*Adv. Carbocation Chem.*
Advances in Carbohydrate Chemistry and Biochemistry	*Adv. Carbohydr. Chem. Biochem.*
Advances in Catalysis	*Adv. Catal.*
Advances in Cycloaddition	*Adv. Cycloadd.*
Advances in Free Radical Chemistry	*Adv. Free Radical Chem.*
Advances in Heterocyclic Chemistry	*Adv. Heterocycl. Chem.*
Advances in Metal-Organic Chemistry	*Adv. Met. Org. Chem.*
Advances in Molecular Modeling	*Adv. Mol. Model.*
Advances in Organometallic Chemistry	*Adv. Organomet. Chem.*
Advances in Oxygenated Processes	*Adv. Oxygenated Processes*
Advances in Photochemistry	*Adv. Photochem.*
Advances in Physical Organic Chemistry	*Adv. Phys. Org. Chem.*
Advances in Protein Chemistry	*Adv. Protein Chem.*
Advances in Theoretically Interesting Molecules	*Adv. Theor. Interesting Mol.*
Fluorine Chemistry Reviews	*Fluorine Chem. Rev.*
Fortshritte der Chemie Organischer Naturstoffe	*Fortshr. Chem. Org. Naturst.*
Isotopes in Organic Chemistry	*Isot. Org. Chem.*
Molecular Structure and Energetics	*Mol. Struct. Energ.*
Organic Photochemistry	*Org. Photochem.*
Organometallic Reactions	*Organomet. React.*
Organic Reactions	*Org. React.*
Organic Synthesis: Theory and Applications	*Org. Synth. Theory Appl.*
Progress in Heterocyclic Chemistry	*Prog. Heterocycl. Chem.*
Progress in Macrocyclic Chemistry	*Prog. Macrocyclic Chem.*
Progress in Physical Organic Chemistry	*Prog. Phys. Org. Chem.*
Reactive Intermediates (Plenum)	*React. Intermed. (Plenum)*
Reactive Intermediates (Wiley)	*React. Intermediates (Wiley)*
Survey of Progress in Chemistry	*Surv. Prog. Chem.*
Topics in Physical Organometallic Chemistry	*Top. Phys. Organomet. Chem.*
Topics in Stereochemistry	*Top. Stereochem.*

compilation, beginning in 1946, of new methods for the synthesis of organic compounds, arranged according to a system based on bond-closing and bond-breaking reactions. Equations, brief procedures, yields, and literature references are given. Volume 44 was issued in 1990. Volumes 3 and 4 are available only in German, but all the rest are in English. There is an index to each volume. Cumulative indexes appear in every fifth volume. Beginning with vol. 8, each volume includes a short summary of trends in synthetic organic chemistry. A more recent series is *Annual Reports in Organic Synthesis*, Academic Press, New York, which has covered the literature of each year since 1970. Equations are listed with yields and references according to a fairly simple system.

C.ii. Awareness Services

Besides the annual reviews and the title and abstract services previously mentioned, there exist a number of publications designed to keep readers aware of new developments in organic chemistry or in specific areas of it.

1. *Chemtracts: Organic Chemistry* is a bimonthly periodical, begun in 1988, that prints abstracts of certain recently published papers (those that the editors consider most important), with commentaries on these papers by distinguished organic chemists. Important current research in bioorganic, organometallic, synthesis, physical-organic and theoretical chemistry, and pharmaceutical/medicinal chemistry is covered in each issue, giving readers updates on the newest trends and developments in organic chemistry by summarizing and commenting on current and past research.
2. The Institute for Scientific Information (ISI), besides publishing *Current Contents* (see Appendix A, B.i) and the *Science Citation Index* (see Appendix A, B.i), also publishes *Index Chemicus* (formerly called *Current Abstracts of Chemistry and Index Chemicus*). This publication, begun in 1960 and appearing weekly, is devoted to printing structural formulas of all new compounds appearing in more than 100 journals, along with equations to show how they were synthesized, and an author's summary of the work. Each issue contains five indexes: author, journal, biological activity, labeled compounds, and intermediates that were not isolated. These indexes are cumulated annually.
3. Theilheimer and the *Annual Reports on Organic Synthesis*, mentioned in the previous section, list new synthetic methods once a year. There are several publications that do this monthly. Among these are *Current Chemical Reactions* (begun in 1979 and published by ISI), *Journal of Synthetic Methods* (begun in 1975 and published by Derwent Publications), and *Methods in Organic Synthesis*, begun in 1984 and published by the Royal Society of Chemistry. *Methods in Organic Synthesis* also lists books and review articles pertaining to organic synthesis.
4. *Natural Product Updates,* a monthly publication (begun in 1987 and published by the Royal Society of Chemistry), lists recent results in the chemistry of natural products, along with structural formulas. It covers new compounds, structure determinations, new properties, and total syntheses, among other topics.

C.iii. General Treatises

There are a number of large-scale multi-volume treatises that cover the whole field of organic chemistry or large areas of it.

1. *Rodd's Chemistry of Carbon Compounds*, edited by S. Coffey, Elsevier, Amsterdam, is a treatise consisting of five main volumes, each of which contains several parts. Publication began in 1964 and is not yet complete. The organization is not greatly different from most textbooks, but the coverage is much broader and deeper. Supplements to many of the volumes have appeared. An earlier edition, called *Chemistry of Carbon Compounds*, edited by E.H. Rodd, was published in 10 parts from 1951 to 1962.
2. Houben-Weyl's *Methoden der Organischen Chemie*, Georg Thieme Verlag, Stuttgart, is a major treatise in German devoted to laboratory methods. The fourth edition, which was begun in 1952 and consists of 20 volumes, most of them in several parts, is edited by E. Muller. The series includes supplementary volumes. The first four volumes contain general laboratory methods, analytical methods, physical methods, and general chemical methods. The later volumes are devoted to the

synthesis of specific types of compounds, e.g., hydrocarbons, oxygen compounds, nitrogen compounds, etc. Beginning in 1990 parts of the series have appeared in English.

3. *Comprehensive Organic Chemistry*, Pergamon, Oxford, ***1979***, is a six-volume treatise on the synthesis and reactions of organic compounds. The first three volumes cover the various functional groups, vol. 4 covers heterocyclic compounds, and vol. 5 covers biological compounds such as proteins, carbohydrates, and lipids. Probably the most useful volume is vol. 6, which contains formula, subject, and author indexes, as well as indexes of reactions and reagents. The last two of these not only refer to pages within the treatise, but directly give references to review articles and original papers Several similar treatises, including the nine-volume *Comprehensive Organometallic Chemistry* (***1982***), the eight-volume *Comprehensive Heterocyclic Chemistry* (***1984***), and the six-volume *Comprehensive Medicinal Chemistry* (***1989***) were also published by Pergamon, Oxford. The indexes to these works also include references.
4. A major treatise devoted to experimental methods of chemistry is *Techniques of Chemistry*, edited first by A. Weissberger and then by J.K.M. Saunders, Wiley, New York. This publication, which began in 1970, so far consists of 21 volumes, most of them in several parts, covers such topics as electrochemical and spectral methods, kinetic methods, photochromism, and organic solvents. *Techniques of Chemistry* is a successor to an earlier series, called *Techniques of Organic Chemistry*, which appeared in 14 volumes, some of them in more than one edition, from 1945 to 1969.
5. *Comprehensive Chemical Kinetics,* edited by C.H. Bamford and C.F.H. Tipper, ***1969***-, Elsevier, Amsterdam, is a multi-volume treatise covering the area of reaction kinetics. Six of these volumes (not all published at the time of writing) deal with the kinetics and mechanisms of organic reactions in a thorough and comprehensive manner.
6. Three multi-volume treatises that cover specific areas are R.C. Elderfield, *Heterocyclic Compounds*, Wiley, New York, ***1950***-; R.H.F. Manske and H.L. Holmes, *The Alkaloids*, Academic Press, New York, ***1950***; and J.L. Simonson, L.N. Owen, D.H.R. Barton, and W.C.J. Ross, *The Terpenes*, Cambridge University Press, London, ***1947–1957***.
7. *Encyclopedia of Reagents for Organic Synthesis*, edited by L. Paquette, Wiley, New York, was published in 1995. It is an 8-volume, alphabetic listing of reagents used in organic chemistry with descriptions of the preparation, use, and chemistry, with references. Each reagent was researched by organic chemists active in research, who contributed to the total publication. This work is available online as ***eEROS***, which provides updated information on approximately 3800 reagents with a database of close to 50 000 reactions. Each reagent entry includes properties such as physical data, solubility, form supplied in, purification, and preparative methods; examples of use in reactions; and literature references. Search options include: name, CAS number, structure, and reaction.
8. *Comprehensive Organic Synthesis*, edited by B.M. Trost and I. Fleming, Pergamon, Oxford, was published in ***1991***. It is a 9-volume compilation.
9. *Comprehensive Organic Functional Group Transformations*, edited by A.R. Katritzky, O. Meth-Cohn, and C.W. Rees, Pergamon, was published in ***1995***. It is a 7-volume compilation.

C.iv. Monographs and Treatises on Specific Areas

There are many books devoted to organic chemistry that provide a thorough coverage of a specific area. Many of these are essentially very long review articles, differing from ordinary review articles only in size and scope. Some are comprised of a series of articles, edited by an organic chemist for a specific area of research. Some of the books are by a single author, and others have chapters by different authors but all are carefully planned to cover a specific area. Many of these books have been referred to in footnotes in appropriate places in this book. There have been several series of monographs, one of which is worth special mention: *The Chemistry of Functional Groups,* under the general editorship of Z. Rappoport (S. Patai was the original editor), published by Wiley, New York. Each volume deals with the preparation, reactions, and physical and chemical properties of compounds containing a given functional group. There are more than 130 volumes in the series, including books on alkenes, cyano compounds, amines, carboxylic acids and esters, quinones, etc. Since 2003, the series has appeared both in print and online.

C.v. Textbooks

There are many excellent textbooks in the field of organic chemistry. Only a few of those published are listed, mostly since 1985. Some of these are first-year texts and some are advanced (advanced texts generally give references; first-year texts do not, though they may give general bibliographies, suggestions for further reading, etc.). Some books cover the whole field, and others cover reactions, structure, and/or mechanism only. All the books listed here are good textbooks and the advanced books are valuable reference books for graduate students and practicing chemists.

Undergraduate Level Books

Smith, M.B. *Organic Chemistry: An Acid-Base Approach*, 2nd ed., CRC Press, Boca Raton, FL, ***2018***.

McMurry, *Organic Chemistry*, 9th ed., Cengage Learning, Independence, KY, ***2015***.

Carey and Giuliano, *Organic Chemistry*, 10th ed., McGraw-Hill, Columbus, OH, ***2016***.

Smith, J.H. *Organic Chemistry*, 5th ed., McGraw-Hill, ***2016***.

Vollhardt and Schore, *Organic Chemistry, Structure and Function*, 7th ed., W.H. Freeman, NY, ***2014***.

Bruice, *Organic Chemistry*, 8th ed., Prentice-Hall, NJ, ***2016***.

Jones and Fleming, *Organic Chemistry*, 5th ed., W.W. Norton, New York, ***2014***.

Klein, *Organic Chemistry*, 2nd ed., Wiley, NJ, ***2013***.

Loudon, *Organic Chemistry*, 6th ed., W.H. Freeman, NY, ***2015***.

Solomons and Fryhle, *Organic Chemistry*, 12th ed., Wiley, NY, ***2016***.

Streitwieser, Heathcock, and Kosower, *Clayton's Introduction to Organic Chemistry*, Medtech, ***2017***.

Graduate Level Books

Smith, M.B. *Organic Synthesis*, 4th ed., Academic Press (Elsevier), NY/London, ***2016***.

Carey and Sundberg, *Advanced Organic Chemistry: Structure and Mechanisms (Part A)*, 5th ed., Springer, ***2008***.

Carey and Sundberg, *Advanced Organic Chemistry: Structure and Mechanisms (Part B)*, 5th ed., Springer, ***2010***.

Carruthers and Coldham, *Some Modern Methods of Organic Synthesis*, 4th ed., Cambridge University Press, Cambridge, ***2004***.

Lowry and Richardson, *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row, New York, ***1987***.

Mundy, Ellerd, and Favaloro Jr., *Name Reactions and Reagents in Organic Synthesis*, 2nd ed., Wiley, ***2005***.

House, *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, New York, ***1972***.

Bruckner, *Advanced Organic Chemistry: Reaction Mechanisms*, Academic Press, ***2001***.

Grossman, *The Art of Writing Reasonable Organic Reaction Mechanisms*, 2nd ed., Springer, **2007**.

Sykes, *A Guidebook to Mechanism in Organic Chemistry*, 6th ed., Longmans Scientific and Technical, Essex, ***1986***.

Ritchie, *Physical Organic Chemistry*, 2nd ed., Marcel Dekker, New York, ***1989***.

Isaacs, *Physical Organic Chemistry*, Wiley, New York, ***1987***.

Maskill, *The Physical Basis of Organic Chemistry*, Oxford University Press, Oxford, ***1985***.

Ingold, *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1969***.

C.vi. Other Books

In this section several books are mentioned that do not fit conveniently into the previous categories. All but the last have to do with laboratory synthesis.

1. *Organic Syntheses*, published by Wiley, New York, is a collection of procedures for the preparation of specific compounds. *Organic Syntheses* is currently available online.[30] The annual volumes have appeared each year since 1921 and currently volume 95 is available. For the first 59 volumes, the procedures for each 10- (or 9-) year period are collected in cumulative volumes. Beginning with vol. 60, the cumulative volumes cover five-year periods. The cumulative volumes published so far are:

Annual volumes	Collective volumes
1–9	**I**
10–19	**II**
20–29	**III**
30–39	**IV**
40–49	**V**
50–59	**VI**
60–64	**VII**
65–69	**VIII**
70–74	**IX**
75–80	**X**
81–84	**XI**

[30] http://www.orgsyn.org/

The advantage of the procedures in *Organic Syntheses*, compared with those found in original journals, is that these procedures are *tested*. Each preparation is carried out first by its author and then by a member of the *Organic Syntheses* editorial board, and only if the yield is essentially duplicated is the procedure published. While it is possible to repeat most procedures given in journals, this is not always the case. All *Organic Syntheses* preparations are noted in *Beilstein* and in *CA*. In order to locate a given reaction in *Organic Syntheses*, the reader may use the OS references given in the present volume (through OS **69**); the indexes in *Organic Syntheses* itself; R. Shriner and R. Shriner, "*Organic Syntheses* Collective Volumes I, II, III, IV, V Cumulative Indices," Wiley, New York, ***1976***, or S. Sugasawa and S. Nakai; "Reaction Index of *Organic Syntheses*," Wiley, New York, ***1967*** (through OS **45**). Another book classifies virtually all the reactions in *Organic Syntheses* (collective vols. I to VII and annual vols. 65 to 68) into eleven categories: annulation, rearrangement, oxidation, reduction, addition, elimination, substitution, C—C bond formation, cleavage, protection/deprotection, and miscellaneous. This is *Organic Syntheses: Reaction Guide*, by D. Liotta and M. Volmer, published by Wiley, New York, in ***1991***. Some of the categories are subdivided further, and some reactions are listed in more than one category. What is given under each entry are the equation and the volume and page reference to *Organic Syntheses*.

2. Volume 1 of *Reagents for Organic Synthesis*, by L. Fieser and M. Fieser, Wiley, New York, ***1967***, is a 1457-page volume that discusses, in separate sections, some 1120 reagents and catalysts. It tells how each reagent is used in organic synthesis (with references) and, for each, tells which companies sell it, or how to prepare it, or both. The listing is alphabetical. There are now a total of 25 volumes published as of 2009, which continue the format of vol. 1 and add more recent material. A cumulative index for vols. 1 to 12, by J. Smith and M. Fieser, was published in ***1990***. A cumulative index for volumes 1–22 was published in ***2005***, by M.B. Smith. The series included volumes 1–18 with Mary Fieser. After the death of Mary Fieser, the series was resumed by T.-L. Ho and now includes volumes 19–25.
3. *Comprehensive Organic Transformations*, 2nd ed., by R.C. Larock, Wiley-VCH, New York, ***1999***, has been frequently referred to in footnotes in Part II of this book. This compendium is devoted to listings of methods for the conversion of one functional group into another, and covers the literature through 1987. It is divided into nine sections covering the preparation of alkanes and arenes, alkenes, alkynes, halides, amines, ethers, alcohols and phenols, aldehydes and ketones, and nitriles, carboxylic acids, and derivatives. Within each section are given many methods for synthesizing the given type of compound, arranged in a logical system. A schematic equation is given for each method, and then a list of references (without author names, to save space) for locating examples of the use of that method. When different reagents are used for the same functional group transformation, the particular reagent is shown for each reference. There is a 164-page index of group transformations. The 2nd edition has only recently been published (and is *not* referenced in this edition) and a CD-ROM version is available.
4. *Survey of Organic Synthesis*, by C.A. Buehler and D.E. Pearson, Wiley, New York, 2 vols., ***1970***, ***1977***, discusses hundreds of reactions used to prepare the principal types of organic compounds. The arrangement is by chapters, each covering a functional group, e.g., ketones, acyl halides, amines, etc. Each reaction is thoroughly discussed and brief synthetic procedures are given. There are many references.

5. A similar publication is S. Sandler and W. Karo, *Organic Functional Group Preparations*, 2nd ed., 3 vols., Academic Press, New York, ***1983–1989***. This publication covers more functional groups than Buehler and Pearson.
6. *Compendium of Organic Synthetic Methods*, Wiley, New York, contains equations describing the preparation of thousands of mono-functional and difunctional compounds, with references. Twelve volumes have been published so far (volumes 1–2, edited by I.T. Harrison and S. Harrison; volume 3, edited by L. Hegedus and L.G. Wade Jr.; volumes 4–5, edited by L.G. Wade Jr.; volumes 6–13, edited by M.B. Smith). The series has now been terminated.
7. *The Vocabulary of Organic Chemistry*, by M. Orchin, F. Kaplan, R.S. Macomber, R.M. Wilson, and H. Zimmer, Wiley, New York, ***1980***, presents definitions of more than 1000 terms used in many branches of organic chemistry, including stereochemistry, thermodynamics, wave mechanics, natural products, and fossil fuels. There are also lists of classes of organic compounds, types of mechanism, and name reactions (with mechanisms). The arrangement is topical rather than alphabetical, but there is a good index. *Compendium of Chemical Terminology*, by V. Gold, K.L. Loening, A.D. McNaught, and P. Sehmi (the "Gold Book"), published by Blackwell Scientific Publications, Oxford, ***1987***, is an official IUPAC list of definitions of terms in several areas of chemistry, including organic.

D. LITERATURE SEARCHING

Until recently, searching the chemical literature meant looking only at printed materials (some of which might be on microfilm or microfiche). Now, however, virtually all of the literature can be searched online. Whether the search is online or uses only the printed material, there are two basic types of search: (i) searches for information about one or more specific compounds or classes of compounds and (ii) other types of searches. Searches using only printed materials will be discussed first and then online searching will be covered.[31]

D.i. Literature Searching Using Printed Materials

Searching for Specific Compounds

Organic chemists often need to know if a compound has ever been prepared and, if so, how, and/or they may be seeking a melting point, an IR spectrum, or some other property. Someone who wants all the information that has ever been published on any compound begins by consulting the formula indexes in *Beilstein* (see Appendix A, B.iii). At the time of writing, there are two ways to do this.

1. The formula index to the second supplement (Vol. 29, see Appendix A, B.iii) will quickly show whether the compound is mentioned in the literature through 1929. If it is there, the searcher turns to the pages indicated, where all methods used to prepare the compound are given, as well as all physical properties, with references. Use of the page heading method described in Appendix A, B.iii will then show the locations, if any, in the third and later supplements.

[31] For a monograph that covers both online searching and searching using printed materials, see Wiggins, G. *Chemical Information Sources*, McGraw-Hill, NY, ***1991***.

2. If one has an idea of the volume of *Beilstein* the compound is in (and the tables of contents at the front of the volumes may help), one may search the cumulative index for that volume. If not sure, one may consult several indexes.

One of these two procedures will locate all compounds mentioned in the literature through 1959. If the compound is heterocyclic, it may be in the fifth supplement. If it is in vols. 17–19 (or in a later volume whose index has been published), the corresponding indexes may be consulted. If not, the page heading method will find it, if it was reported before 1960.[32]

However, there is a way by which all of the above can be avoided. At this point the investigator will know (i) all information published through 1959 or 1979,[31] or (ii) that the compound is not mentioned in the literature through 1959 or 1979.[33] In some cases, scrutiny of *Beilstein* will be sufficient, perhaps if only a boiling point or a refractive index is required. In other cases, especially where specific laboratory directions are needed, the investigator will have to turn to the original papers.

To carry the search to more recent articles, the chemist needs to turn to the collective formula indexes of *Chemical Abstracts* and such later collective indexes as have appeared and the semiannual indexes thereafter. However, such searches now would use *SciFinder*.

If a compound has not been reported, the investigator *must know this fact* before proceeding with any research or attempts to publish. Indeed, this knowledge is perhaps the most important consideration when considering a new area of research. It should be pointed out that for common compounds, such as benzene, ether, acetone, etc., trivial mentions in the literature are not indexed (so they will not be found by this procedure), only significant ones. Thus, if acetone is converted to another compound, an index entry will be found, but not if it is used as a solvent or an eluant in a common procedure.

While online searching is extraordinarily powerful, it should be pointed out that there are two problems with computer searches.

First of all, far too many "hits" may be returned. For example, a 2011 research topic search (see Appendix A, D.iii) of the topic "macrolactones from hydroxy acids" using *SciFinder* gave these results:

Research Topic Candidates	Number of references
159 references were found containing the two concepts "macrolactones" and "hydroxy acids" closely associated with one another	159
474 references were found where the two concepts "macrolactones" and "hydroxy acids" were present anywhere in the reference	474
35157 references were found containing the concept "macrolactones"	35157
193323 references were found containing the concept "hydroxy acids"	193323

Clearly, only examining a few of these many references is practical. The search can, and must be, refined. Depending on the scope of the search, this fact can be a limitation.

[32] Compounds newly reported in the fifth supplement that are in a volume whose index has not yet been published will not be found by this procedure. To find them in Beilstein it is necessary to know something about the system, but they may also be found by consulting *SciFinder*.

[33] For those heterocyclic compounds that would naturally belong to a volume for which the fifth supplement has been published.

The second problem relates to the search words used (the keywords). If they are too broad, little useful information is returned. If the keywords are too narrow in scope, many useful references may be missed.

The point of these two cautions is to take care in choosing keywords. On the other hand, using many related keywords and doing multiple searches is very easy using *SciFinder*, and is probably a good strategy.

Often, all the information one needs about a compound will be found in one of the handbooks (see Appendix A, C.i), in the *Dictionary of Organic Compounds* (see Appendix A, C.i), or in one of the other compendia listed in this chapter, most of which give references to the original literature.

Other Searches

There is no definite procedure for making other literature searches using only printed materials. Any chemist who wishes to learn all that is known about the mechanism of the reaction between aldehydes and HCN, for example, or which compounds of the general formula Ar_3CR have been prepared, or which are the best catalysts for *Friedel-Crafts acylation* of naphthalene derivatives with anhydrides, or where the group $-C(NH_2)=N-$ absorbs in the IR, is dependent on ingenuity and knowledge of the literature.

If a specific piece of information is needed, it may be possible to find it in one of the compendia mentioned previously. If the topic is more general, the best procedure is often to begin by consulting one or more monographs, treatises, or textbooks that will give general background information and often provide references to review articles and original papers.

In many cases this is sufficient, but when a complete search is required, it is necessary to consult the *CA* subject and/or chemical substance indexes, and also *SciFinder*, where the ingenuity of the investigator is most required, becasue now it must be decided which words to look under. This statement relates to the keyword used for a computer search, as indicated above. If one is interested in the mechanism of the reaction between aldehydes and HCN, one might look under "aldehydes," or "hydrogen cyanide," or even under "acetaldehyde" or "benzaldehyde," etc., but then the search is likely to prove long. A better choice in this case would be "cyanohydrin," since these are the normal products and references there would be fewer. It would be a waste of time to look under "mechanism." In any case, many of the abstracts would not prove helpful. If it is necessary to search before 1907 (and even before 1920, since *CA* was not very complete from 1907 to about 1920), recourse may be made to *Chemisches Zentralblatt* and the abstracts in the *Journal of the Chemical Society*.

D.ii. Literature Searching Online[17]

Most of the *Chemical Abstracts* literature can be accessed online via *CAS*, using *SciFinder* (see Appendix A, D.iii), which is the largest and most current database of chemical substance information in the world. *CAS* is located in Columbus, Ohio, and is a division of the American Chemical Society. *CAS* can be contacted at Chemical Abstracts Service, 2540 Olentangy River Road, P.O. Box 3012, Columbus, Ohio 43210 (E-mail: help@cas.org; online, http://web.cas.org/forms/feedback.html?_ga=2.160480317.1255697471.1528740358-141076529.1528740358. *CAS* is a team of scientists who provide a digital information environment for scientific research and discovery. *CAS* provides pathways to published research in the world's journal and patent literature back to the beginning of the 20th century. Since 1907, *CAS* has indexed and summarized chemistry-related articles from more

than 40 000 scientific journals, in addition to patents, conference proceedings, and other documents pertinent to chemistry, life sciences, and many other fields. Through the printed *CA* (*Chemical Abstracts*), *CA* on CD, STN (The Scientific & Technical Information Network), the *CAS* files distributed through licensed vendors, the *SciFinder* and *SciFinder Scholar* desktop research tools, and the *STN Easy* or *STN* on the Web services, data produced by *CAS* is accessible to virtually any scientific researcher worldwide in industry, governmental research institutions, and academia.

Substance identification is a special strength of *CAS*. It is widely known as the *CAS Registry*, the largest substance identification system in existence. When a chemical substance, newly encountered in the literature, is processed by *CAS*, its molecular structure diagram, systematic chemical name, molecular formula, and other identifying information are added to the Registry and it is assigned a unique *CAS Registry Number*.

The *CAS REGISTRY* mostly covers substances identified in the scientific literature from 1957 to the present, with some classes (fluorine- and silicon-containing compounds) going back to the early 1900s. An important piece of information that assists in such a search is the *CAS* Registry Number. Each substance in *REGISTRY* is identified by a unique numeric identifier called a CAS Registry Number.[34] "The *CAS* Registry Number is a unique number assigned to a chemical by the Chemical Abstracts Service.[35] A fairly large collection of *CAS* numbers, with links to safety data for many chemicals, can be found at the listing of chemicals by *CAS* number at the Safety Home Page of the Physical and Theoretical Chemistry Laboratory at Oxford University."[36] The *CAS* Registry Number is a unique numeric identifier that designates only one substance, has no chemical significance, and is a link to finding information about a specific chemical substance. A *CAS* Registry Number includes up to 9 digits that are separated into 3 groups by hyphens. The first part of the number, starting from the left, has up to 6 digits; the second part has 2 digits. The final part consists of a single check digit.[37]

Online searching means using a computer terminal to search a *database*. Although databases in chemistry are available from several organizations, STN International is important because it is comprehensive and available in many countries. STN has dozens of databases, including many that cover chemistry and chemical engineering. To access these databases a chemistry department, a library, or an individual subscribes to STN (for a nominal fee), and receives code numbers that will permit access to the system, usually via a desktop computer.

D.iii. Sci-Finder – the CAS database[38]

Tutorials are available to help use *SciFinder*.[39] *SciFinder* can search a research topic[40] or a compound can be searched by structure.[41] The search engine is known as STN Express with Discover![42] and can easily and efficiently search over 200 scientific and technical databases

[34] http://www.cas.org/EO/regsys.html
[35] http://www.cas.org/
[36] http://ptcl.chem.ox.ac.uk/MSDS/glossary/casnumber.html
[37] http://www.cas.org/EO/checkdig.html
[38] http://www.cas.org/
[39] http://www.cas.org/SCIFINDER/SCHOLAR/interact/
[40] http://www.cas.org/SCIFINDER/SCHOLAR/page2a.html
[41] http://www.cas.org/SCIFINDER/SCHOLAR/scholstruc.html
[42] http://www.cas.org/ONLINE/STN/discover.html

online through STN®.[43] The Analysis Edition of STN Express with Discover! allows one to search, analyze, visualize, and discover sci-tech information by the ability to create a table for substance analysis that identifies the common substructure for an answer set of structurally related substances:

- Group related author/inventor names and company names for better analysis and visualization results.
- Analyze and tabulate data from single- or multi-file search results, and create a data table and 3-D chart
- Save an answer set from databases such as CAplusSM, PCTFULL, and USPATFULL with the Save for STN AnaVist Wizard, and then import and open it in STN® AnaVist™.
- Create an interactive spreadsheet from all or only hit CAS Registry Numbers and their corresponding CAS Roles through the CAS Registry Number®.
- Upload lengthy genetic sequences automatically for searching in DGENE and PCTGEN via the Upload Query Wizard.

STN Express was developed in collaboration with Hampden Data Services.

To illustrate how STN is used, an online tutorial is available.[44] A few online windows from a *SciFinder* search are provided to illustrate how searches can be done. This presentation is by no means complete or intended as an alternative to the actual tutorial. Indeed, one could *not* use *SciFinder* properly after simply reading this discussion. The intent is to illustrate some features that are available and to present an overview of the use of this important tool.

Using *SciFinder*®, a search can be done in one of several different ways. Searches can be done by research topic, by substances, or by reactions. The latter two searches use drawing tools that are part of *SciFinder*. An example is shown of a search done by research topic.[45] The example shown in Figure A.1 shows a search for intramolecular hydroamination of aminoalkenes. To begin, click "Explore by Research Topic" and enter the appropriate information.

It is possible to use filters (see Figure A.1) in order to refine the search by year, document type (journal, patent, review, etc.), author, or company. A window is returned that contain references categorized by their relationship to the search phrase, as shown in Figure A.2. One simply checks those reference lists that appear closest to those of interest.

After clicking on "Get References," a screen is returned (Figure A.3) that has the original references, as shown in the window. One is given the option of refining this list further, and for each reference, most browsers allow viewing the abstract or the full references as an HTML or a PDF file. However, your library must have paid the appropriate fees so the journal and volumes of interest are available online. Otherwise, interlibrary loan or direct ordering of the article may be necessary.

Other examples of typical searches allowed by *SciFinder* include search by author's name,[46] as with the example of Professor K. Barry Sharpless shown in Figure A.4. Search by structure is also possible,[47] such as the example shown in Figure A.5, using the *SciFinder*

[43] http://www.cas.org/stn.html
[44] http://www.cas.org/ONLINE/STN/expressmac.pdf
[45] http://www.cas.org/SCIFINDER/topic.html
[46] http://www.cas.org/SCIFINDER/author.html
[47] http://www.cas.org/SCIFINDER/structure.html

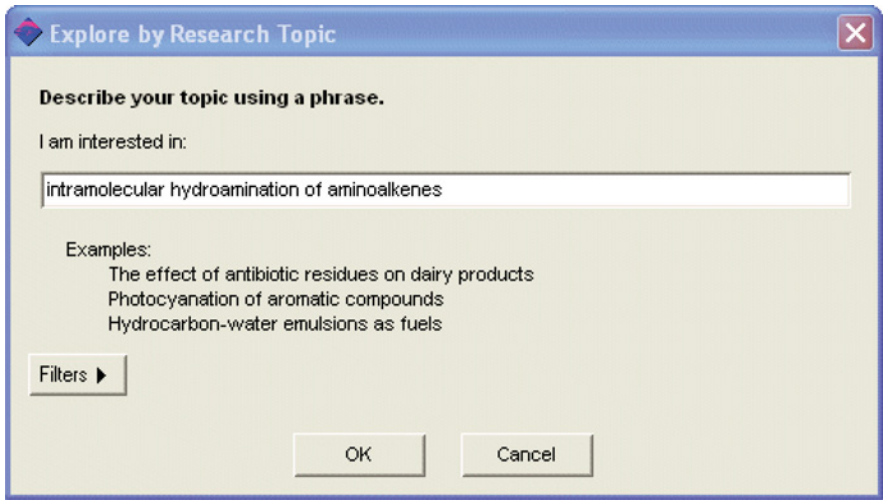


FIGURE A.1. Explore by research topic.

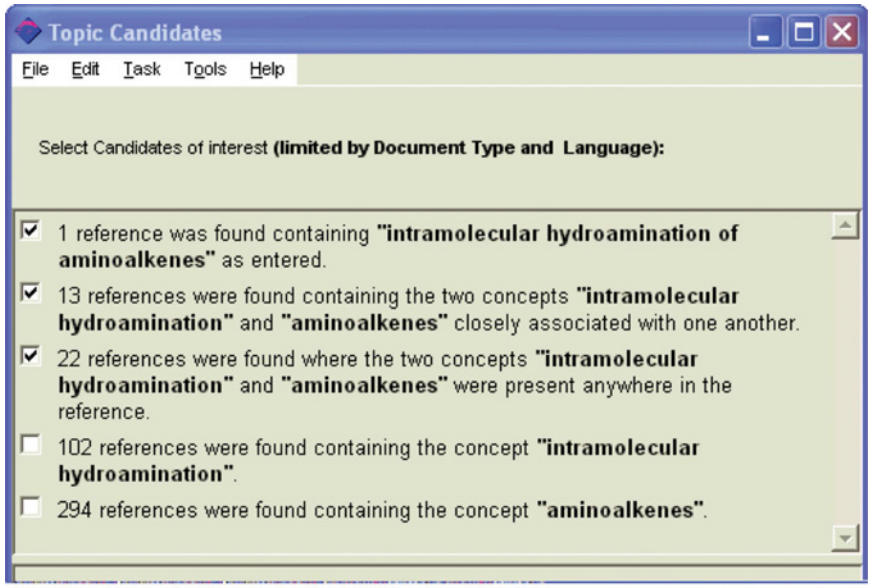


FIGURE A.2. Selection of candidates of interest for search by research topic.

drawing tools. Once a structure is drawn, *SciFinder* searches to find matches based on that structure. The drawing tools can be used to show a reaction, and reaction information is returned, as shown in Figure A.6. Ultimately, journal article and/or patents are returned that provide direct access to the literature of interest.

D.iv. Science Citation Index

As seen in the *SciFinder* search tutorials, it is possible to track papers that have cited a particular article or author. A publication that can greatly facilitate literature searching is

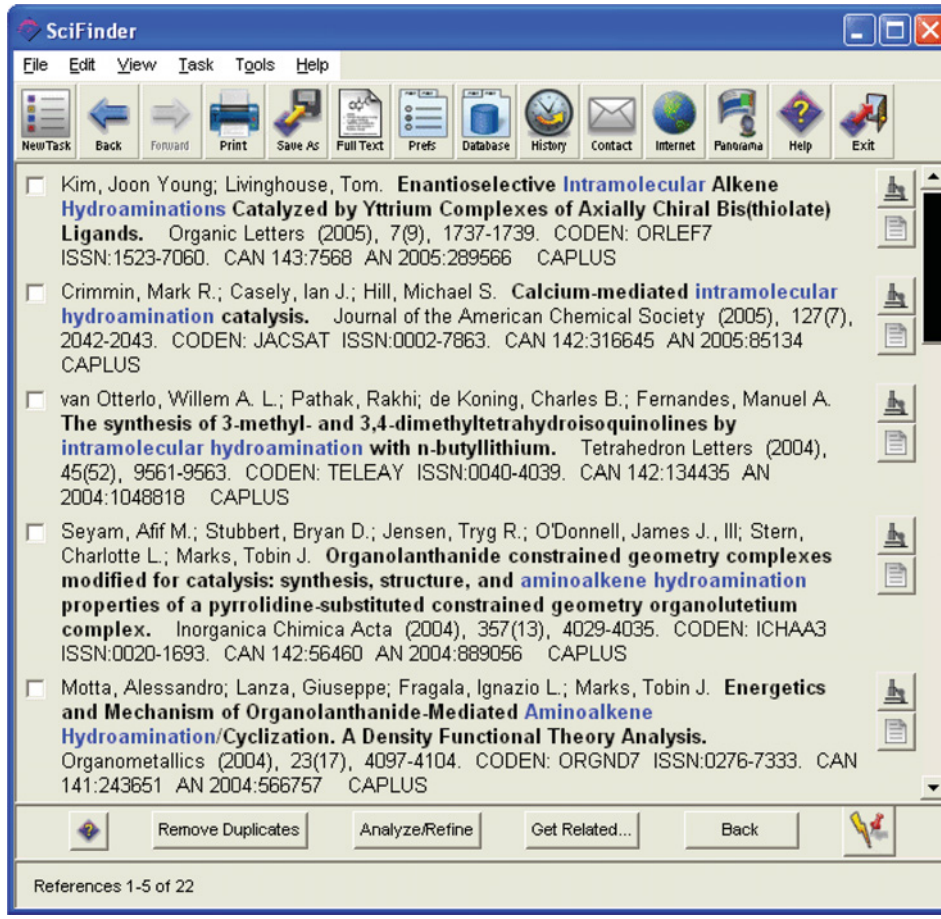


FIGURE A.3. Original literature references returned for search by research topic.

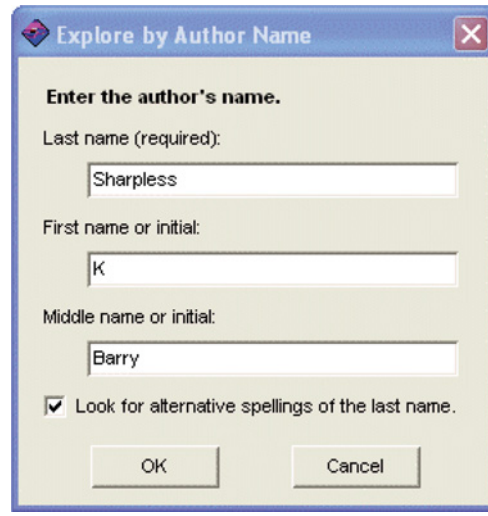


FIGURE A.4. Screen shot for beginning a search by author.

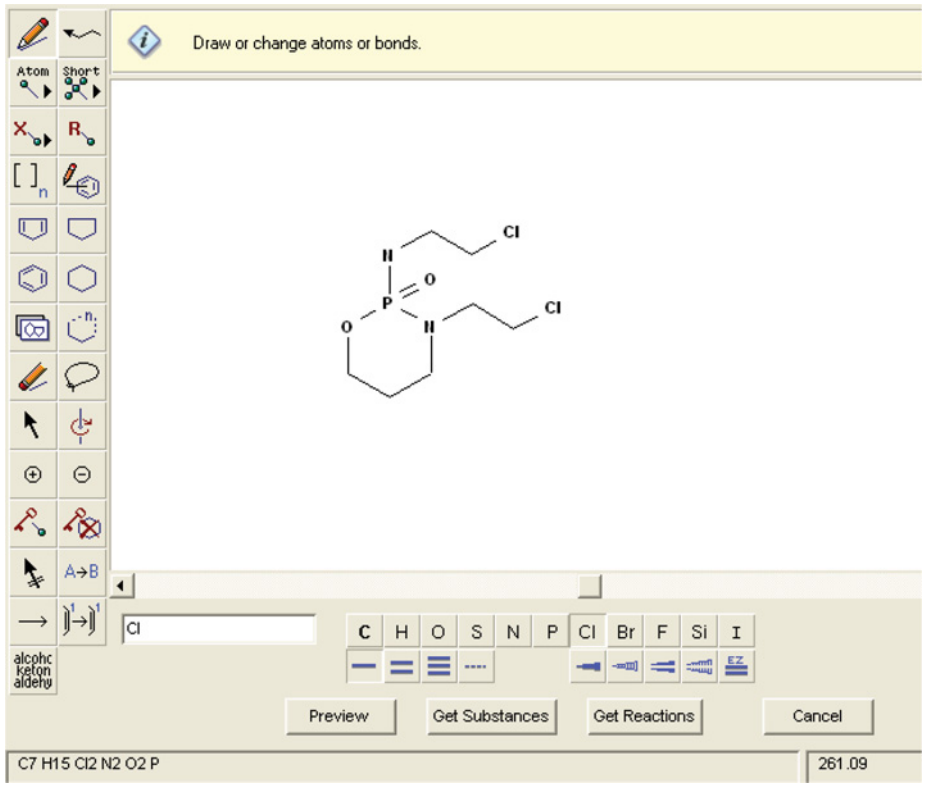


FIGURE A.5. Screen shot for beginning a search by structure, using the drawing tools.

Science Citation Index (*SCI*), begun in 1961. This publication, which is quite different from any other mentioned in this chapter, gives a list of all papers in a given year that have cited a given paper, patent, or book. Its utility lies in the fact that it enables the user to search *forward* from a given paper or patent, rather than backward, as is usually the case. For example, suppose a chemist is familiar with a paper by W.P. Jencks and M. Gilchrist (*J. Am. Chem. Soc.*, ***1968***, *90*, 2622) entitled "Nonlinear Structure-Reactivity Correlations. The Reactivity of Nucleophilic Reagents toward Esters." The chemist is easily able to begin a search for earlier papers by using references supplied in this paper and can then go further backward with the aid of references in those papers, etc. But for obvious reasons the paper itself supplies no way to locate *later* papers. *SCI* is designed to make up for this gap. The citation index of *SCI* lists all papers, patents, or books cited in a given year or 2-month period (by first author only) and then gives a list of papers that have done the citing. The index is published bimonthly and cumulated annually. For example, column 43901 of the 1989 citation index shows that the Jencks paper mentioned above was cited as a footnote in 16 papers published in 1989. It is reasonable to assume that most of the papers that cited the Jencks paper were on closely related subjects. For each of the 16 papers the first author, journal abbreviation, volume number, page numbers, and year are listed. In a similar manner, if one consulted *SCI* for all the years from 1968 on, one would have a complete list of papers that cited that paper. One could obviously broaden the search by then consulting *SCI* (from 1989 on) for papers that cited these 16 papers and so on. Papers, patents, or books

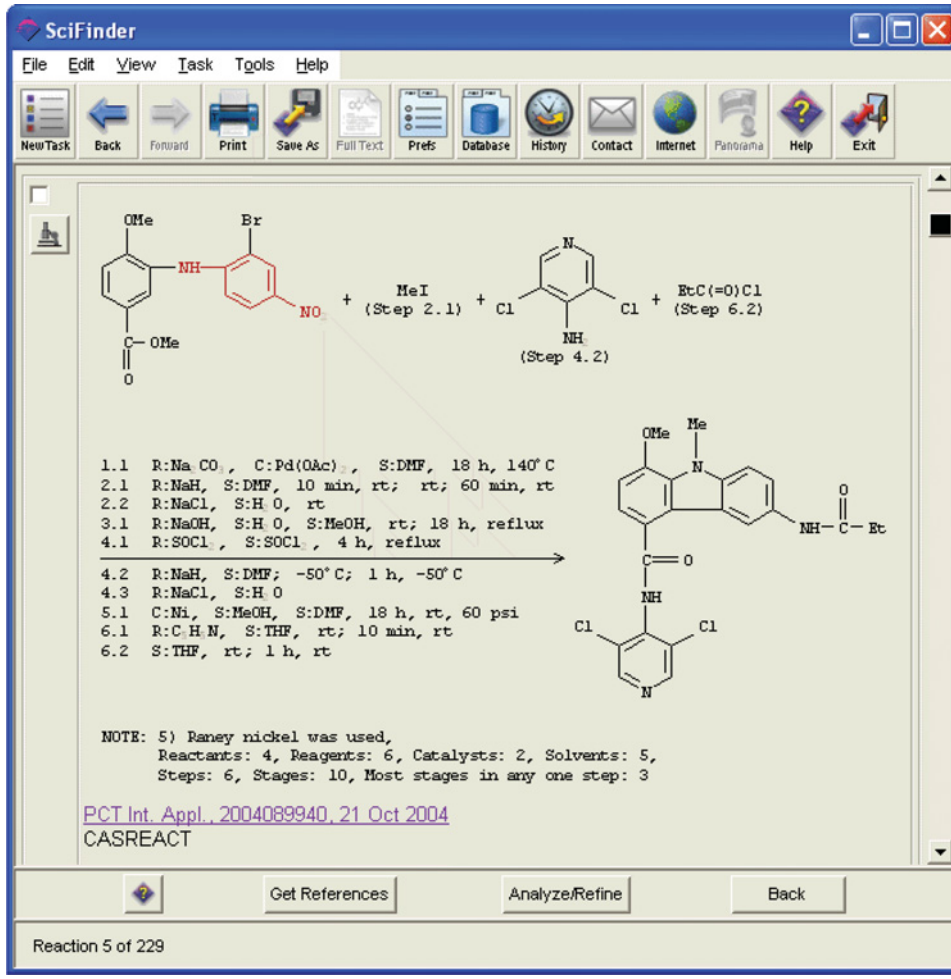


FIGURE A.6. Screen shot of results for a search by reaction, using the drawing tools.

listed, for example, in the 1989 *SCI* may go back many years, e.g., papers published by A. Einstein in 1905 and 1906 are included. The only requirement is that a paper published in 1989 (or late 1988) has mentioned the earlier paper in a footnote. The arrangement of cited papers or books is alphabetical by cited first author and then by cited year. Cited patents are listed in a separate table, in order of patent number, though the inventor and country are also given.

SCI covers about 3200 journals in the physical and biological sciences, as well as in medicine, agriculture, and technology. In addition to the citation index, each bimonthly and annual *SCI* also includes three other indexes. One of these, called *Source Index*, is similar to the *CA* author index. It lists the titles, journal abbreviations, volume, issue, page numbers, and year of all papers published by a given author during that two-month period or year. All authors are listed, not just first authors. The second, called the *Corporate Index*, lists all publications that have been published from a given institution during that period, by first author. Thus, the corporate index for 1989 lists 63 papers by 45 different first authors

emanating from the Department of Chemistry of Rutgers University, New Brunswick, NJ. The main section of the corporate index (the Geographic Section) lists institutions by country or (for the U.S.) by state. There is also an Organization Section, which lists the names of institutions alphabetically, and for each gives the location, so it can be found in the geographic section. The third index included in *SCI* is the *Permuterm*[48] *Subject Index*. This index alphabetically lists every significant word in the titles of all papers published in that year or bimonthly period, paired with all other significant words in the same title. Thus, for example, a title with seven significant words appears at 42 separate places in the index. Each of the seven words appears six times as the main word, each time paired with a different word as the co-word. The user is then led to the *Source Index*, where the full reference is given. *SCI* is also available online (though not through STN) and on CD-ROM discs. A version of *SCI* that is restricted to chemistry, but also includes searchable abstracts, is available only in the CD-ROM format.

The publishers of *SCI* also produce another publication, called *Index to Scientific Reviews*, that appears semiannually. This publication, which began in 1974, is very similar to *SCI* but confines itself to listing citations to review articles. The citations come from about 2500 journals in the same general areas as covered by *SCI*. The review articles cited appeared in about 215 review journals and books, as well as in those journals that publish occasional review articles. Like *SCI*, the *Index to Scientific Reviews* contains citation, source, corporate, and *Permuterm* indexes. It also contains a "Research Front Specialty Index," which classifies reviews by subject.

D.v. How to Locate Journal Articles

Having obtained a reference from various sources or searches, one often needs to consult the original journal (patents are discussed in Appendix A, A.ii). The first step is to ascertain the full name of the journal, since it is the abbreviation that is generally given. Of course, everyone should be familiar with the abbreviations of the very important journals, such as *J. Org. Chem.*, *Chem. Ber.*, etc., but references are often found to journals whose titles are not at all familiar (e.g., *K. Skogs Lantbruksakad. Tidskr.* or *Nauchn. Tr. Mosk. Lesotekh. Inst.*). In such cases, one consults the chemical *Abstracts Service Source Index* (*CASSI*), 1989 edition, which contains the names of all the journals covered by *CA* from 1907 to 1989 (even those no longer published), with the most recent abbreviations in bold print. CASSI also lists journals covered by *Chemisches Zentralblatt* and its predecessors from 1830 to 1969, and journals cited in *Beilstein* before 1907. The journals are listed in alphabetical order of the *abbreviations*, not of the titles. Journal title changes have not been infrequent, and *CASSI* also contains all former names, with cross-references to the current names. Quarterly supplements to *CASSI*, cumulated annually, have appeared since 1990, listing new journals and recent changes in journal titles. It should be pointed out that, while many publications use the *CA* abbreviations, not all do. Usage will vary from country to country, and even from journal to journal within a country. Furthermore, the *CA* abbreviations have changed from time to time. This latter point is particularly important when doing keywords searches. Using a structure search in *SciFinder* may get around this problem.

Once the complete title is known, the journal can easily be obtained if it is in the library customarily used by the chemist, or if that journal is available in electronic form. If not, one

[48] Registered trade name.

must use another library, and the next step is to find out which libraries carry the journal. *CASSI* answers this question too, since it carries a list of some 360 libraries in the United States and other countries, and for each journal it tells which of these libraries carries it and, furthermore, says which volumes of that journal are carried by each library if the holdings are incomplete. However, most libraries have an inter-library loan service that will provide access to such journal articles. It may be possible to visit the closest library personally. *CASSI* also includes lists of journal publishers, sales agents, and document depositories. Photocopies of most documents cited in *CA* can be obtained from Chemical Abstracts Document Delivery Service, Customer Services, 2540 Olentangy River Road, Columbus OH, 43210, U.S.A. Orders for documents can be placed by mail, telephone, telex, fax, or online through STN or other services.

These latter comments are largely out of date given the online status of most journals. As mentioned above, PDF files of an article can be downloaded, or they can be read directly via the HTML file using any current browser. The reader is encouraged to contact the librarian in your establishment that is responsible for chemical literature and so learn which online services are available through your local library.

D.vi. REAXYS®[49]

Launched in 2009, *Reaxys* was created through the merger of the existing *CrossFire* databases [see Appendix A, B.iii] into a single database with a new and intuitive user interface. *Reaxys* is a fully integrated content source providing in-depth coverage of inorganic, organic and organometallic small molecule chemistries excerpted from appropriate journal and patent literature.[50] *Reaxys* is available online with drawing tools that allows entry of a structure, or multiple structures as part of a reaction. Once the structure is drawn, *Reaxys* offers several options for the search.

Reaxys is a unique workflow solution for research chemists providing in depth coverage of inorganic, organic, and organometallic small molecule chemistries. The database consists of chemical compounds and related factual properties, chemical reaction and synthesis information, related bibliographic data, all of which have been excerpted from a carefully selected list of journals and patents, with the patent information being sourced from carefully selected patent classes and patent offices. This content is delivered through a web-based interface, designed for chemists, with powerful functionality which delivers the content in a flexible and intuitive way and which helps a chemist with his/her major information tasks. A method has been promoted that uses *Reaxys* and also *SciFinder* in a "hybrid retrosynthesis" approach to organic synthesis.[51]

At the heart of *Reaxys* is the concept of "Chemistry as the organizing principle." This means that the chemical compound or reaction is central to the way in which the data is organized in the database. This is fundamentally different from bibliographic databases, in which a journal or patent record is at the center. This chemically focused approach allows all data from multiple sources to be combined together in one de-duplicated record for a

[49] https://www.reaxys.com/info/

[50] https://www.elsevier.com/__data/assets/pdf_file/0005/91616/RDS_FactSheet_Reaxys_Oct_2016-WEB.pdf

[51] *Hybrid Retrosynthesis. Organic Synthesis using Reaxys and SciFinder*, D'Angelo, J.D.; Smith, M.B. Elsevier, ***2015***. Designed to supplement existing organic textbooks, *Hybrid Retrosynthesis* presents a relatively simple approach to solving synthesis problems, using a small library of basic reactions along with the computer-searching capabilities of Reaxys and SciFinder.

given compound or reaction (i.e. a single compound or reaction can have multiple source citations whereas a bibliographic database will have one record per published item, so the same compound or reaction may be found in multiple records).

The value of *Reaxys* to organic chemists may be understood best in relation to the synthesis of compounds, which is at the core of organic chemistry. Devising new routes to unique and artificial scaffolds requires the skills of planning and executing multi-step syntheses and having a toolbox of methodologies at one's disposal. However, even the best conceived synthesis plans may require modifications, fine-tuning, or entire rerouting, and chemists are faced with the daily challenge of choosing the right combination of reagents and building blocks for a whole set of problems: Which building blocks are optimal? In which sequence should they be assembled? Which reactions accomplish the task best? The *Reaxys* synthesis planning tool has been designed to make these choices as painless as possible using information and data from the journal and patent literature to investigate a number of possible alternative synthetic routes.

As an example, we will search for papers that have reported direct arylation of indoles at the C3 position. A graphical search query is constructed, using one of the common graphical chemical structure editors, such as ChemDraw, with GH on the indole nitrogen and also at the 5- and 6-positions of indole. The screen in Figure A.7 shows the entry information required for the search. This query retrieved 164 reactions from 45 citations (search results obtained in February 2012).

The *Reaxys* version used in the above example is Application version: 1.0.9619; Content last updated: February 2012; Reactions: 31.681.788; Substances: 20.286.045; Citations: 4.504.504. Figure A.8 shows details for one of the reactions returned for this search. Also shown on this screen are various parameters that are available for searching for this example. The original publication from which the reaction was taken is readily available.

It is also possible to expand the literature review by viewing the details of any recent articles that cite articles of interest. This is easily achieved by clicking on the "view citing

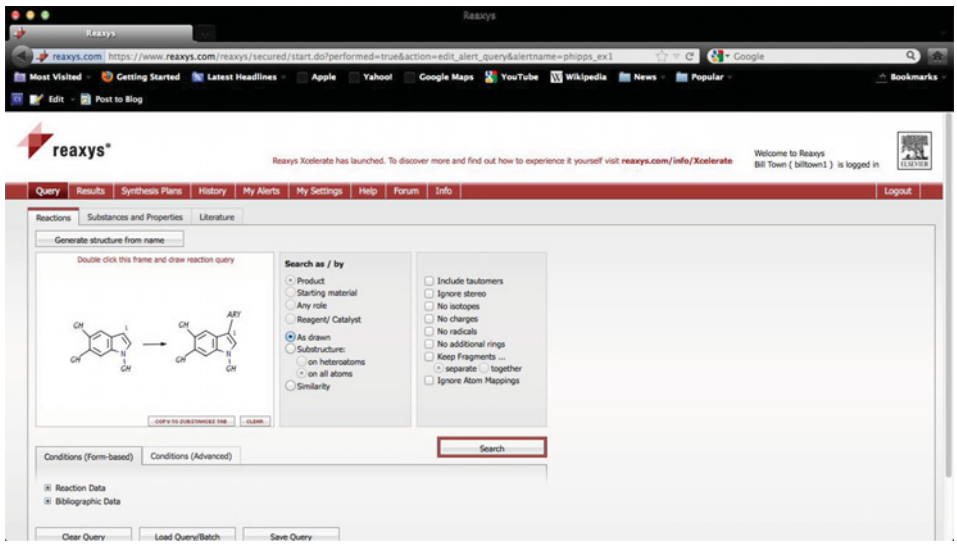


FIGURE A.7. Search for direct arylation of indoles at C3.

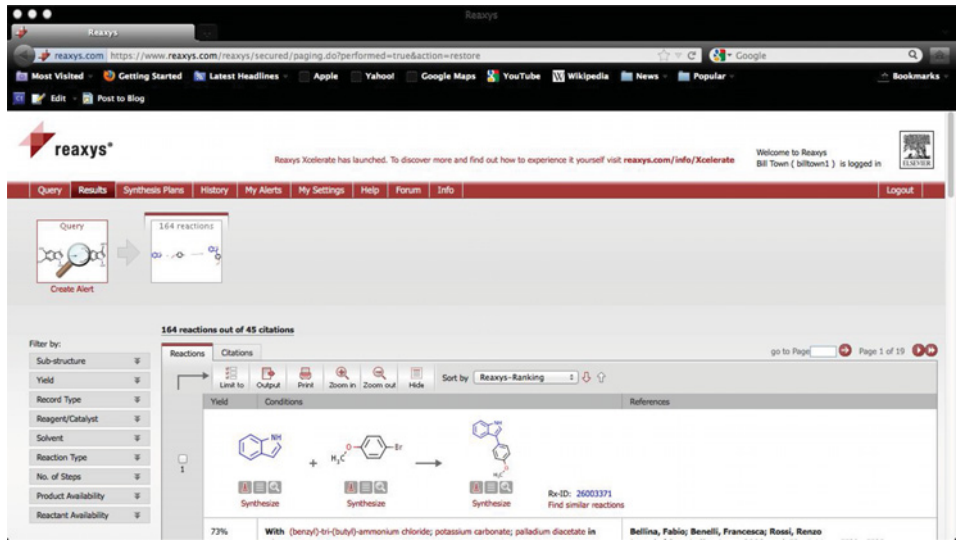


FIGURE A.8. One reaction returned for this search.

articles" hyperlink. The reaction shown in Figure A.8 was cited m the patent literature and also in the *Journal of Organic Chemistry*, as shown in Figure A.9. In this manner, relevant, more recent articles may be identified and explored using citation data from *Scopus*. A few citations are shown in Figure A.10.

The synthesis planning tool allows a more in depth investigation. The *Reaxys* synthesis tool makes it easy to add more steps to the synthesis plan by searching the journal and patent literature for reactions designed to prepare the precursor molecules in any reaction

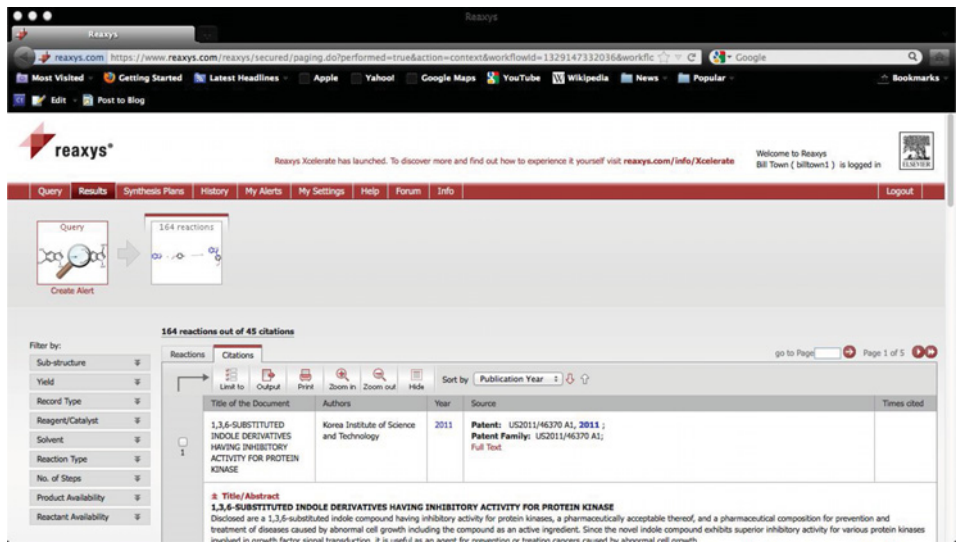


FIGURE A.9. Papers that cited the work in Figure A.8.

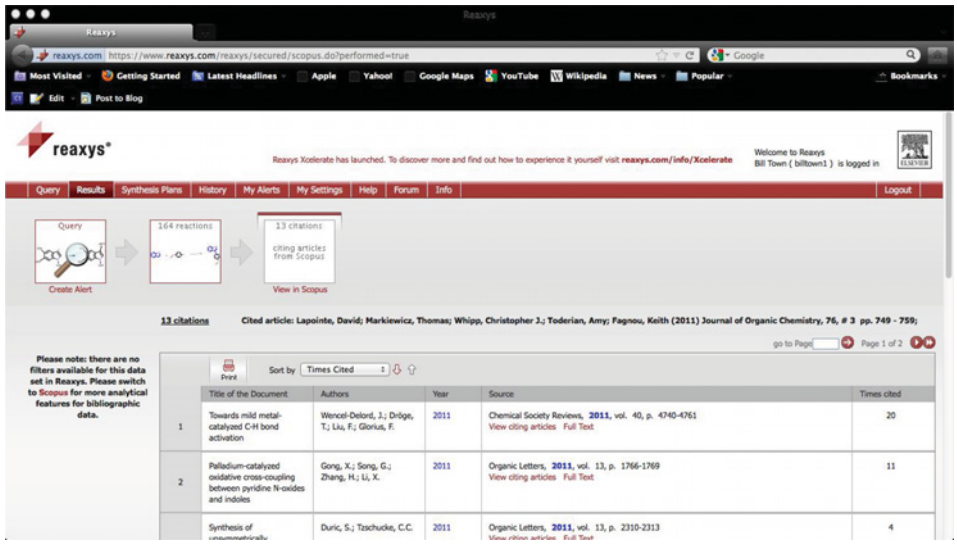


FIGURE A.10. Other potentially relevant papers based on an expanded search.

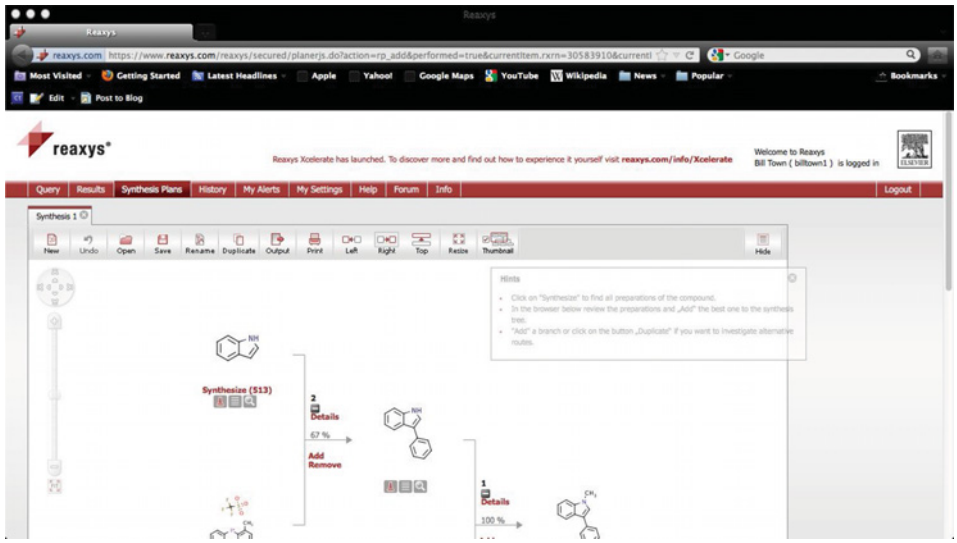


FIGURE A.11. Synthesis plan for 3-phenylindole.

step. Figure A.11 illustrates how a synthesis of a target that is consistent with the original search parameters may be constructed. Extensive property data for chemical substances is available at every stage in the process. *Reaxys* is a valuable addition to the information resources used by synthetic chemists.

APPENDIX B

Classification of Reactions by Type of Compounds Synthesized

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

AUTHOR INDEX

Note that only initials are used with each surname. Therefore, several different authors may be represented by a single entry. There are several authors named Smith, M.B., for example, and citations for all are listed after the single entry.

Entries in the index refer to chapter number (**boldface**) and reference number.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

SUBJECT INDEX

The vast use of transition metal catalysts in organic chemistry makes the citation of every individual metal impractical, so there are limited citations of individual metals. Palladium is one exception where individual citations are common, in keeping with the widespread use of that metal. However, in most cases, the term metal catalyst, or catalyst, metal is used as a heading, usually representing transition metals.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Eighth Edition. Michael B. Smith.

WILEY END USER LICENSE AGREEMENT

Go to www.wiley.com/go/eula to access Wiley’s ebook EULA.